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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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TABLE OF CONTENTS

ACKNOWLEDGEMENTS **4**

1 INTRODUCTION **5**

1.1 Overview 5
1.2 Summary of Part 1 of the Risk Evaluation 6
1.3 Scope and Purpose of Part 2 of the Risk Evaluation 6

2 STRUCTURE OF THE WHITE PAPER **9**

3 SYSTEMATIC APPROACH TO IDENTIFY DOSE-RESPONSE INFORMATION **10**

3.1 Step 1: Comprehensive Literature Search 11
3.2 Steps 2 & 3: Studies Meeting PECO Criteria at Title/Abstract and Full-Text Screening 12
3.3 Steps 4 & 5: Filtering of Studies for Dose-Response Consideration 12
3.3.1 Step 4: Standardized Mortality Ratios and Regression Analysis 12
3.3.2 Step 5: Exposure Measurement and Exposure Assignment in Analysis 12
3.3.2.1 Exposure Measurement 12
3.3.2.2 Exposure Assignment in Analysis 13
3.4 Step 6: Consideration of Cohorts for Dose-Response Analysis 13

4 NON-CANCER DOSE-RESPONSE FOR ASBESTOS **15**

4.1 Systematic Approach for Identification of Epidemiologic Cohorts for Non-cancer Effects 15
4.2 IRIS Libby Amphibole Assessment: Non-cancer Dose-Response 17
4.3 Quantitative Non-cancer Approach for the Risk Evaluation for Asbestos Part 2 18

5 CANCER DOSE-RESPONSE FOR ASBESTOS **20**

5.1 Identification of Epidemiologic Cohort for Cancer Dose-Response 20
5.2 1988 IRIS Asbestos Assessment 25
5.3 IRIS Libby Amphibole Assessment Cancer Dose-Response 26
5.4 Part 1 Risk Evaluation for Asbestos: Dose-Response 27
5.5 Part 2 Risk Evaluation for Asbestos: Quantitative Cancer Approach 29

6 SUMMARY AND NEXT STEPS **32**

REFERENCES **33**

APPENDICES **38**

Appendix A ABBREVIATIONS AND ACRONYMS **38**

Appendix B SYSTEMATIC REVIEW APPROACH **40**

B.1 Data Search and Screening 43
B.1.1 Data Search 43
B.1.2 Data Screening 43
B.2 Identification of Studies Potentially Informative for Dose-Response Analysis 44
B.3 Data Quality Evaluation 49
B.4 Consideration of Epidemiologic Cohorts for Dose-Response Analysis 50

Appendix C NON-CANCER EPIDEMIOLOGIC COHORTS **51**

C.1 Cohorts Included in the IRIS Libby Amphibole Assessment 51
C.2 Cohorts Not Previously Considered in Non-cancer Assessments 52

Appendix D CANCER EPIDEMIOLOGIC COHORTS 54

D.1 Cohorts Included in the Risk Evaluation for Asbestos Part 1 54
D.2 Cohorts Included in the IRIS Libby Amphibole Asbestos Assessment 59
D.3 Cohorts (Mixed-Fiber) Included in the IRIS Asbestos Assessment 59
D.4 Cohorts Not Included in Existing EPA Assessments 61

Appendix E LITERATURE INVENTORY FORM 63

Appendix F POPULATIONS, EXPOSURES, COMPARATORS, AND OUTCOMES (PECO) CRITERIA FOR PART 2 OF THE RISK EVALUATION FOR ASBESTOS 65

Appendix G DATA QUALITY EVALUATION CRITERIA 68

LIST OF TABLES

Table 4-1. Cohorts Identified for Consideration in Asbestos Part 2 Non-cancer Dose-Response Analysis 15
Table 5-1. Cohorts Identified for Consideration in Asbestos Part 2 Cancer Dose-Response Analysis 21
Table 5-2. Comparison of EPA Inhalation Unit Risk Values for Asbestos 30

LIST OF FIGURES

Figure 3-1. Schematic of the Approach Used to Identify Epidemiologic Studies for Dose-Response Consideration 11

LIST OF APPENDIX TABLES

Table_Apx F-1. PECO Criteria for Asbestos Part 2 (Legacy Uses and Associated Disposals) 65
Table_Apx F-2. Major Categories of "Potentially Relevant Supplemental Material" 67
Table_Apx G-1. Mesothelioma Criteria 68
Table_Apx G-2. Other Outcomes Data Quality Evaluation Criteria 83

LIST OF APPENDIX FIGURES

Figure_Apx B-1. Literature Inventory Tree – Environmental and Human Health Hazard for Asbestos Part 2 41
Figure_Apx B-2. Literature Flow Diagram Presenting the Identification, Screening, and Evaluation of Literature 42

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1 INTRODUCTION

1.1 Overview

EPA's programs have evaluated various aspects of asbestos hazard and exposure over many decades. Pursuant to TSCA section 6(b)(2)(A), asbestos was designated as one of the first 10 chemical substances for the OPPT's initial risk evaluations in December 2016 (81 FR 91927). EPA's Integrated Risk Information System (IRIS) in 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 risk assessments conducted under the Superfund program in the Office of Land and Emergency Management (OLEM).

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 (U.S. EPA, 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 and is solely focused on ongoing uses. EPA is currently developing Part 2 of the Risk Evaluation for Asbestos (hereafter "Part 2 of the Risk Evaluation" or "Part 2") that 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, which EPA agreed to consider 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.[1] The purpose of this 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, see also Footnote 3) 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.

In summary, OPPT has made the following findings:

- OPPT conducted 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 (U.S. EPA, 2014b). 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/cc from the IRIS LAA Assessment to assess non-cancer risks in Part 2 with application of appropriate uncertainty factors (UFs).

[1] While the white paper specifically focuses on the quantitative human health assessment and dose-response considerations, Part 2 of the Risk Evaluation for Asbestos will address studies relevant to hazard identification but not informative for dose-response assessment.

- 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.

EPA is soliciting comment on these proposals and associated analyses. This document, and associated independent, expert peer review, are 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) (U.S. EPA, 2017a). OPPT will also release an accompanying Systematic Review Protocol for Asbestos at that time.

1.2 Summary of Part 1 of the Risk Evaluation

For Part 1 of OPPT's Risk Evaluation for Asbestos, EPA initially adopted the definition of asbestos as defined by TSCA Title II (added to TSCA in 1986), section 202 as the "asbestiform varieties of six fiber types – chrysotile (serpentine), crocidolite (riebeckite), amosite (cummingtonite-grunerite), anthophyllite, tremolite or actinolite." However, a choice was made to focus Part 1 solely on chrysotile asbestos as this is the only asbestos fiber type that is currently imported, processed, or distributed in the United States. EPA informed the public of this decision to focus on ongoing uses of asbestos and exclude legacy uses and disposals in the *Scope of the Risk Evaluation for Asbestos*, released in June 2017 (U.S. EPA, 2017b). However, in late 2019, the court in Safer Chemicals, Healthy Families v. EPA, 943 F.3d 397 (9th Cir. 2019) held that EPA's Risk Evaluation Rule (82 FR 33726 [July 20, 2017]) should not have excluded "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 disposals" (*i.e.*, past disposals). Following that court ruling, EPA continued development of the risk evaluation for the ongoing uses of chrysotile asbestos and determined that the complete Risk Evaluation for Asbestos would be issued in two parts. The *Risk Evaluation for Asbestos Part 1: Chrysotile Asbestos* was released in December (2020), allowing the Agency to expeditiously move into risk management for the unreasonable risk identified in Part 1.

1.3 Scope and Purpose of Part 2 of the Risk Evaluation

Following the finalization of Part 1 of the Risk Evaluation for Asbestos, EPA OPPT immediately began development of Part 2, starting with the issuance of a draft scope document. The *Final Scope of the Risk Evaluation for Asbestos Part 2: Supplemental Evaluation Including Legacy Uses and Associated Disposals of Asbestos* (87 FR 38746) (EPA-HQ-2021-0254-0044; hereafter "Final Scope") was released in June 2021, reflecting consideration of public comments on a draft scope document. Although Part 1 of the Risk Evaluation adopted the TSCA Title II definition of asbestos, the consideration of legacy uses and associated disposals that will be evaluated in Part 2 warrant broader considerations as asbestos can be co-located geologically with commercially mined substances. In particular, LAA is known to have been present with vermiculite, extracted from an open pit mine near Libby, Montana, until the mine closed in 1990. Vermiculite was widely used in building materials which are an important focus of the

evaluation of legacy uses of asbestos. Thus, LAA (and its tremolite, winchite, and richterite constituents) will be considered in Part 2 of the Risk Evaluation. EPA will also determine the relevant conditions of use of asbestos-containing talc, including any "legacy use" and "associated disposal" where asbestos is implicated in Part 2 of the Risk Evaluation. Where the Agency identifies reasonably available information demonstrating asbestos-containing talc conditions of use that fall under TSCA authority, these will be evaluated in Part 2 of the Risk Evaluation for Asbestos.

An additional expansion of considerations in Part 2, as described in the Final Scope, pertains to the evaluation of human health effects. Although Part 1 focused on certain cancer outcomes known to be causally related to asbestos exposure (IARC, 2012, 1977), Part 2 will consider non-cancer outcomes at the system level or higher. Historically, there has been a focus on inhalation exposures in health assessments conducted by the EPA and other organizations, but there has also been interest in the updated literature on dermal and oral exposures. These routes of exposure are being considered in Part 2, which EPA agreed to consider 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)). A broad range of health effects are examined in the asbestos epidemiologic literature including cancer (*e.g.*, mesothelioma, lung, ovarian, laryngeal, gastrointestinal cancers) and non-cancer (*e.g.*, asbestosis, lung function decrements, pleural plaques/abnormalities, immune-related effects, cardiovascular effects) outcomes. This range of human health outcomes was presented in Figure 2-10 in the Final Scope, and an interactive version of this diagram is available Heat Map of Hazard Screening Results for Asbestos.[2]

In considering the broad range of health effects and routes of exposure, EPA will continue to focus on the epidemiologic evidence for dose-response as was done in Part 1 and supported by EPA's Science Advisory Committee on Chemicals (SACC). Prior assessments of asbestos conducted by EPA and other agencies have conducted extensive reviews of the literature including epidemiologic and toxicological studies in animals (U.S. EPA, 2020, 2014b; IARC, 2012; ATSDR, 2001; U.S. EPA, 1988, 1986; IARC, 1977). The human health hazards related to asbestos exposure are well-established and there is a robust epidemiologic evidence base. In 1977 and 2012, an International Agency for Research on Cancer (IARC) Working Group reviewed a large body of evidence that covered all fiber types in various epidemiologic studies and settings and found that there is a causal relationship between asbestos inhalation exposure and cancer (mesothelioma and lung, ovarian and laryngeal cancers) and mortality (IARC, 2012, 1977). Additionally, respiratory effects including histopathologic changes (*e.g.*, pleural thickening [LPT], fibrosis, inflammation, etc.) and lung function decrements are consistently observed following asbestos exposure. Some studies have described cardiovascular and immune-related effects, but these effects are demonstrated to occur subsequent to observed respiratory effects (U.S. EPA, 2014b). From a qualitative point of view, the hazards for asbestos are well characterized. Thus, EPA is focusing its efforts on Part 2 on epidemiologic evidence that support quantitative dose-response relationships as needed for the risk evaluation.

EPA has conducted an updated systematic review of the literature to identify and evaluate relevant information. In addition, there are three peer-reviewed, existing Agency assessments on asbestos that

[2] Details on how the Heat Map of Hazard Screening Results for Asbestos and evidence tables were generated are described in Section 4.7.5 of *Draft Systematic Review Protocol Supporting TSCA Risk Evaluations for Chemical Substances* (U.S. EPA, 2021a).

have derived cancer inhalation unit risk (IUR)[3] values and a reference concentration (RfC) for non-cancer effects based on a POD:

1. The IRIS Asbestos Assessment (U.S. EPA, 1988) – presenting an IUR of 0.23 per fiber/cc based on combined risk for lung cancer and mesothelioma;
2. The IRIS Libby Amphibole Asbestos (LAA) Assessment (U.S. EPA, 2014b) – presenting an IUR of 0.17 per fiber/cc based on combined risk for lung cancer and mesothelioma and an RfC of 9×10^{-5} mg/m^3 based on a POD of 2.6×10^{-2} fiber/cc for LPT in the lungs; and
3. The *Risk Evaluation for Asbestos Part 1: Chrysotile Asbestos* (U.S. EPA, 2020) – presenting an IUR of 0.16 per fiber/cc based on combined risk for lung cancer and mesothelioma, including a quantitative adjustment for laryngeal and ovarian cancer.

[3] An IUR is a value representing the upper-bound excess lifetime cancer risk estimated to result from continuous exposure to an agent per fiber/cc of exposure. The IUR can be multiplied by an estimate of lifetime exposure (in fibers/cc) to estimate the lifetime cancer risk.

2 STRUCTURE OF THE WHITE PAPER

This white paper presents the approach taken to identify and evaluate the most relevant of the reasonably available information to inform human health dose-response considerations in Part 2 of the Risk Evaluation for Asbestos. The remainder of the document is organized into the following major sections:

- Section 3 presents an overview of the systematic approach employed to identify the relevant reasonably available information and how the information was screened and categorized to efficiently identify the epidemiologic studies informative for dose-response assessment.
- Section 4 presents an overview of identification of non-cancer dose-response information, a synopsis of the selection of the POD and associated evidence from the IRIS LAA Assessment (U.S. EPA, 2014b), and the proposed quantitative non-cancer approach to be applied in Part 2.
- Section 5 presents an overview of the cancer dose-response information, a synopsis of the existing IURs from the IRIS Asbestos Assessment (U.S. EPA, 1988), the IRIS LAA Assessment (U.S. EPA, 2014b), the *Risk Evaluation for Asbestos Part 1: Chrysotile Asbestos* (U.S. EPA, 2020), and the proposed quantitative cancer approach to be applied in Part 2.
- Section 6 describes the next steps in this process resulting in the release of a draft Part 2 of the Risk Evaluation for Asbestos for public comment.

Additional details on the systematic review approach OPPT used and the underlying evidence for each of the IURs and POD are included in the following seven appendices and one supplemental document:

- Appendix A: Abbreviations and Acronyms
- Appendix B: Systematic Review Approach
- Appendix C: Non-cancer Epidemiologic Cohorts
- Appendix D: Cancer Epidemiologic Cohorts
- Appendix E: Literature Inventory Form
- Appendix F: Populations, Exposures, Comparators, and Outcomes (PECO) Criteria for Part 2 of the Risk Evaluation for Asbestos
- Appendix G: Data Quality Evaluation Criteria
- Supplemental File: Systematic Review of Data Quality Evaluation Information for Human Health Hazard Epidemiology (U.S. EPA, 2023)

3 SYSTEMATIC APPROACH TO IDENTIFY DOSE-RESPONSE INFORMATION

This section presents an overview of the process used to identify, screen, and evaluate the reasonably available information in accordance with TSCA section 6. Details of the TSCA systematic review process are described in EPA's *Draft Systematic Review Protocol Supporting TSCA Risk Evaluations for Chemical Substances* (hereafter "2021 Draft Systematic Review Protocol") (U.S. EPA, 2021a), including Appendix A, which describes updates made to that Protocol in response to recommendations from the National Academies of Sciences, Engineering, and Medicine (NASEM), SACC, and public. Subsequent comments from the April 2022 SACC Meeting on the Draft TSCA Systematic Review Protocol included a recommendation of developing chemical-specific protocols. Therefore, an asbestos-specific, supplemental protocol will be included in the forthcoming Part 2 of the Risk Evaluation that will address asbestos-specific updates for all disciplines. Appendix B in this white paper provides details on the systematic review process for epidemiologic studies for asbestos, including updates to and fit-for-purpose application of the methods described in the 2021 Draft Systematic Review Protocol. Figure 3-1 presents a schematic of the process, beginning with a comprehensive literature search (including all disciplines), followed by successive steps to screen the studies, and ultimately considers the most relevant studies for dose-response assessment.

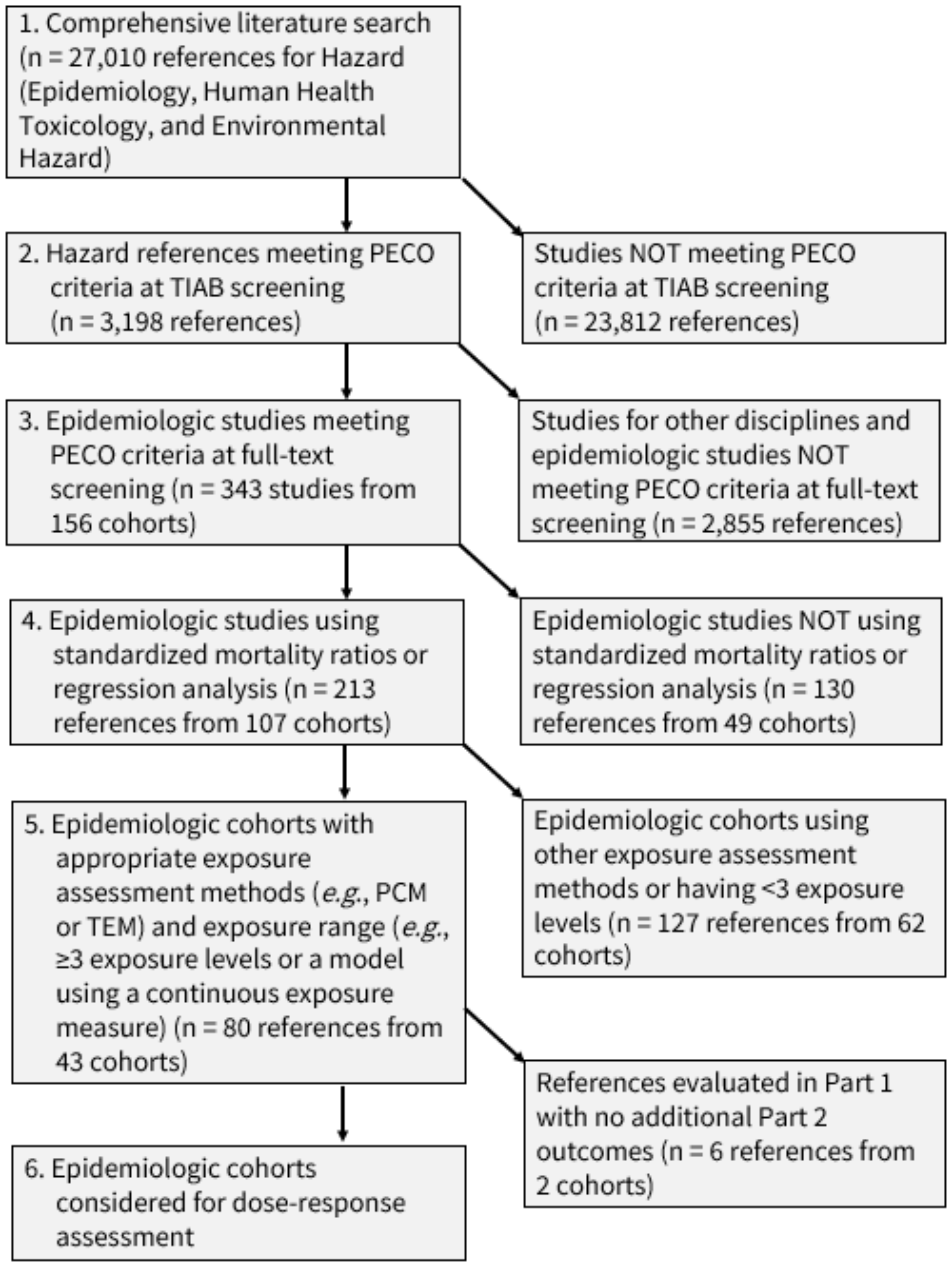

Figure 3-1. Schematic of the Approach Used to Identify Epidemiologic Studies for Dose-Response Consideration

TIAB = title/abstract (screening); PCM = phase-contrast microscopy; TEM = transmission electron microscopy

3.1 Step 1: Comprehensive Literature Search

For each risk evaluation conducted under TSCA, EPA conducts a comprehensive literature search for reasonably available information (Step 1 in Figure 3-1; see also Appendix B in this document and Section 4 of the 2021 Draft Systematic Review Protocol Supporting TSCA Risk Evaluations for Chemical Substances (U.S. EPA, 2021a). For asbestos, literature searches were conducted for Part 1 of the Risk Evaluation for Asbestos in 2016 and then updated in April 2021 for Part 2 (see Appendix Section C.1.24 of the 2021 Draft Systematic Review Protocol). The comprehensive literature search casts a broad net and includes references for hazard (epidemiology, human health toxicology, and environmental hazard).

3.2 Steps 2 & 3: Studies Meeting PECO Criteria at Title/Abstract and Full-Text Screening

Following the literature search, initial screening for relevance was conducted at the title/abstract (TIAB) screening level and then subsequently conducted at the full-text level (Steps 2 and 3, respectively, in Figure 3-1). These processes are more thoroughly described in Appendix B in this white paper and the 2021 Draft Systematic Review Protocol (U.S. EPA, 2021a). TIAB and full-text screening was conducted based on criteria specified in the hazard PECO statement. Generally, for the epidemiologic literature, studies on any human population with exposure to one of the fibers included in the asbestos definition (specific to Part 2 of the Risk Evaluation, see PECO in Appendix F) and examining any outcome or route of exposure (inhalation, dermal, oral) were selected for inclusion. The full PECO statement applied for hazard is included in Appendix F. After screening for these criteria at TIAB and full-text, a total of 343 epidemiologic studies were identified as relevant (Step 3 in Figure 3-1).

3.3 Steps 4 & 5: Filtering of Studies for Dose-Response Consideration

Following the PECO-based screening of the epidemiologic studies, studies were further characterized according to route of exposure, outcome assessed, analysis type and cohort. In an effort to streamline the identification of dose-response information, OPPT identified criteria to filter the literature that met PECO screening criteria. These modifications to the process described in the 2021 Draft Systematic Review Protocol (U.S. EPA, 2021a) were implemented to efficiently identify studies with dose-response data for full data quality evaluation. They included consideration of the data analysis methods used in the study, exposure measurement methods, and use of exposure assignment in analysis. These modifications and the rationale for their development and use are briefly described below and more thoroughly in Appendix B.

3.3.1 Step 4: Standardized Mortality Ratios and Regression Analysis

Given the approach to dose-response analysis conducted in prior asbestos assessments, including Part 1 of the Risk Evaluation for Asbestos, identification of studies that either used standardized mortality ratios (SMRs) or conducted analyses with regression models were determined most likely to be informative for dose-response (Step 4 in Figure 3-1). An SMR is a ratio or percentage describing the increase or decrease in mortality in a given study population relative to the general population and is typically used in studies examining cancer. Regression analyses, in general, describe quantitatively the relationship between an exposure and a response and are typically used in studies examining non-cancer effects. The outputs from studies using SMRs and regression analyses can be used in assessing dose-response. Overall, there were 213 studies using either SMR or regression analyses.

3.3.2 Step 5: Exposure Measurement and Exposure Assignment in Analysis

3.3.2.1 Exposure Measurement

It is well-established that the most reliable methods to detect and accurately quantify asbestos fibers are phase-contrast microscopy (PCM)[4] and transmission electron microscopy (TEM) (U.S. EPA, 1985). Multiple measurements taken by PCM or TEM for a given exposure setting is preferred over a single measurement. In addition, some studies have utilized measurements of dust from midget impingers, and if a combination of methods are used such that an appropriate conversion factor is available to yield fiber concentrations from dust measurements, these data can also be informative for dose-response.

[4] PCM was recommended by the National Institute for Occupational Safety and Health (NIOSH) and Occupational Safety and Health Administration (OSHA) as the preferred asbestos measurement method in 1979 as there was a recognized need for reliable measurement and evaluation of occupational exposure to asbestos to put practices into place to prevent asbestos-related disease (Leidel et al., 1979).

OPPT evaluated exposure measurement methods in studies before evaluating other data quality evaluation criteria to identify those with reliable methods for dose-response (Step 5 in Figure 3-1). Notably, some epidemiologic cohorts considered in the 1988 IRIS Asbestos Assessment were not initially identified in the systematic review approach because the individual publications for these cohorts lacked sufficient detail to meet PECO criteria, including for exposure measurement; however, additional related publications were identified through citations and the information in the 1988 IRIS Asbestos Assessment (U.S. EPA, 1988) and the 1986 Airborne Asbestos Health Assessment Update (U.S. EPA, 1986) provided important information about these cohorts and analyses such that these cohorts warranted consideration in this white paper for dose-response (see Appendix D.3).

Studies were considered by cohort groupings. For example, if multiple publications were available on a particular occupational cohort, they were considered as a set of information rather than as independent publications. For the 343 studies that met PECO screening criteria, a total of 156 epidemiologic cohorts were identified, and 66 of these cohorts were the subject of multiple publications.

3.3.2.2 Exposure Assignment in Analysis

A variety of approaches can be used in the quantitative analysis within an epidemiologic study; however, understanding the exposure-response relationship in a given population/cohort is best informed when the analysis is conducted with consideration of three or more exposure levels or a model using a continuous exposure measure (Step 5 in Figure 3-1). For example, analyses presenting results based on only an unexposed and an exposed group is minimally informative for dose-response relative to studies presenting responses for a broader range of exposure levels. Thus, studies using appropriate exposure measurement methods and containing three or more exposure groups or a continuous measure of exposure were identified to undergo data quality evaluation.

A total of 43 cohorts meeting these additional criteria of using regression or SMR and having appropriate exposure measurement and exposure assignment in analysis were identified for further consideration. These cohorts subsequently underwent data quality evaluation (Step 5 in Figure 3-1), as explained in Appendix B of this white paper and in Appendix R of the *Draft Systematic Review Protocol Supporting TSCA Risk Evaluations for Chemical Substances* (U.S. EPA, 2021a). Study quality evaluations were conducted using DistillerSR, and the summary of the data evaluation results are included in a Supplemental File (U.S. EPA, 2023). Briefly, the evaluation of study quality includes consideration of 22 different metrics that are rated as High, Medium, Low, or Critically Deficient based on pre-defined criteria. The assessment of each of the metrics contributes to an overall quality determination (OQD) of High, Medium, Low, or Uninformative. Cohorts with an OQD of Medium or High were further considered for dose-response assessment. of this white paper and in Appendix R of the *Draft Systematic Review Protocol Supporting TSCA Risk Evaluations for Chemical Substances* (U.S. EPA, 2021a). Study quality evaluations were conducted using Distiller SR, and the summary of the data evaluation results are included in a Supplemental File (U.S. EPA, 2023). Briefly, the evaluation of study quality includes consideration of 22 different metrics that are rated as High, Medium, Low, or Critically Deficient based on pre-defined criteria. The assessment of each of the metrics contributes to an overall quality determination (OQD) of High, Medium, Low, or Uninformative. Cohorts with an OQD of Medium or High were further considered for dose-response assessment.

3.4 Step 6: Consideration of Cohorts for Dose-Response Analysis

Cohorts with studies receiving an OQD of Medium or High were categorized for examination of cancer and/or non-cancer outcomes. Review of the exposure and outcome data and analysis performed was done to confirm (1) the use of PCM or TEM for measurement of asbestos fibers or application of appropriate conversion factors to dust measurements, (2) the use of air measurements in the analysis, (3)

the analysis was conducted with health outcome data, and (4) there was adequate assessment of the outcome (*e.g.*, sufficient follow-up time). While these four aspects were considered as part of the data quality evaluation, considering these factors in light of dose-response analysis provides a more detailed perspective. Ultimately, 32 cohorts were removed from further consideration at this point because the quantitative analyses were done with dust measurements or fiber measurements not using PCM or TEM and did not have conversion factors or because they had received a Low or Uninformative OQD rating in data quality evaluation. As noted previously, in the case of some cohorts considered in the Airborne Asbestos Health Assessment Update (U.S. EPA, 1986), additional information on conversion of dust measurements to fiber counts was available to enable use and consideration of these studies in the context of dose-response (see Appendix D.3).

Finally, the extent to which cohorts may inform an exposure-response relationship was evaluated using considerations primarily aimed at the identification of high-quality exposure and outcome data to inform the estimation of an IUR and/or a POD. The list of considerations provided below was used to aid in making judgements regarding which studies or studies from a group of studies quantitatively evaluated the exposure-response relationship for asbestos to derive an estimation of its effect on the outcome in the studied population. EPA considered time since first exposure (TSFE) because it is a predictor of risk. The job exposure metric (JEM) was used because the table provides estimated exposure levels in air (fibers/cc) for workers in each job for each year. The Agency utilized these considerations, which were identified in the IRIS LAA Assessment as characteristics necessary for identifying principal studies with the greatest confidence that might inform the dose-response assessment (U.S. EPA, 2014b). A total of 19 cohorts were under consideration at this stage. Cohorts that were deemed most useful for dose-response assessment adhered to the following considerations:

1. Medium or High OQD;
2. Asbestos fibers collected on membrane filters and analyzed using PCM or TEM or a conversion factor from early measurement of total dust particles in million particles per cubic foot (mppcf) to estimate fiber/mL or the equivalent fiber/cc;
3. Used continuous measure of exposure rather than categorical exposure levels (*e.g.*, quartiles) to provide more granular details on the exposure-response relationship;
4. Models that used individual-level exposure assignment methods;
5. Availability of data on TSFE matched to the exposure data, as this is needed to model asbestos-related outcomes in dose-response analysis (U.S. EPA, 2014b);
6. Timing of exposure relative to the outcome;
7. Sufficient length of follow-up for outcome assessment, recognizing the extended latency of asbestos-related outcomes;
8. Studies that provide information on the exposure-response relationship between asbestos exposure and outcome; and
9. Use of a JEM to accurately reconstruct workers' exposure histories to derive a cumulative exposure for each individual over the course of the relevant exposure period.

While Appendix C and Appendix D provide a description of each of the non-cancer and cancer cohorts, respectively, Sections 4 and 5 focus more specifically on the key dose-response information for cancer and non-cancer, respectively, for Part 2 of the Risk Evaluation. Each of these sections provides an overview of cohorts available and describes the relevant non-cancer POD or IURs and the underlying data and specific cohort upon which they are based. The approach to be applied in Part 2 of the Risk Evaluation for Asbestos for non-cancer and cancer outcomes is also described in each of these sections.

4 NON-CANCER DOSE-RESPONSE FOR ASBESTOS

Section 4.1 presents an overview of the literature identified for non-cancer dose-response information for asbestos exposures. Section 4.2 presents an overview of the non-cancer dose-response analysis from the IRIS LAA Assessment (U.S. EPA, 2014b), while Appendix C provides additional discussion of other cohorts for which dose-response data were available. Ultimately, new dose-response analyses were not warranted for Part 2. Section 4.3 describes the non-cancer quantitative approach to be applied in Part 2 of the Risk Evaluation for Asbestos.

4.1 Systematic Approach for Identification of Epidemiologic Cohorts for Non-cancer Effects

Application of the systematic review approach described in Section 3 resulted in the identification of seven cohorts for consideration in assessing dose response of non-cancer outcomes related to asbestos exposures. All of the cohorts identified examined inhalation exposures. Epidemiologic studies examining oral or dermal exposures with dose-response information were not identified by the systematic review approach. The outcomes assessed in the identified cohorts included non-cancer mortality (including asbestosis and pneumoconiosis), pleural changes/thickening, and lung function changes. Some of these cohorts were identified and considered in the IRIS LAA Assessment (U.S. EPA, 2014a), which is the only EPA assessment that quantitatively considered non-cancer effects. The cohorts are listed and briefly described in Table 4-1 and are more thoroughly presented in Appendix C. Based on the considerations described in Appendix C, it was determined that the O.M. Scott Marysville, OH, Plant Cohort provides 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. This cohort and the selection of the POD, uncertainty factors, and derivation of RfC are described further in Section 4.2. The other six cohorts OPPT identified, which were not within the scope of the IRIS LAA Assessment, were less suitable for non-cancer dose-response assessment because the outcomes examined were less sensitive (*i.e.*, mortality-related outcomes) and/or because there was greater uncertainty in the exposure data (*e.g.*, community-based measurements rather than personal sampling). Generally, for dose-response assessment, preference is given to studies examining the most sensitive outcome(s), so although mortality can be used in the assessment, it is less sensitive than a well-described outcome preceding mortality from a disease state. Appendix C provides more details on the dose-response considerations for each cohort.

Table 4-1. Cohorts Identified for Consideration in Asbestos Part 2 Non-cancer Dose-Response Analysis

Cohort Name (Reference[s])	Cohort Description	Non-cancer Outcome(s)	Data Quality Evaluation Rating
IRIS Libby Amphibole Asbestos Assessment, 2014			
O.M. Scott Marysville, OH, Plant Cohort (Lockey et al., 1984) (Rohs et al., 2008)	• Cohort included 530 workers with known vermiculite exposure participated in the 1980 investigation. Eight different worksite operations at the ore processing plant were represented. • Monitoring of industrial hygiene at the facility started in 1972, including personal breathing zone sampling. PCM measurements beginning after 1976. • Job exposure matrix used to determine cumulative exposures.	Pulmonary function Mortality	High

Cohort Name (Reference[s])	Cohort Description	Non-cancer Outcome(s)	Data Quality Evaluation Rating
	• Follow-up including chest x-rays and interview information from 280 of the 431 workers who were known to be alive between 2002 and 2005. • Followed up on the respiratory effects in the cohort conducted in 2012.		
Libby, MT, Vermiculite Mining and Milling Cohort	• Participants were white men who had worked for at least 1 year in the mine and mill. • Reports based on follow-up data from 1960 to 2006. • Air sampling data were used to build a job-exposure matrix assigning daily exposures (8-hour time-weighted average [TWA]) for selected job codes. • Individual work histories and the mine and mill job-exposure matrix were used to determine individual exposure metrics.	Mortality	Medium
Cohorts not included in previous EPA assessments for non-cancer effects			
SC Textiles Cohort	• Textile plant in Charleston, SC and used asbestos from 1909 to 1977. • Original cohort of textile workers limited to white males employed for at least 1 month between 1940 and 1965. Later expanded to included non-whites and females. • Individual-level exposures estimates derived from detailed work histories and extensive air measurements using PCM and conversion of dust measurements from analysis of paired sampling.	Mortality	Medium
SC Vermiculite Miners Cohort (W. R. Grace & Co, 1988)	• Cohort composed of 194 men hired between 1949 and 1974 in mining/milling of vermiculite in Enoree, SC. • 58 air samples collected in 1986 and analyzed by PCM.	Mortality, parenchymal abnormalities including pleural thickening and sputum analysis	Medium
Anatolia, Turkey, Villagers Cohort (Metintas et al., 2005)	• Field-based, cross-sectional study of 991 villagers from 10 randomly selected villages with known asbestos-containing white soil. • Indoor and outdoor air sample taken for each village; fibers counted by PCM.	Pleural plaques, asbestosis, diffuse pleural fibrosis	High
Wittenoom, Australia, Residents Cohort	• Residential cohort included 4659 individuals residing for at least 1 month in Wittenoom between 1943 and 1992. Mine workers excluded.	Mortality	Medium

Cohort Name (Reference[s])	Cohort Description	Non-cancer Outcome(s)	Data Quality Evaluation Rating
	• Follow-up in 1993, 2000, and 2004 • Ambient exposures from nearby crocidolite assigned based on dates of residence, assigned exposure intensity, and period personal monitoring after operations ceased.		
Chinese Chrysotile Textile Factory Cohort (Huang, 1990)	• Cohort of 776 workers employed for at least 3 years in chrysotile textile product factory; Shanghai. • 17 workplaces in the factory selected for routine sampling; dust and fiber measurements collected by membrane filters. • Follow-up through September 1982 for asbestos diagnosis.	Asbestosis incidence	Medium

4.2 IRIS Libby Amphibole Assessment: Non-cancer Dose-Response

The IRIS LAA Assessment conducted a dose-response assessment for non-cancer effects utilizing data from a cohort of workers in the O.M. Scott plant in Marysville, Ohio. 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). Workers were drawn from a variety of departments/facilities, including production and packaging of commercial products, maintenance, research, the front office, and the polyform plant. The initial study of this cohort utilized 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 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, 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 benchmark response (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. More specific details and results of model-fitting are presented in Section 5.2.2.6.1 in the IRIS LAA Assessment (U.S. EPA, 2014b). A POD based on a 10 percent BMR for LPT was calculated to be 2.6×10^{-2} fiber/cc.

The IRIS program noted important uncertainties related to the underlying evidence base for this POD and applied 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 (U.S. EPA, 2014b).

- Regarding the UF_H, the occupational cohort included individuals healthy enough to work, and when taking into account human variability, it is plausible that there are more sensitive individuals in the population. This uncertainty remains at this time; thus, UF_H of 10 continues to be applied.
- Regarding the UF_D of 3, applied in the IRIS LAA Assessment because of the limited number of cohort studies evaluating the most sensitive non-cancer effects of chronic asbestos exposure, the Agency has reevaluated the appropriateness of UF_D of 3 in light of the systematic review. As described in Section 4, no new cohort studies have been published that would inform the dose response relationship for hazards beyond pleural effects and asbestosis for the non-cancer POD. Therefore, the Agency will continue to apply a UF_D of 3.
- Regarding the UF_S, it was anticipated that if the cohort had been followed for longer, even more cases of LPT would have been identified. The cohort used to derive the 2014 IRIS RfC, O.M. Scott Marysville, OH, was followed for approximately 30 years. The IRIS LAA Assessment determined that it was appropriate to apply a UF_S because even 30 years of observation is insufficient to describe lifetime risk of LPT, which continues to increase over a person's lifetime (see page 5-42 of the IRIS LAA Assessment for further rationale for applying the UF_S (U.S. EPA, 2014a)). The IRIS LAA Assessment, therefore, derived a data informed UF_S of 10 based on the fact that "the central estimate of the risk at TSFE = 70 years is ~10-fold greater than the central estimate of the risk at TSFE = 28 years (from 6% to 61%)" (see page 5-43 of the IRIS LAA Assessment for further details (U.S. EPA, 2014a)). TSFE in the model was set at 28 years due to limitations in the statistical uncertainty.

4.3 Quantitative Non-cancer Approach for the Risk Evaluation for Asbestos Part 2

As described in Section 3.1, seven epidemiologic cohorts were identified for consideration in dose-response analysis (Table 4-1): two occupational cohorts considered in the IRIS LAA Assessment as well as three additional occupational cohorts and two community-based cohorts. When considering specific attributes of the cohorts and available data (see Appendix B), the two occupational cohorts from the Libby assessment were the most informative for dose-response, and the O.M. Scott Marysville, OH, Fertilizer Plant Workers Cohort continues to be the most robust. This is because of the confidence in the individual-level exposure and outcome data in addition to having sufficient follow-up time, as described more fully in the IRIS LAA Assessment and as summarized in the preceding section (4.2) (U.S. EPA, 2014b). 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.

Given the above, use of the LAA POD from the IRIS assessment in Part 2 of the Risk Evaluation is a reliable approach to quantitatively consider non-cancer risks from asbestos exposures. While there is some uncertainty in application of a Libby-specific POD for exposures to a broader range of asbestos fibers, the uncertainty of using other studies for quantitative assessment would be even greater given the limited exposure characterization for those cohorts (SC Vermiculite Miners Cohort; Anatolia, Turkey, Villagers Cohort) (see Appendix C). For example, for the SC Vermiculite Miners Cohort, non-cancer outcomes were only categorically analyzed as exposed and unexposed. In addition, details of the exposure assessment are insufficient for dose-response assessment, and there is a lack of information on TSFE. The Anatolia, Turkey, Villagers Cohort constructed individual-level exposure estimates, but these were based on broad assumptions of time spent indoors, outdoors, and sleeping. The other cohorts available for dose-response assessment similarly had exposures to a single fiber type and examined mortality as the outcome, which would not be representative of the most sensitive effects known to result from asbestos exposures.

Based on the comprehensive approach to identify and evaluate the relevant epidemiologic literature for dose-response assessment of non-cancer effects resulting from asbestos exposures, use of the POD presented in the IRIS LAA Assessment for Part 2 of the Risk Evaluation is proposed. In the IRIS LAA Assessment, LPT was selected as the critical non-cancer effect for POD selection with a BMR of 10 percent extra risk. LPT, as indicated by the presence of pleural plaques is the most effective endpoint to select because it is the outcome that generally appears at lower doses after asbestos inhalation exposure. In summary, 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 as described in Section 4.2. Those specific details will be further developed and described in the draft Part 2 Risk Evaluation that will subsequently be released for public comment.

5 CANCER DOSE-RESPONSE FOR ASBESTOS

5.1 Identification of Epidemiologic Cohort for Cancer Dose-Response

As described in Section 3 and Appendix B, epidemiologic cohorts providing information for dose-response assessment were identified for non-cancer and cancer outcomes. This process included a comprehensive literature search, PECO-based screening at the TIAB and full-text level, and further filtering of epidemiologic cohorts for exposure measurement and assignment methods, as well as the study analysis. Studies identified describing hazards but not informative for dose-response will be addressed in Part 2 of the Risk Evaluation for Asbestos.

Overall, 16 cohorts were identified for consideration in assessing dose response of cancer outcomes related to asbestos exposures. Most of these cohorts were identified and considered in previous assessments, including the 1988 IRIS Asbestos Assessment, the 2014 IRIS LAA Assessment, and the 2020 Part 1 of the Risk Evaluation for Asbestos. Only one cohort was identified that was not previously considered in an EPA assessment—and as a community-based cohort (Wittenoom, Australia, Residents Cohort), rather than an occupational cohort—was unique. All 16 cohorts are listed and briefly described in Table 5-1 and are more thoroughly presented in Appendix C.

Because the cohorts identified for dose-response were considered in the derivation of the existing IURs, OPPT focused on these existing IURs and their derivation, as described below in Section 5.2. The single cohort identified that was not considered in any of the existing IURs, while meeting systematic review criteria, did not have exposure data that was better suited for dose-response analysis given the uncertainties in community-based exposure assignment (see Appendix D.4). Thus, this study did not warrant an updated quantitative analysis. The proposed quantitative approach for cancer in Part 2 of the Risk Evaluation is described in Section 5.3 and accounts for each of the existing IURs (see Section 5.2).

623 **Table 5-1. Cohorts Identified for Consideration in Asbestos Part 2 Cancer Dose-Response Analysis**

Cohort Name	Cohort Description	Cancer Outcomes*	Overall Quality Determination (OQD) Rating
Risk Evaluation for Asbestos Part 1: Chrysotile Asbestos, 2020			
NC Textiles Cohort	• Four textile plants imported raw chrysotile fibers to make yarns and woven goods. • 5,770 workers employed for at least 1 day between 1950 and 1973. • Cohort followed through 2003.	Mesothelioma, pleural cancer, lung cancer	High
SC Textiles Cohort	• Textile plant in Charleston, SC, and used asbestos from 1909 to 1977. • Original cohort of textile workers limited to white males employed for at least 1 month between 1940 and 1965. Later expanded to included non-white and females. • Individual-level exposures estimates derived from detailed work histories and extensive air measurements using PCM and conversion of dust measurements from analysis of paired sampling.	Lung cancer, mesothelioma	Medium
Quebec, Canada Asbestos Mines and Mills Cohort	• Study of chrysotile miners and mill in Thetford mines in Quebec, Canada. • The original cohort was made up of men who were born between 1891 and 1920 and who had worked for at least 1 month in the mines and mills. • Cohort followed from first employment in 1904 to May 1992. • Detail work histories as well as total dust measurement from 4,000 midget impinger dust counts in mppcf per year were analyzed.	Mesothelioma, lung cancer	Medium
Qinghai, China Asbestos Mine Cohort	• Study of chrysotile mine in Qinghai Province, China. • Cohort made up of 1,539 male workers who were on the registry January 1, 1981, and who had worked for at least 1 year. • Occupational and work history of cohort was obtained from personnel records and employee. • Cohort followed for vital stats from 1981 to 2006. • Total dust concentrations were measured by area sampling in fixed locations and converted to fiber/cc.	Lung cancer, gastrointestinal cancer	Medium

Cohort Name	Cohort Description	Cancer Outcomes*	Overall Quality Determination (OQD) Rating
Chongqing, China Asbestos Products Factory Cohort	• Chrysotile asbestos plant in Chongqin, China, which produces textile, asbestos cement products, friction materials, rubber products and heat-resistant materials. • Cohort of 515 men were followed from January 1, 1972, to December 31, 1996; workers (men and women) who had worked for less than 1 year were excluded. • Cohort followed until 2008 when women who were employed between 1970 and 1972 were added to analysis. • Airborne dust and fiber concentrations were measured from personal samplers.	Lung cancer	High
Balangero, Italy Mining Cohort	• Balangero mine and mill of the Amiantifera Company started in 1916 and produced pure chrysotile asbestos. • Cohort consisted of 1,056 men who worked in mines for at least 1 year between January 1, 1930, and December 31, 1975. • Cohort followed up from January 1, 1946, or date of first employment, to December 31, 2003, or when subjects reached 80 years of age. • Information on cohort collected from mine records. • First fiber counts were first carried out in 1969 and exposure levels before 1969 were reconstructed to represent earlier years.	Lung cancer, laryngeal cancer, gastrointestinal cancer, lip cancer, oral cavity and pharynx cancer, esophageal cancer, liver cancer, stomach cancer, colon cancer, rectal cancer peritoneal cancer, pleural cancer, bladder cancer, nervous system cancer, kidney cancer, mesothelioma	Medium (lung cancer, laryngeal cancer, oral cavity and pharynx cancer, esophageal cancer, liver cancer, peritoneal cancer, pleural cancer, kidney cancer, mesothelioma)
Salonit Anhovo, Slovenia Asbestos Factory Cohort	• Salonit Anhovo factory in western Slovenia produced asbestos-cement products made from chrysotile and amphibole asbestos. • Cohort made up of 6,714 workers who had worked for at least 1 day between 1964 and 1994. • Air sampling measurements taken at fixed location close to worker's breathing zone. • Work histories were obtained from personnel files.	Lung cancer	Medium

Cohort Name	Cohort Description	Cancer Outcomes*	Overall Quality Determination (OQD) Rating
IRIS Libby Amphibole Asbestos Assessment, 2014			
Libby, MT, Vermiculite Mining and Milling Cohort	• Cohort included 1,871 vermiculite miners, millers, and processors hired prior to 1970 and employed for at least 1 year at the Montana site. • Subjects followed through December 2006. • Historical air sampling data used to estimate 8-hour TWA. • Work histories including job title and dates of employment were obtained and used to calculate cumulative fiber exposures.	Lung cancer, mesothelioma	Medium (lung cancer) High (mesothelioma)
IRIS Asbestos Assessment, 1988			
US Asbestos Company Employees Cohort	• Cohort consisted of 1,075 men obtained from company records. • Subjects were retired between 1941 and 1967 and receiving a pension from company. • Cohort followed through 1973. • Total dust measured in mppcf.	Mesothelioma, lung cancer, digestive cancer	Medium
New Orleans Asbestos Cement Building Material Plants Cohort	• Includes two asbestos cement building material plant producing products containing chrysotile, crocidolite, and amosite asbestos. • Cohort consisted of 5,645 men who had worked in either plant and had at least 20 years of follow up. • Detail work history obtained from plant records.	Lung cancer, mesothelioma, digestive cancer	High
Ontario, Canada Asbestos Cement Factory Cohort	• Cohort included 241 production and maintenance employees who worked for at least 9 years at the factory prior to 1960. • Impingers were used to prior to 1973 and membranes fiber counts used thereafter. • Mortality was followed through October 1980.	Lung cancer, mesothelioma, gastrointestinal cancer	Medium
NY-NJ Asbestos Insulation Workers Cohort	• Cohort located in Paterson, NJ, and manufactured amosite products. • Cohort included 820 men that worked for at least 5 years in factory. • Cohort followed through 1982. • No fiber counts available, but used counts for similar plant in Tyler, TX.	Lung cancer	Medium

Cohort Name	Cohort Description	Cancer Outcomes*	Overall Quality Determination (OQD) Rating
Asbestos Textile Workers Cohort	• Cohort consisted of white males who worked at the plant for at least 1 month prior to January 1, 1959. • Work histories obtained from this U.S. textile cohort included all 1,261 white males who worked at the plant for at least a month between January 1, 1940, and December 31, 1965. All workers who had a social security administration (SSA) record and had worked for at least 1 month prior to January 1, 1959, were considered to be part of the cohort. The cumulative dust exposures were assigned to each study participant using the same data that (Dement et al., 2008) used to calculate historical exposures.	Lung cancer, mesothelioma	Medium
International Association of Heat and Frost Insulators and Asbestos Workers Cohort	• Plant located in the NY-NJ metro area and produced chrysotile and amosite products between 1943 and 1976. • Cohort included 623 men employed prior to 1943 and 833 men employed after 1943. • Follow-up in 1962 and 1976. • Asbestos concentration in facilities not measured but used counts from other U.S. insulation facilities that operated between 1968 and 1971.	Mesothelioma	Medium
Cohort not included in existing EPA assessments			
Wittenoom, Australia, Residents Cohort	• Residential cohort included 4,659 individuals residing for at least 1 month in Wittenoom between 1943 and 1992. Mine workers excluded. • Follow-up in 1993, 2000, and 2004. • Ambient exposures from nearby crocidolite assigned based on dates of residence, assigned exposure intensity, and period personal monitoring after operations ceased.	Lung cancer, ovarian cancer, mesothelioma, brain cancer, leukemia	Medium
*As indicated in Section 1.3 and the Final Scope document, Part 2 of the Risk Evaluation will focus on mesothelioma and lung, ovarian and laryngeal cancers.			

624

5.2 1988 IRIS Asbestos Assessment

The IRIS Asbestos Assessment, released in 1988 (U.S. EPA, 1988), utilizes the Airborne Asbestos Health Assessment Update from 1986 (U.S. EPA, 1986). The latter was developed as the scientific foundation to support EPA's review and revision of the designation of asbestos as a hazardous air pollutant under the 1973 National Emission Standards for Hazardous Air Pollutants (NESHAP) under the 1977 Clean Air Act Amendments (U.S. EPA, 1986). The original designation of asbestos was based upon a qualitative review of the evidence prior to 1972 establishing associations between exposure and carcinogenicity. The objectives of the Airborne Asbestos Health Assessment Update (U.S. EPA, 1986) were to identify any new asbestos-related health effects from studies published after 1972, examine the dose-response relationship, and establish unit risk values for asbestos, if warranted.

At the time of assessment, the prevailing thought was that creating an exposure-response relationship for asbestos could be done in one of two ways. The first would be to choose the study or studies that have the best exposure data, presuming a sufficient measure of effect. The second approach would use all studies that provide exposure-response information along with estimates of the uncertainty of the data. In this approach, an overall exposure-response relationship is produced by taking an appropriate weighted average of the relationships discovered across studies accounting for observable variations in exposure conditions. The benefits of taking into account all research for which exposure-response data can be generated are as follows:

1. any bias in the selection of the research to be analyzed is largely eliminated;
2. information on the degree of uncertainty in the estimate of the average K_L value can be acquired; and
3. more accurate estimations of the impact of different fiber types or manufacturing processes can be made.

Based on this information, the assessment utilized data from all studies that provided exposure response data, rather than basing the assessment on a single study with the strongest exposure assessment (as was done in the later EPA assessments on Libby and chrysotile). The assessment included occupational studies with exposures to any of the principal commercial varieties of asbestos fibers (*i.e.*, amosite, anthophyllite, crocidolite, and chrysotile). A total of 14 occupational studies for lung cancer and 4 occupational studies for mesothelioma provided data for a dose-response assessment. The data for a best estimate of increased risk of lung cancer per unit exposure are provided by 14 studies across a range of occupational activities. The mixed fiber cohorts are explicitly described in Appendix D.3; however, the cohorts in the 1988 Asbestos Assessment that were chrysotile-specific were not explicitly described because they had been extended and encompassed by studies included in Part 1 of the Risk Evaluation for Asbestos (see also Appendix D.4). In the 1988 Asbestos Assessment, studies of mining and milling were excluded due to a substantial difference in risk observed and the notion that exposure assessment in these operations is significantly more challenging due to a wide array of fibers being present. Factories have a more limited set of sources of dust and fibers, making fiber counts more straightforward. In deriving the overall K_L (slope factor for lung cancer), the geometric mean was calculated from the 14 epidemiologic studies, representing exposures to chrysotile, amosite, and crocidolite.

Of the four studies examining mesothelioma mortality in occupational cohorts (see Table II.C.2 in the *IRIS Asbestos Summary* (U.S. EPA, 1988)), three of these cohorts had mixed-fiber exposures and also examined lung cancer mortality. However, mesothelioma risk was calculated for the 10 studies examining lung cancer and not mortality by developing an adjustment factor (the ratio of K_M [slope factor for mesothelioma] to K_L in the 4 studies examining both mortality outcomes) and applying that

adjustment factor to the K_L for each study (see Table 3-31 in the *Airborne Asbestos Health Assessment Update* (U.S. EPA, 1986). The resulting relative mesothelioma hazard was closely examined across cohorts and occupational categories (*e.g.*, mining/milling, insulation workers, textiles, etc.) and because there were no obvious outliers, a geometric mean was calculated considering all studies. The assessment discusses the postulation that crocidolite was thought to have higher potency with regard to mesothelioma, but quantitative investigation of this concern demonstrated that the overall impact of this uncertainty was minimal, and an overall adjustment was not made for cohorts with potential crocidolite exposures. Because under-ascertainment of mesothelioma was also a concern, a quantitative adjustment was made to account for this uncertainty.

The cancer slope factors for lung cancer and mesothelioma were separately derived and then statistically combined. Subsequently, a life table analysis was conducted using the K_L and K_M to represent the epidemiologic data, 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. It is important to note that in the original studies identified in this assessment, exposure data was commonly collected as a measure of dust, and some studies additionally presented fiber counts using filter or membrane-based techniques, allowing for the development of a conversion factor. This conversion factor is necessary in order to conduct quantitative assessment of asbestos exposure in studies where measurements were initially taken for dust. These are further described in Appendix D.4, where applicable. Additionally, the assessment found that the risk from lung cancer increased with time since first exposure and death from mesothelioma increased rapidly after onset of exposure—an important observation. Limitations of the analysis that were described include (1) variability in the exposure-response relationship at high exposure; (2) uncertainty in extrapolating to much lower exposures (*i.e.*, background exposures that can be 1/100th the levels seen in occupational settings); and (3) uncertainties in converting between detection methods (*e.g.*, optical fiber counts, mass determination). The asbestos IUR is widely recognized and is used in other EPA programs, including Superfund risk assessments conducted under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) (U.S. EPA, 2021b).

5.3 IRIS Libby Amphibole Assessment Cancer Dose-Response

The IRIS LAA Assessment, released in 2014, included a detailed toxicological review that provides the scientific foundation to support the risk and dose-response assessment of chronic inhalation exposure specific to LAA in the Rainy Creek complex and from the vermiculite mine near Libby, Montana (U.S. EPA, 2014b). The LAA Assessment evaluated the possible risks associated with exposure to LAA, including those related to cancer and non-cancer health effects, and presents risk values for use in risk assessments, including an RfC for non-cancer health effects (summarized in Section 4.2 above) and an IUR to address cancer risk. The LAA Assessment considered several occupational and community-based cohorts for dose-response assessment (see Figure 4-1 in the LAA Assessment); however, OPPT identified two of those occupational cohorts as being most relevant for dose-response consideration (Appendix C.2).

For derivation of the IUR, the Libby, Montana, workers cohort (including miners and millers) was ultimately selected as the cohort with the most robust data for dose-response assessment (*i.e.*, individual-level exposure data based on impinger and PCM measurements, complete demographic data, and vital status with extended follow-up through 2006).

For mesothelioma mortality in this dataset, Poisson modeling was conducted to fit mortality data and exposure data with a range of exposure metrics. The best model was based upon a subcohort with employment beginning in 1959 and a cumulative exposure metric with a 5-year half-life and a 10-year

lag time. The central estimate for K_M was 3.11×10^{-4} per fibers/cc. Following selection of the K_M, a life table procedure was applied to the U.S. general population using age-specific mortality statistics to estimate the exposure levels that would be expected to result in a 1 percent increase in absolute risk of mesothelioma over a lifetime of continuous exposure. Linear low-dose extrapolation was used to find an effective concentration corresponding to the central tendency, which was estimated to be 0.032 per fiber/cc and 0.074 per fiber/cc when adjusted to account for under-ascertainment of mesothelioma.

Lung cancer unit risk values were also calculated separately and based on a subcohort of the Libby, Montana, workers hired after 1959. Multivariate extended Cox models were run with a range of exposure metrics, and the best fit was based on cumulative exposure with a 10-year half-life and a 10-year lag. The resulting K_L from this model was 0.0126 per fiber/cc-yr. As was done for the mesothelioma cancer slope factor, a life-table analysis was applied to the K_L to determine an exposure level of asbestos expected to result in a 1 percent increase in relative cancer risks when taking into account age-specific background risk. The corresponding effective concentration relating to the central tendency was 0.0399 per fiber/cc for a lifetime continuous exposure with an upper bound unit risk of 0.0679 per fiber/cc.

The upper bound unit risks for mesothelioma and lung cancer were statistically combined to yield an appropriate upper bound value representing overall cancer risk for continuous lifetime asbestos exposure. Importantly, the statistical derivation of a combined upper bound unit risk value accounted for overprediction resulting from combining individual upper bound estimates. The upper bound combined risk from the best fitting models applied to individual-level data from the Libby, Montana, workers was 0.17 per fiber/cc. The 2014 IRIS LAA Assessment notes some limitations, including the difficulty in controlling for smoking as a confounder, the potential for under-ascertainment of mesothelioma, and uncertainties in the exposure measurements in the facility. The LAA IUR is widely recognized and is specifically used in Superfund risk assessments conducted under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) (U.S. EPA, 2021b).

5.4 Part 1 Risk Evaluation for Asbestos: Dose-Response

The most recent asbestos IUR was developed as part of the *Risk Evaluation for Asbestos Part 1: Chrysotile Asbestos* that was finalized in 2020 (U.S. EPA, 2020). As previously described, asbestos was identified as one of the first 10 substances to undergo risk evaluation under the amended TSCA. The consideration and evaluation of human health evidence primarily focused epidemiologic studies of lung cancer or mesothelioma resulting from inhalation exposures to chrysotile asbestos. Thus, OPPT made a distinction between (1) studies of exposure settings where only commercial chrysotile asbestos was used or where workers exposed only to commercial chrysotile asbestos could be identified, and (2) situations where chrysotile asbestos was used in combination with amphibole asbestos forms and the available information would not allow exposures to chrysotile and amphibole asbestos forms to be separated. The studies that were found to be useful for the study of mesothelioma and lung cancer were all based on historical occupational cohorts with use of the longest follow-up for each cohort or the most pertinent exposure-response when a cohort had been the subject of more than one publication.

In Part 1, an IUR of 0.16 per fiber/cc was derived based upon thorough consideration and analysis of data from epidemiological studies on mesothelioma and lung cancer in cohorts of workers using chrysotile. As described in Appendix D.1 and presented in Table 5-1, data from several cohorts was available for dose-response modeling following a systematic approach to literature identification and evaluation. Ultimately, data from cohorts of workers in textile plants in North and South Carolina were selected for IUR derivation. For the NC cohort, individual-level exposure-response data was available for lung cancer in Loomis et al. (2009) and Elliott et al. (2012) as well as mesothelioma in Loomis et al.

(2019). For these studies, the Part 1 Risk Evaluation presents cancer potency values based on Poisson regressions of the individual-level data using both logistical and additive relative rate model forms with adjustment for age, sex, race, calendar period, and birth cohort (see Table 3-4 in (U.S. EPA, 2020)). For the SC cohort, individual-level data was available for lung cancer in Hein et al. (2007) and Elliott et al. (2012) as well as for mesothelioma from Berman and Crump (2008). Lung cancer potency values for these studies were based on Poisson regression models using a linear relative rate model form with adjustment for sex, race, and age. Mesothelioma cancer potency values were reported in Berman and Crump (2008) based on analyses of the original cohort data using the Peto model (see Table 3-3 in U.S. EPA (2020)).

Part 1 also describes uncertainty related to under-ascertainment of mesothelioma as an International Classification of Diseases (ICD) code specific to mesothelioma that was not available prior to 1999. Thus, some cases of mesothelioma are missed on death certificates prior to 1999 and likely even during the initial use of the ICD code. This uncertainty was also considered in the IRIS LAA Assessment (U.S. EPA, 2014b) and a multiplier was derived (1.39) based on data from the Libby cohort that was not fiber-specific, but rather specific to outcome ascertainment for mesothelioma. This multiplier was used to adjust IURs in Part 1 of the Risk Evaluation (see Section 3.2.3.8.1 in U.S. EPA (2020)). Part 1 also describes uncertainty related to under-ascertainment of mesothelioma as an International Classification of Diseases (ICD) code specific to mesothelioma that was not available prior to 1999. Thus, some cases of mesothelioma are missed on death certificates prior to 1999 and likely even during the initial use of the ICD code. This uncertainty was also considered in the IRIS LAA Assessment (U.S. EPA, 2014b) and a multiplier was derived (1.39) based on data from the Libby Cohort that was not fiber-specific, but rather specific to outcome ascertainment for mesothelioma. This multiplier was used to adjust IURs in Part 1 of the Risk Evaluation (see Section 3.2.3.8.1 in U.S. EPA (2020)).

Additionally, the IUR was adjusted to account for cancer risk from other cancer endpoints beyond lung cancer and mesothelioma. As explained in Section 3.2.3.8.1 of Part 1, IARC concluded that exposure to asbestos is causally related to lung cancer and mesothelioma as well as laryngeal and ovarian cancer (U.S. EPA, 2020; Straif et al., 2009). Data was not available to derive potency factors for laryngeal and ovarian cancer, so an adjustment factor was developed to account for potential underestimation of cancer risk when only considering data for lung cancer and mesothelioma. The combined adjustment factor applied to lung cancer to address other cancers was 1.06 (see Table 3-11 in U.S. EPA (2020)).

For each modeling result from the NC and SC datasets, the unit risks were calculated separately for lung cancer and mesothelioma. Lung cancer unit risks were adjusted to account for other cancers and mesothelioma unit risks were adjusted to account for under-ascertainment. The unit risks were then statistically combined for central unit risk and upper bound risk. Overall, six IUR values were available for the datasets and modeling results, and the median IUR was ultimately selected because there was low model uncertainty (see Table 3-12 in U.S. EPA (2020)). The median lifetime cancer incidence IUR was 0.16 per fiber/cc based upon a linear model of the data from the NC textile workers cohort (Elliott et al., 2012).

Part 1 notes a few important uncertainties in the IUR (see Section 4.3.5 in U.S. EPA (2020)). First, PCM measurements were used despite TEM being a more precise analytical technique. However, it was determined that when TEM and PCM were available in the same dataset, TEM and PCM model results were similar. Thus, this uncertainty was considered to be low for the NC textile worker cohort. Another source of uncertainty in exposure measurements is the use of impinger sampling data for early asbestos exposures. The most robust approach to account for this is to use paired and concurrent sampling data to derive a conversation factor, and this was performed in the analysis of the NC and SC textile cohorts

resulting in low uncertainty. When considering uncertainties related to outcome data, use of mortality data rather than incidence, which was not available, was of concern. To account for this, background rates of lung cancer incidence were used in lifetable analyses. However, this was not possible for mesothelioma. While this remains a bias, it is noteworthy that median survival for mesothelioma is less than 1 year. Finally, confounding must be considered with regard to uncertainties. Smoking is considered a strong confounder for lung cancer related to asbestos exposure, but in the NC and SC cohorts, 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. Smoking is not a confounder for mesothelioma.

In Part 1 of the Risk Evaluation, this IUR was applied for all chrysotile asbestos exposure scenarios, with less-than-lifetime adjustments applied where appropriate for less-than-lifetime exposures. Risk determinations were based, in part, on quantitative risk characterization computer with this IUR. Risk management rulemaking that is currently underway will address the unreasonable risk identified in Part 1 of the Risk Evaluation for Asbestos (U.S. EPA, 2020).

5.5 Part 2 Risk Evaluation for Asbestos: Quantitative Cancer Approach

Across decades of epidemiologic research in various occupational settings, employing diverse exposure measurement methods and approaches to exposure assignment, and based upon a wide range of dose-response modeling with application of adjustment factors, all three IURs are numerically very similar (Table).

Inherent strengths and uncertainties pertain to each IUR, and all were developed for a distinct purpose and application. The IUR of 0.16 per fiber/cc presented in Part 1 of the Risk Evaluation for Asbestos (U.S. EPA, 2020) benefits from the most recent data available and generally, the longest follow-up periods. Advanced exposure measurement methods are reflected in the underlying data resulting in exposure estimates that are of high confidence. Furthermore, longer follow-up times increase the statistical power of the study as more mortality is observed. Other notable strengths include accounting for laryngeal and ovarian cancers, which are causally associated with asbestos exposure, and accounting for under-ascertainment of mesothelioma. However, this IUR was strictly limited to exposures to chrysotile asbestos and is therefore most appropriately applied in cases where exposures are chrysotile-specific.

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 IUR. EPA ORD was able to conduct robust analyses based on very detailed individual-level exposure measurements and outcome data for lung cancer and mesothelioma as the cohort was established from one operation, the mine in Libby, Montana. There were not sufficient data on laryngeal or ovarian cancers in this cohort for quantitative consideration[5], but under-ascertainment of mesothelioma was accounted for. As described in Section 5.2, herein, the comprehensiveness of the data yielded quantitative analyses of high confidence. However, this IUR is based on data specific to scenarios of exposure to only LAA, and therefore, is most appropriately applied in risk estimates based on Libby-specific exposures.

[5] The quantitative adjustment for lung cancer to address laryngeal and ovarian cancers developed in Part 1 of the Risk Evaluation for Asbestos would not have impacted the LAA IUR and proposed IUR for application in Part 2 because it was small and is only appropriate for lung cancer, which accounts for the minority of risk relative to mesothelioma in the Libby IUR.

The earliest IUR of 0.23 per fiber/cc presented in the IRIS Asbestos Assessment (U.S. EPA, 1988) was developed to describe risks related to all asbestos fiber types. Development of this IUR was based on historically robust data at a time when standard fiber measurement methods had not yet been established and reporting and publication standards were highly variable. Although additional uncertainty exists in the exposure measurement provided in these published studies, it is important to note that EPA technical experts were diligent in advancing their understanding and use of data beyond what was available in original publications to reduce uncertainties, as reflected in the 1988 Asbestos Assessment and related publications. A major strength of this IUR is that it represents exposures to a range of fiber types and is most appropriately applied to describe risks related to mixed-fiber exposures, which is pertinent to exposure scenarios in Part 2 of the Risk Evaluation for Asbestos. The authors of the report acknowledged this objective when they described the use of data from all cohorts and not isolating data from the cohort with the most detailed exposure assessment that may have been specific to only a single fiber.

Table 5-2. Comparison of EPA Inhalation Unit Risk Values for Asbestos

IUR per fiber/cc	EPA Assessment	Fiber Type	Cancer Outcomes
0.23	IRIS Asbestos Assessment (U.S. EPA, 1988)	Mixed fiber (chrysotile, amosite, crocidolite)	Lung cancer and mesothelioma
0.17	IRIS LAA Assessment (U.S. EPA, 2014b)	Libby Amphibole Asbestos fiber	Lung cancer and mesothelioma
0.16	Risk Evaluation for Asbestos Part 1: Chrysotile Asbestos (U.S. EPA, 2020)	Chrysotile fiber	Lung cancer and mesothelioma, with quantitative adjustment to account for laryngeal and ovarian cancers

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 would round to 0.2 per fiber/cc. This approach is well-supported in taking into account a broad range of information that is applicable to Part 2. This value reflects exposures in a variety of settings and levels, an array of asbestos fibers, and relevant cancer outcomes. 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.

In applying an IUR of 0.2 per fiber/cc in the Part 2 of the Risk Evaluation for Asbestos, it is recognized that this value applies to risks associated with a continuous lifetime exposure, which will not be expected for all exposure scenarios in Part 2. Thus, as was done in Part 1 of the Risk Evaluation, partial or less-than-lifetime (LTL) values corresponding to the IUR will be applied. The general equation for estimating cancer risks for LTL exposure from inhalation of asbestos, from the OLEM Framework for Investigating Asbestos-contaminated Superfund Sites (U.S. EPA, 2008), is:

$$ELCR = EPC \times TWF \times IUR_{LTL}$$

where:

ELCR = Excess lifetime cancer risk, the risk of developing cancer as a consequence of the site-related exposure

EPC = Exposure point concentration, the concentration of asbestos fibers in air (fiber/cc) for the specific activity being assessed

IUR_{LTL} = Less-than-lifetime inhalation unit risk per fiber/cc
For example: the notation for the LTL IUR could start at age 16 with 40 years duration $IUR_{(16,40)}$.

TWF = Time weighting factor, this factor accounts for less-than-continuous exposure during a one-year exposure, and is given by:

$$TWF = [Exposure\ time\ (hours\ per\ day) / 24\ hours] \times [Exposure\ frequency\ (days\ per\ year) / 365\ days]$$

For more information on the general approach for estimating cancer risk for less-than-lifetime exposure from inhalation of asbestos, see Section 4.4.1 in Part 1 of the Risk Evaluation (U.S. EPA, 2020). Assessing asbestos-related health effects is unique because of the timing of exposure related to outcomes as TSFE plays an important role in risk modeling. Exposures occuring decades prior to the observed outcome are most relevant—particularly for understanding risk. Following the approach described in the Part 1 of the Risk Evaluation (see Appendix K), which was reviewed by the SACC, LTL values will be determined based on age of first exposure and duration of exposure. These will be presented in the risk characterization of the draft Part 2 of the Risk Evaluation for Asbestos.

6 SUMMARY AND NEXT STEPS

As described in preceding sections of this white paper, prior to OPPT's efforts to develop Part 2 of the Risk Evaluation, the Agency has developed three IURs describing the relationship between cancer and asbestos exposure and an RfC for non-cancer effects related to asbestos exposure. To ensure that the consideration of human health effects in Part 2 is based upon the best available science, OPPT employed a systematic approach to identify and evaluate the epidemiologic evidence available for dose-response assessment and to consider if an updated IUR is warranted.

OPPT determined that the most appropriate epidemiologic cohorts available for dose-response assessment were previously considered in deriving the existing IURs and RfC. Thus, OPPT is proposing that an updated dose-response assessment for cancer and non-cancer effects related to asbestos exposures is not needed at this time and that the existing, peer-reviewed EPA values are appropriate for application in Part 2 of the Risk Evaluation for Asbestos. As described in Section 4.3, for non-cancer effects, application of the LAA POD of 2.6×10^{-2} fiber/cc is proposed for application in Part 2 with three associated UFs ($UF_H = 10$, $UF_D = 3$, $UF_S = 10$). Because there are three relevant IURs for cancer effects that are all numerically similar, EPA is proposing use of an IUR of 0.2 per fiber/cc in Part 2 as this value at one significant figure reflects an appropriate level of precision when considering the range of IURs (Section 5.5).

OPPT is soliciting input through a letter peer-review. Following peer review of this proposed approach, OPPT will release a draft Part 2 Risk Evaluation for Asbestos that will be made available for public comment. Peer reviewer input and public comment will be taken into consideration and appropriate revisions will be made to finalize the Part 2 Risk Evaluation for Asbestos on or before December 1, 2024, consistent with the consent decree timeline in ADAO, et al. v. Regan, No. 4:21-cv-03716 (N.D. Cal. Oct. 2021). Ultimately, in the finalized Part 2 risk evaluation, OPPT will determine, based on assessments of risk for the conditions of use examined, whether or not unreasonable risks are posed to human health or the environment. As required by TSCA, any unreasonable risk must be addressed via subsequent risk management rulemaking.

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APPENDICES

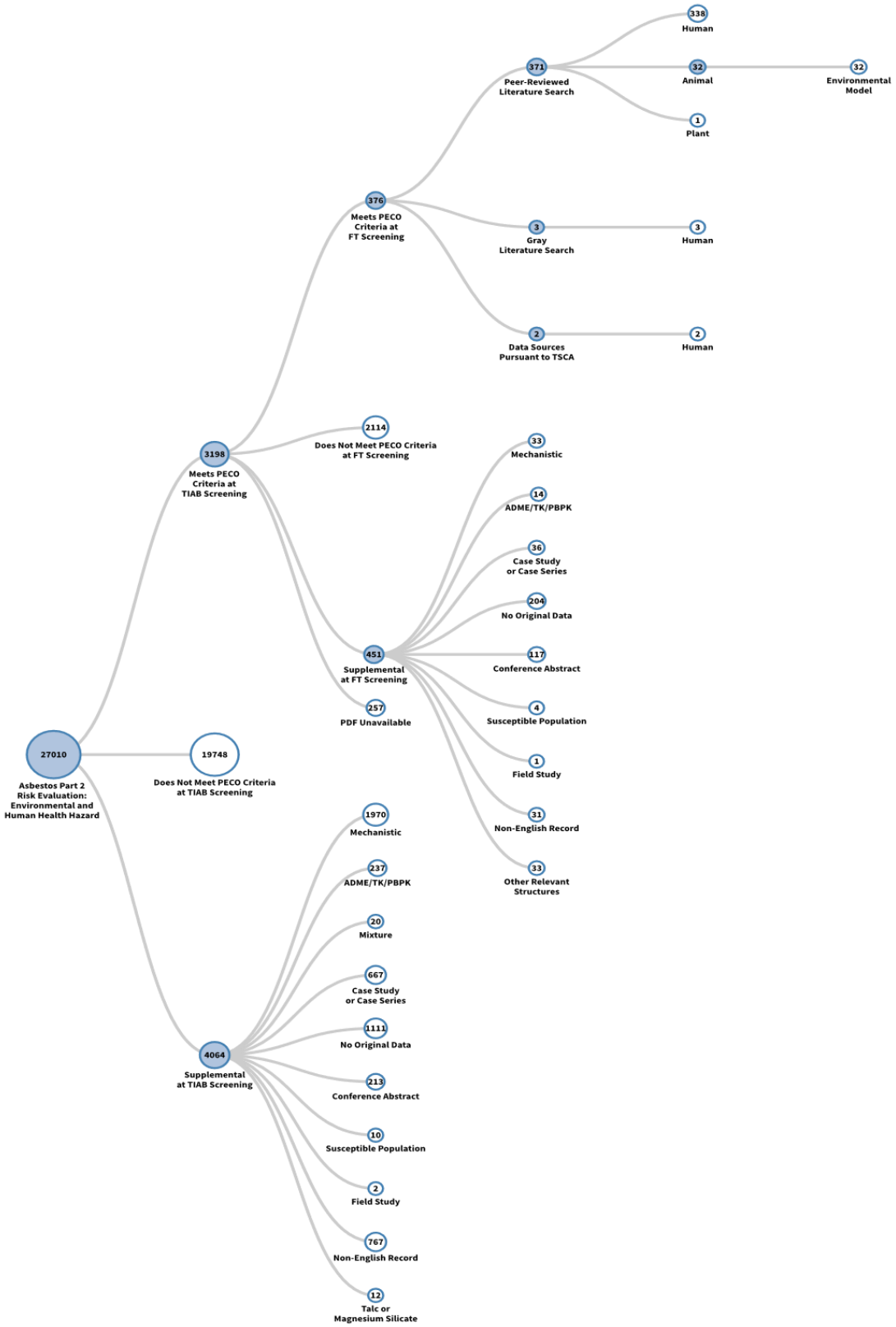
Appendix A ABBREVIATIONS AND ACRONYMS

ADME	Absorption, distribution, metabolism, and excretion
ATSDR	Agency for Toxic Substances and Disease Registry
BMR	Benchmark response
CAA	Clean Air Act
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
COPD	Chronic obstructive pulmonary disease
Cr^{6+}	Hexavalent chromium
CT	Computerized tomography
DLCO	Diffusing capacity of the lungs for carbon monoxide
DPT	Diffuse pleural thickening
ELCR	Excess lifetime cancer risk
EPA	Environmental Protection Agency
EPC	Exposure point concentration
f/cc	Fibers per cubic centimeter
f/mL	Fibers per milliliter
FEV	Forced expiratory volume
FT	Full text
FVC	Forced vital capacity
GC–ECD	Gas chromatography with electron capture detector
GC–FID	Gas chromatography with flame-ionization detection spectrometry
GC–HRMS	Gas chromatography/high-resolution mass spectrometry
GC–MS	Gas chromatography mass spectrometry
GC–MS/MS	Gas chromatography with tandem mass spectrometry
HRCT	High resolution computed tomography
IARC	International Agency for Research on Cancer
ICD	International Classification of Diseases
ILO	International Labour Organization
IRIS	Integrated Risk Information System
IUR	Inhalation unit risk
JEM	Job exposure metric
KL	Lung cancer potency factor
KM	Mesothelioma potency factor
LAA	Libby Amphibole Asbestos
LC–MS/MS	Liquid chromatography with tandem mass spectrometry
LPT	Localized pleural thickening
LTL	Less-than-lifetime
Meso	Mesothelioma
µm	Micrometers
mppcf	Million particles per cubic foot of air
MT	Montana
NC	North Carolina
NASEM	National Academies of Sciences, Engineering, and Medicine
NESHAP	National Emission Standards for Hazardous Air Pollutants
NIOSH	National Institute for Occupational Safety and Health
NJ	New Jersey

NY	New York
OCSPP	Office of Chemical Safety and Pollution Prevention
OH	Ohio
OLEM	Office of Land and Emergency Management
OPPT	Office of Pollution Prevention and Toxics
OQD	Overall quality determination
ORD	Office of Research and Development
OSHA	Occupational Safety and Health Administration
PA	Pennsylvania
PBPK	Physiologically based pharmacokinetic
PCM	Phase-contrast microscopy
PCMe	Phase-contrast microscopy equivalent
PECO	Population, exposure, comparator, and outcome
POD	Point of departure
QC	Quality control
RfC	Reference concentration
SACC	Science Advisory Committee on Chemicals
SC	South Carolina
SIR	Standardized incidence ratio
SMR	Standardized mortality ratio
SSA	Social Security Administration
TSFE	Time since first exposure
TEM	Transmission electron microscopy
TIAB	Title/abstract (screening)
TLV	Total Liquid Ventilation
TSCA	Toxic Substances Control Act
TWA	Time-weighted average
TWF	Time weighting factor
TX	Texas
UF	Uncertainty factor
UF_D	Database uncertainty factor
UF_H	Intraspecies uncertainty factor
UF_S	Subchronic uncertainty factor
U.S.	United States

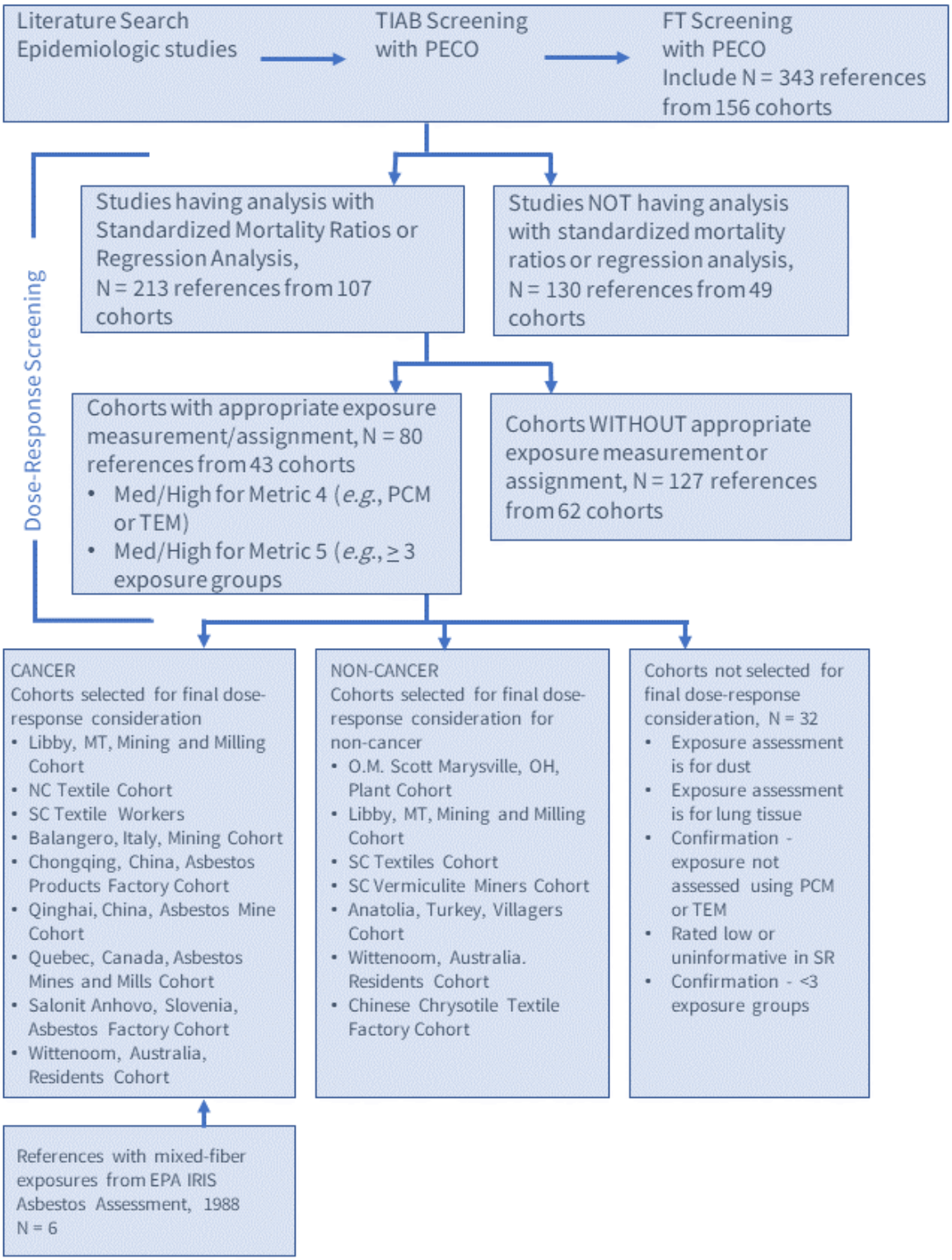
Appendix B SYSTEMATIC REVIEW APPROACH

The sections below describe the process used to identify, screen, and evaluate the reasonably available information. Many aspects of this process are described thoroughly in the 2021 Draft Systematic Review Protocol (U.S. EPA, 2021a). However, some aspects of the process were modified or extended in a fit-for-purpose manner. The modifications were performed to build off of systematic review efforts from Asbestos Part 1 and utilize data evaluation elements from the prior assessment while providing a similar structure for evaluating new and existing studies for other noncancer and cancer endpoints of concern not evaluated in Asbestos 1. In addition, based upon recommendations from NASEM and SACC on systematic review methodology, OPPT identified high quality studies based on previous assessments by the IRIS program and evaluated these critical studies in a systematic way leading to robust set of cohort studies for this dose response analysis. Figure_Apx B-1 and Figure_Apx B-2 present schematics of the process. Further descriptions below in B.1.2 explain how the 338 peer-reviewed, 3 gray literature, and 2 data sources pursuant to TSCA (total 343 data sources) that met PECO screening criteria (Figure_Apx B-1) were considered for dose-response screening (Figure_Apx B-2).



Figure_Apx B-1. Literature Inventory Tree – Environmental and Human Health Hazard for Asbestos Part 2

View the interactive literature inventory tree in HAWC. Data in this figure represent all references obtained from the publicly available databases and gray literature references searches that were included in systematic review as of March 20, 2023. Additional data may be added to the interactive version as they become available.



Figure_Apx B-2. Literature Flow Diagram Presenting the Identification, Screening, and Evaluation of Literature

B.1 Data Search and Screening

B.1.1 Data Search

As described in Section 4 of the 2021 *Draft Systematic Review Protocol Supporting TSCA Risk Evaluations for Chemical Substances* (U.S. EPA, 2021a), EPA conducts a comprehensive search for reasonably available information to support TSCA risk evaluations. Details on the methodology used to search for chemical-specific peer-reviewed and gray literature are available in Sections 4.2 and 4.3 of the 2021 Draft Systematic Review Protocol (U.S. EPA, 2021a). Of note, the search for and screening of hazard information considered for Part 2 of the Risk Evaluation for Asbestos includes all receptors (humans, animals, plants, and other organisms); however, this section focuses on specific details for the systematic review of epidemiologic (human) data to identify the most relevant information for informing both the cancer and non-cancer dose-response human health hazard assessments.

Appendix Section C.1.24 of the 2021 Draft Systematic Review Protocol contains the specific strategy and search string used to identify reasonably available hazard information for asbestos in Part 2 (U.S. EPA, 2021a). Literature searches for asbestos hazard information were conducted in April 2021 (U.S. EPA, 2021a). As stated in the 2021 Draft Systematic Review Protocol, "[t]he literature strategy for Asbestos Part 2 is composed of three pieces: (1) reevaluation of all references used in Part 1 [of the Risk Evaluation for Asbestos]; (2) evaluation of new literature produced by performing a Part 1 search update; and (3) evaluation of new literature produced by inclusion of additional asbestos fiber types." (U.S. EPA, 2021a p. 240). Although references from Part 1 were included in the literature search for Part 2, these references were only reevaluated for outcomes that had not been previously evaluated in Part 1. All reasonably available information submitted to EPA under TSCA authorities was also considered for Part 2 of the Risk Evaluation. Appendix Section C.1.24 of the 2021 Draft Systematic Review Protocol contains the specific strategy and search string used to identify reasonably available hazard information for asbestos in Part 2 (U.S. EPA, 2021a). Literature searches for asbestos hazard information were conducted in April 2021 (U.S. EPA, 2021a). As stated in the 2021 Draft Systematic Review Protocol, "[t]he literature strategy for Asbestos Part 2 is composed of three pieces: (1) reevaluation of all references used in Part 1 [of the Risk Evaluation for Asbestos]; (2) evaluation of new literature produced by performing a Part 1 search update; and (3) evaluation of new literature produced by inclusion of additional asbestos fiber types." (U.S. EPA, 2021a p. 240). Although references from Part 1 were included in the literature search for Part 2, these references were only reevaluated for outcomes that had not been previously evaluated in Part 1. All reasonably available information submitted to EPA under TSCA authorities was also considered for Part 2.

Following the data search, SWIFT-Review was used to identify peer-reviewed references predicted to be relevant for human health hazard (epidemiology) for asbestos. SWIFT-Review is a freely available text mining and machine learning software that can be used for topic modeling, categorization, and prioritization of search results (Howard et al., 2016). Search strings were developed and validated in collaboration with ORD and Sciome. The generic search strings used in SWIFT-Review to automatically tag and categorize references can be found on the SWIFT-Review website. Peer-reviewed references proceeded to TIAB screening if the SWIFT-Review search string terms were present in the title, abstract, or keywords of a given reference. Additional details about the SWIFT-Review application itself are described in the 2021 Draft Systematic Review Protocol (U.S. EPA, 2021a)

B.1.2 Data Screening

Sections 4.2.5 and 4.3.2 of the 2021 Draft Systematic Review Protocol describe TIAB and full-text screening, respectively, were conducted to identify references that may contain relevant information for

use in risk evaluations under TSCA using discipline-specific screening criteria (U.S. EPA, 2021a). Screening of environmental and human health hazard data sources was conducted using the specialized web-based software programs: SWIFT-Active-Screener[6,7] and DistillerSR.[8] Specifically, for Part 2, TIAB screening was conducted using SWIFT-Active-Screener that utilizes a machine-learning algorithm to automatically compute which unscreened documents are most likely to be relevant based on the results of manual screening conducted by two independent screeners. Subsequent to TIAB screening, full-text screening was conducted manually by two independent reviewers for each reference using DistillerSR, and conflict resolution was conducted for any discrepancies in screening results.

The same PECO screening criteria (presented in Appendix F) were utilized during both TIAB and full-text screening of data sources containing environmental and human health hazard information relevant for Part 2. During screening, calibration was conducted to increase consistency in interpretation of PECO screening criteria between reviewers. Calibration allowed for clarifying modifications to be made to the PECO screening criteria, published in Appendix H.5.13 of the 2021 Draft Systematic Review, to reduce discrepancies in interpretation where identified (U.S. EPA, 2021a). The PECO screening criteria for asbestos include a requirement for quantitative asbestos exposure concentration. Although the PECO screening criteria encompass considerations and updates following screening calibration for both environmental and human health hazard data, the PECO screening criteria modifications relevant for the screening of environmental hazard data will be described in the forthcoming systematic review protocol supplemental document included in the Part 2 of the Risk Evaluation for Asbestos.

As shown in the literature inventory tree above in Figure_Apx B-1, 343 references met full-text PECO criteria (338 peer-reviewed studies, 3 gray literature references, and 2 data sources pursuant to TSCA). These references were further screened as described in Section 3.3 to identify a subset of these studies potentially informative for dose-response that proceeded to data quality evaluation and extraction.

Studies were considered by cohort groupings. For example, if multiple publications were available on a particular occupational cohort, they were considered as a set of information rather than as independent publications.

B.2 Identification of Studies Potentially Informative for Dose-Response Analysis

An additional screening was conducted after full-text screening to identify the subset of studies that met PECO screening criteria that contained dose-response data. 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 (U.S. EPA, 2021a). The modifications included conducting further screening of studies that met PECO criteria to identify the most relevant evidence

[6] SWIFT-Active Screener is another systematic review software that EPA uses in the TSCA systematic review process. From Sciome's SWIFT-Active Screener web page: "As screening proceeds, reviewers designate articles as having met or not having met criteria, while an underlying statistical model in SWIFT-Active Screener automatically computes which of the remaining unscreened documents are most likely to be relevant. This 'Active Learning' model is continuously updated during screening, improving its performance with each reference reviewed. Meanwhile, a separate statistical model estimates the number of relevant articles remaining in the unscreened document list."

[7] SWIFT is an acronym for "*Sciome Workbench for Interactive Computer-Facilitated Text-mining.*" SWIFT-Active Screener uses machine learning approaches.

[8] As noted on the DistillerSR web page, this systematic review software "automates the management of literature collection, triage, and assessment using AI and intelligent workflows...to produce transparent, audit ready, and compliant literature reviews." EPA uses DistillerSR to manage the workflow for screening and evaluating references; the literature search is conducted external to DistillerSR.

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).

Step 1 of Further Screening for Fit for Purpose Context: Identification of Studies that Used Standardized Mortality Ratios and Regression Analysis

Prior asbestos assessments, including Part 1 of the Risk Evaluation for Asbestos (U.S. EPA, 2020), focused their dose-response analyses on studies that assessed exposure-response relationships using either SMRs or multivariate regression analyses.

An SMR is a ratio or percentage of the observed mortality in a given study sample relative to the mortality in a specified general population (examples include males in Montana, U.S. adults, etc.). Multivariate regression analyses generally estimate the average relationship between an exposure and an outcome in a given study population, while holding other factors constant (adjusting for other variables). Both SMRs and regression analyses can be used to assess a dose-response relationship, particularly when the modeled relationship has either three or more exposure groups or is continuous.

Because of the utility of SMR and regression studies in dose-response assessment, EPA further screened PECO-relevant studies to identify the subset of these studies that used SMR and/or regression analyses. During this screening, study inventorying was also conducted, capturing details on route of exposure, endpoint analyzed, study type, study design, cohort name/location, and analysis characterization. The Distiller Form for this binning/inventory is included in Appendix E. Studies that were tagged as SMR studies or regression analyses based on this binning/inventory process moved on to the next step of further screening.

Step 2 of Further Screening for Fit for Purpose Context: Identification of Studies with Sufficient Exposure Measurement and Range

For all studies identified as either regression or SMR studies, for each outcome in the paper or cohort group, Metrics 4 and 5 were evaluated before other data quality evaluation metrics. Each paper or cohort group of papers was evaluated by two epidemiologists: an initial evaluator and a quality control (QC) reviewer. If the paper or cohort group was rated as Medium or High for Metrics 4 and 5, then the initial evaluator moved on to data quality evaluation for all metrics, and then all data quality evaluation metrics and comments went on to QC review. If either Metric 4 or 5 was rated Low or Uninformative, then the initial reviewer submitted for QC without evaluation of the remaining metrics. If the QC reviewer determined that Metrics 4 and 5 should have been rated Medium or High, then the paper or cohort group was sent back to the initial reviewer for evaluation of the remaining metrics prior to completion of QC.

Exposure Measurement: In epidemiology studies, asbestos exposure is typically expressed as the product of the amount of asbestos dust in the air (fibers or particles per mL) and the total amount of time (years) exposed to each concentration (fibers/mL-years). Prior to 1968, the midget impinger method was (Dement et al., 2008) the most commonly used method for determining the level of asbestos in occupational air. With no details on fiber type or particle size distribution, data from midget impingers only give a rough estimation of the amount of asbestos in the air (SAB, 2008). With advancement in methodological techniques, it was later determined that use of PCM was a more accurate method to detect and quantify asbestos fibers in air samples (Leidel et al., 1979). PCM identifies fibers according to the NIOSH 7400 Method. More specific characterization of asbestos can be achieved using TEM. In contrast to optical microscopy, which uses a beam of light, TEM uses a high-energy electron beam to view structures that are considerably smaller. Compared to PCM, the majority of TEM instruments used

for asbestos analysis feature technology that enables a more thorough characterization of a particle. The total number of fibers counted on a sample grid as well as the number of PCM equivalent (PCMe) fibers are typically recorded and estimated using TEM in order to measure the fiber size, distribution, and dimension. TEM examination of mineral fibers is often used to confirm fiber analysis by PCM. By comparing the fiber's ionic spectrum to a recognized standard and determining the mineralogy of a target fiber, TEM analysis enables microscopists to identify the target fiber (U.S. EPA, 2014a). In addition, multiple measurements taken by PCM or TEM for a given exposure setting is preferred over a single measurement.

Although some studies collect measurements of dust using midget impingers, these exposure measurements alone are less reliable in the context of dose-response assessment because the differentiation of fiber types is not possible. In cases where exposure data collected by midget impingers was used in analyses, it is strongly preferred that a conversion factor is applied based on paired sampling measurements using impingers and PCM.

Because of the importance of the of exposure measurement in dose-response assessment, OPPT evaluated the exposure measurement (Metric 4) before evaluating other data quality evaluation metrics to focus on the subset of studies with the most reliable asbestos fiber detection and quantification methods (*i.e.,* PCM or TEM). Studies that were rated Low or Uninformative for Metric 4 did not move on to data quality evaluation.

The data quality evaluation criteria for Metric 4 are as follows:

Mark as High if:

For all study types:

Quantitative estimates of exposure were consistently assessed (*i.e.,* using the same method and sampling time-frame) during multiple time periods and using either PCM or TEM.

OR

A combination of methods were used over time (*i.e.,* midget impinger, PCM or TEM), but side-by-side sampling and analyses were conducted to develop appropriate conversion criteria.

AND

For an occupational population, contains detailed employment records and quantitative estimates of exposure using either PCM or TEM which allows for construction of job-matrix for entire work history of exposure (*i.e.,* cumulative or peak exposures and time since first exposure).

Mark as Medium if:

For all study types:

Exposure was assessed during one time period but this time period is judged to be reasonably representative of the entire study time period.

AND

Exposure was assessed using a combination of midget impingers, PCM, and/or TEM measurements, but side-by-side sampling and analyses were not conducted for all operations and thus there is a lack of confidence in the conversion factors.)

OR

For an occupational study population, contains detailed employment records and quantitative estimates of exposure using a combination of midget impingers and PCM or TEM measurements 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.

Mark as Low if:

For all study types:

Exposure was estimated solely using professional judgement.

OR

Exposure was directly measured and assessed using a quantitative method other than PCM or TEM and conversion factors were not determined.

OR

The method of quantifying/counting fibers was not specified (PCM, TEM, or other method not specified).

*If "acceptable," refer to the evaluation guide to see confidence level criteria.

Mark as Uninformative if:

For all study types:

Methods used to quantify the exposure were not well defined, and sources of data and detailed methods of exposure assessment were not reported (STrengthening the Reporting of OBservational studies in Epidemiology [STROBE] Checklist 7 and 8 (Von Elm et al., 2008).

OR

There was no quantitative measure or estimate of exposure.

OR

There is evidence of substantial exposure misclassification that would significantly bias the results.

Mark as N/A if:

Do not select for this metric.

Range, Distribution, and Levels of Exposure: To derive a dose-response relationship from an epidemiologic study, it is necessary for the study analysis to inform how a unit change in exposure relates to a unit change in risk for a health outcome. This is most easily accomplished with studies that estimate the relationship between a continuous measure of exposure and a health outcome. However, a dose-response relationship can also be estimated for studies that report the relationship between a categorical measure of exposure and a health outcome as long as there are a sufficient number of exposure groups to approximate a continuous relationship. This is done by estimating a dose-response line that passes through the mid-points of each of the exposure categories. Three or more exposure groups, including one unexposed or lower-exposed group and at least two additional exposed groups, is considered the minimum for being able to adequately approximate a dose-response relationship in this manner. Thus, studies that were rated Low or Uninformative for Metric 5 did not move on to data quality evaluation.

Metric 5 explicitly evaluates whether the study includes sufficient exposure data for dose-response assessment, regardless of potential bias or lack of bias in the study methodology. Thus, Metric 5 was evaluated before the other data quality evaluation metrics, and only those studies that were rated as Medium (High is not an option) for Metric 5 moved on to data quality evaluation. The data quality evaluation criteria for Metric 5 are:

Mark as High if:

Do not select for this metric.

Mark as Medium if:

For all study types:

The range and distribution of exposure is sufficient or adequate to develop an exposure-response estimate (Cooper et al., 2016).

AND

Reports 3 or more levels of exposure (*i.e.*, referent group +2 or more) or an exposure-response model using a continuous measure of exposure.

Mark as Low if:

For all study types:

The range of exposure in the population is limited.

OR

Reports 2 levels of exposure (*e.g.*, exposed/unexposed)) (Cooper et al., 2016) (Source: IRIS)

Mark as Uninformative if:

For all study types:

The range and distribution of exposure are not adequate to determine an exposure-response relationship (Cooper et al., 2016).

OR

No description is provided on the levels or range of exposure.

Mark as N/A if:

Do not select for this metric.

B.3 Data Quality Evaluation

All references that met PECO screening criteria, as described above in Section 3.2 and that used regression or SMR analyses and were rated as Medium or High for Metrics 4 and 5 underwent full data quality evaluation as an individual reference or as part of a cohort group, as described in Appendix R of the 2021 Draft Systematic Review Protocol and the Draft Risk Evaluation for *Asbestos Part 1 Systematic Review Supplemental File: Data Quality Evaluation of Human Health Hazard Studies: Mesothelioma and Lung Cancer Studies* (March 2020), with some modifications described below (U.S. EPA, 2021a).

Part 1 of the Risk Evaluation for Asbestos evaluated the association between inhalation exposures to asbestos and the outcomes of mesothelioma, lung cancer, laryngeal cancer, and ovarian cancer. Part 2 included additional outcomes including other cancers and asbestosis, pulmonary function/spirometry results, pleural plaques, and other non-cancer outcomes.

For mesothelioma, the mesothelioma data quality evaluation form used in Part 1 of the Risk Evaluation for Asbestos was used for Part 2, with some modifications based on the calibration for data quality evaluation. For other outcomes, the lung cancer data quality evaluation form from Part 1 was used with additional modifications to evaluate other outcomes that were not considered in Part 1.

Prior to beginning calibration and then data quality evaluation for asbestos, the data quality evaluation criteria from the *Draft Risk Evaluation for Asbestos: Systematic Review Supplemental File: Data Quality Evaluation of Human Health Hazard Studies: Mesothelioma and Lung Cancer Studies* (March 2020) were reviewed, and changes were made to the criteria to address the additional outcomes included in Part 2. In Part 1 of the Risk Evaluation for Asbestos, there were separate data quality evaluation forms for mesothelioma and lung cancer due to the differences between these health outcomes. In comparison to lung cancer and other health outcomes, mesothelioma has a lower incidence and a longer latency period. Furthermore, mesothelioma has few known causes other than asbestos and few potential confounders, and thus has different data quality considerations than lung cancer as well as other outcomes. Therefore, for Part 2 of the Risk Evaluation, a separate data quality evaluation form was maintained for mesothelioma, and the lung cancer data quality evaluation form was modified to include considerations of other cancer and non-cancer outcomes. Calibration was then conducted, resulting in additional clarifying modifications to the data quality evaluation criteria. The data quality evaluation criteria for Asbestos Part 2 are presented in Appendix G. Table_Apx G-1 presents the data quality evaluation criteria for mesothelioma and Table_Apx G-2 presents the data quality evaluation criteria for other outcomes.

B.4 Consideration of Epidemiologic Cohorts for Dose-Response Analysis

Following the data quality evaluation of each cohort, those receiving Medium or High OQD ratings were further reviewed to confirm suitability for dose-response assessment. The cohorts were categorized for examination of cancer and/or non-cancer outcomes. Additionally, the exposure and outcome data and analysis performed were reviewed to confirm the use of PCM or TEM for measurement of asbestos fibers or application of an appropriate conversion factor, use of air measurements in the analysis, analysis conducted with outcome data, and adequate assessment of the outcome (*e.g.*, sufficient follow-up time).

At this point, some cohorts were removed from further consideration because the quantitative analyses were not done with PCM or TEM measurements or a conversion factor even though the study may have presented some PCM or TEM data (*e.g.*, passing Metric 4). Other cohorts were removed from consideration because they had received a Low or Uninformative OQD rating in data quality evaluation. Cohorts that were used in the derivation of the existing IURs or RfC were automatically included for dose-response consideration so that a complete assessment of each IUR and RfC could be achieved, noting strengths and uncertainties related to the underlying data. Sections 4 and 5 provide detailed descriptions of the cohorts and the existing IURs and RfC, respectively.

Appendix C NON-CANCER EPIDEMIOLOGIC COHORTS

C.1 Cohorts Included in the IRIS Libby Amphibole Assessment

The IRIS LAA Assessment presents the cohorts considered in Figure 4-1 of the Toxicological Review (U.S. EPA, 2014b). There were two distinct occupational cohorts including miners and millers in Libby, Montana, and fertilizer plant workers in Marysville, Ohio, where vermiculite from Libby was received, processed, and packaged for distribution.

Libby, MT, Mining and Milling Cohort

As described in Section 5.2.2, the Libby, MT, Mining and Milling Cohort included men who worked in the open-pit vermiculite mine outside of Libby in either mining or milling operations. There were several different investigations of this cohort that differed in inclusion criteria; however, each examined non-cancer morbidity and mortality. The exposure assessment data used in analyses the non-cancer outcomes are the same as those described for the cancer mortality as described in Section 5.2.2 and in greater detail in Table 4-1 and Section 4.1.1.1 of the IRIS LAA Assessment (U.S. EPA, 2014b). For outcome assessment in all investigations, mortality was determined by death certificates with a certified underlying cause of death. Examination of pulmonary outcomes in workers were assessed by chest x-ray. Films were randomized and independently read by three qualified readers using the 1980 ILO classification system to identify parenchymal abnormalities.

O.M. Scott, Marysville, OH, Fertilizer Plant Workers

The O.M. Scott plant in Marysville, Ohio, was a site that received vermiculite ore by rail where it was process into expanded form for use as an inert carrier for herbicides and fertilizers. A total of 512 workers participated in the 1980 investigation on the pulmonary effects in Ohio plant workers (Lockey et al., 1984). Follow-up of the original cohort including chest x-rays and interview was conducted in 2004 (Rohs et al., 2008) and vital status for mortality in 2011 (Dunning et al., 2012).

For this cohort, there were eight main departments at the vermiculite ore processing plant in Marysville, Ohio, including production and packaging of commercial products, maintenance, research, the front office, and the polyform plant. The vermiculite ore was delivered by train or truck to the facility, processed and packaged, and stored. Dust controls were implemented beginning in 1967 leading to a marked improvement in dust management during the course of the 1970s. Monitoring of industrial hygiene at the facility started in 1972 which consisted of an industrial hygienist following a worker with a sampling device. After 1976, personal breathing-zone samples were collected and analyzed by PCM. Cumulative exposures for each worker were estimated using detailed work histories and industrial hygiene data. Overall, employees were divided into three different exposure groups: nonexposed workers (chemical processing, research, front office), low exposed workers (central maintenance, packing, and warehouse), and high exposed workers (expander, plant maintenance, and pilot plant) (U.S. EPA, 2014b; Lockey et al., 1984). In 2009, the exposure analyses were updated based on the inclusion of newly available information on sampling and industrial hygiene records resulting from litigation records related to Libby vermiculite (U.S. EPA, 2014b; Borton et al., 2012).

Exposure-response analyses were conducted for respiratory outcomes and mortality based on the detailed exposure estimates in 2004, and 2009, respectively. Comprehensive, individual-level data was available from physical examination and interviews with each participant, allowing more control for confounding in the analysis. Also notable is that the extended follow-up periods provided time from first exposure that ranged from 23 to 47 years (U.S. EPA, 2014b).

C.2 Cohorts Not Previously Considered in Non-cancer Assessments

SC Textiles Cohort

The workers included in the SC Textile Cohort studies described in Appendix D.1 and included in Part 1 of the Risk Evaluation for Asbestos were also followed for non-cancer outcomes, primarily asbestosis pneumoconiosis mortality. The exposure measurement and assignment methods for the non-cancer analyses are the same as those used in the exposure-response analyses for cancer. Hein et al. (2007) and Stayner et al. (2008) included the longest follow-up for non-cancer mortality in this cohort with vital status through 2001. These studies included an extension of the original cohort to include non-white workers and females. Strong associations between asbestos exposure and asbestosis and pneumoconiosis-related mortality were demonstrated in the analysis of this cohort.

SC Vermiculite Miners and Millers Cohort

W.R. Grace & Company conducted a study of vermiculite miners in Enoree, South Carolina, in 1988 drawing comparisons to the health effects observed in the Libby, Montana, mines (W. R. Grace & Co, 1988). The study included a cohort of 194 men involving in milling and mining vermiculite with exposures to tremolite fibers. The mine opened in 1946 and employment was at 80 men in the 1960s. Dust control procedures were implemented in 1970. In 1985 and 1986, 21 bulk samples and 58 static air samples were collected. Bulk sample analysis showed the presence of tremolite-actinolite, vermiculite fragments, talc/anthophyllite, and iron rich fibers. Air samples form 10 different areas were analyzed by PCM, all below 0.01 f/cc. Additionally, the study references other exposure measurement data, including 125 air samples from Mine Safety and Health Administration and personal samples of longer durations than static samples, but details are not provided. Estimates of exposure were calculated based on work history and calculated fibers concentrations in wet and dry zones. Mortality data was collected through 1985, providing a minimum latency of 15 years. Radiographic films were taken and sputum collected in April to May 1986. Overall, mean length of employment for the cohort was 9.2 years and mean length of time between start of employment and death was 19.7 years. Exposure-response analyses were conducted for mortality and excess mortality was observed. Results for sputum and parenchymal abnormalities were only categorically reported for exposed and unexposed employees.

Anatolia, Turkey, Villagers Cohort

In Anatolia, Turkey, there are deposits of asbestos, known as white soil, that has been used in as many as 196 villages in the past, Metintas et al. (2005) conducted a study to examine respiratory outcomes among villagers in a subset of villages with ongoing environmental exposures to asbestos. Ten villages were randomly selected and 991 residents at least 30 years of age were included in the cohort. Assessment of soil samples showed the presence of tremolite, anthophyllite, actinolite, and chrysotile asbestos. For each village, indoor and outdoor air samples were collected and fibers counted by PCM. Cumulative fiber estimates for each villager were calculated based on the assumption of an 8-hour workday outside of the home, 8 hours sleeping within the home, 8 hours of household activity, and 11 months spent in the village each year. Villagers completed questionnaires and had clinical and radiological examining conducted with a portable roentgenogram and had additional follow-up if abnormalities were detected. Outcomes of interest included pleural plaques, diffuse pleural fibrosis, and asbestosis. Multivariate logistic regression analysis was performed, but few details of the analysis are provided in the study. Additionally, TSFE was not characterized for the cohort.

Chinese Chrysotile Textile Factory Cohort

In the suburb of Shanghai, China, a chrysotile textile product factory opened in 1958 that employed 1,059 workers between opening and follow-up in September of 1982. Huang (1990) examined exposures to workers and asbestosis. In the exposure-response analysis, exposures for each of the 776

workers with at least 3 years of employment with sufficient documentation for study inclusion were determined by combining detailed work histories with asbestos routine air measurements collected from 17 worksites across the factory using membrane filters. For earlier asbestos exposures, fiber estimates were derived from dust concentrations converted based on site-specific conversion factors and linear regression. Onset of asbestosis was assessed based on chest x-ray films using ILO classification. Linear regression showed strong correlation between asbestos exposure and asbestosis in this cohort.

Wittenoom, Australia, Residents Cohort

As described in Appendix D.4, the Wittenoom, Australia, Residence Cohort comprised all individuals residing in Wittenoom for at least 1 month between 1943 and 1992. The exposure assessment data used in analyses the non-cancer mortality outcomes are the same as those described for the cancer mortality. Only one study identified for this this cohort examined non-cancer mortality; Reid et al. (2008) described excess mortality in women and girls of the cohort for a variety of causes including pneumoconiosis. Overall, there is only limited non-cancer data available from this cohort for dose-response consideration.

Appendix D CANCER EPIDEMIOLOGIC COHORTS

D.1 Cohorts Included in the Risk Evaluation for Asbestos Part 1

South Carolina Textiles Cohort, U.S.

Many publications have reported on the mortality of a group of workers at a textile plant in Charleston, South Carolina, which produced asbestos. The plant produced textiles from raw chrysotile asbestos fibers that were imported from Rhodesia (Zimbabwe) and Canada. Crocidolite yarns were also used in a small operation within the plants, but overall, only accounted for 0.03 percent of the annual asbestos processed.

In terms of exposure assessment for the cohort, beginning in the 1930s, the facility implemented engineering measures to manage dust levels, and at the time, it was regarded as the industry's "gold standard." Based on 5,952 industrial hygiene air samples taken between 1930 and 1975, estimates of personal exposure were derived. Prior to 1965, only midget impinger samplers were used to collect all samples. From 1965 to 1971, both impinger and membrane filter samplers were employed. Post-1971, only membrane filter samplers were employed (U.S. EPA, 2020).

To determine the concentrations of fibers 5 μm or longer, PCM and membrane filter sampling were used. Conversion factors between membrane and impinger samples were derived to calculate job and operation-specific asbestos measurements. In 1965, 120 paired samples were collected, and between 1968 and 1971, 986 concurrent samples were also collected, and statistical analysis showed no significant changes in the fiber/dust ratios over time or between operations. Overall, asbestos measurements were estimated for nine departments and four job categories using linear regression with adjustment for time-related changes in process and dust control, and individual cumulative exposures for workers were determined based on detailed occupation histories and the constructed job exposure matrix (U.S. EPA, 2020).

A follow-up of 3,072 workers through 2001 provided the most recent data for lung cancer and mesothelioma in the cohort. For study inclusion, workers needed to be employed for at least 1 month between 1940 and 1965, which primarily consisted of white men initially, but later study years included non-white men and women. Using Poisson regression modeling and a linear relative rate form, quantitative exposure-response associations for lung cancer were calculated. Chrysotile asbestos exposure cumulative in f/cc-yr was entered as a continuous variable with sex, race, and age as variables, and it was lagged by 10 years (U.S. EPA, 2020).

Of the available information and data in publications, individual-level lung cancer and mesothelioma data from Hein et al. (2007), Elliot et al. (2012), and Berman and Crump (2008) were used in linear and exponential modeling to derive K_L and K_M values.

North Carolina Textiles Cohort, U.S.

In four North Carolina textile mills that used asbestos, authors reported on mortality in a cohort of workers that had not been previously researched. Three of these plants produced yarns and woven goods from raw chrysotile fibers while one, smaller plant produced asbestos products using purchased yarns. One of the larger factories also used amosite fibers, however, this was a separate operation from that using raw chrysotile. These factories, unlike the South Carolina plants, did not use exposure controls.

Company records listed 5,770 workers (3,975 men and 1,795 women) with at least 1 day of employment between 1950 and 1973 and vital status and state or national health agency records were collected

through 2003. These records included ICD codes indicating cause of death, including intermediate causes and any relevant conditions. Of note, prior to the introduction of a unique code for mesothelioma in 1999, death certificate data were reviewed for any mention of mesothelioma and for ICD codes frequently used to indicate mesothelioma (U.S. EPA, 2020).

Between 1935 and 1986, 3,420 air samples were collected and the presence of asbestos fibers was assessed. Both impinger sampling and membrane filter sampling were utilized up until 1971, when impinger sampling was no longer used. Sampling prior to 1964 was done using impingers. To estimate concentrations, fibers longer than 5 μm were counted on membrane filters. To determine plant-, operation-, and period-specific parameters for converting dust to PCM-equivalent fiber concentrations, paired and contemporaneous samples by both methods were used. Fiber/dust ratios did not change significantly (U.S. EPA, 2020).

Multivariable mixed models were used to assess fiber concentration data and estimate average concentrations by factory, department, job, and time period. The employment-exposure matrix's functioning and job categories were the same as those created for South Carolina. To determine each worker's average and cumulative exposure to asbestos fibers, these estimations were correlated with their individual work history records. Where records lacked detailed job titles within departments (27% of employees, primarily those with short-term positions), exposure was calculated using the averages for the plant, time, and department. Exposures during the years before 1935, when there were no exposure measurements and little work history records available, were presumed to be the same as those in 1935, before dust restrictions were put in place (U.S. EPA, 2020).

A Poisson regression analysis with both log-linear and additive relative rate model types, was used to examine exposure-response relationships for lung cancer in the North Carolina cohort. Age, sex, race, the year of birth, and birth cohort were taken into account during modeling. With lags of 0, 10, or 20 years, the results were presented per 100 f/cc-yr of cumulative fiber exposure. K_L and K_M values were reported for the individual-level data presented in Loomis et al. (2009) and Elliott et al. (2012) based on linear and exponential model results. A Poisson regression analysis with both log-linear and additive relative rate model types, was used to examine exposure-response relationships for lung cancer in the North Carolina cohort. Age, sex, race, the year of birth, and birth cohort were taken into account during modeling. With lags of 0, 10, or 20 years, the results were presented per 100 f/cc-yrs of cumulative fiber exposure. K_L and K_M values were reported for the individual-level data presented in Loomis et al. (2009) and Elliott et al. (2012) based on linear and exponential model results.

Quebec, Canada, Asbestos Mines and Mills Cohort

Several investigations of workers at various mining, milling, and production facilities in Quebec, Canada, are available. The oldest publication included 11,379 Canadian miners and mill workers from Quebec who were born between 1891 and 1920 and had worked for at least a month in the mines and mills. The cohort was followed to 1975 where additional findings were published based on the cohort's follow-up through 1988, and extended analysis to include data through 1992 (U.S. EPA, 2020).

In these studies, exposure assessment methods varied. Midget impinger readings from 1948 to 1966 were used to estimate total dust concentrations in mppcf, and studies report a range of 3,096 to 10,205 samples for 5,782 unique job assignments according to a 13-point scale ranging from 0.5 to 140 mppcf. Although the categories are described by the authors as "approximating the mean," the procedures used to analyze the exposure measures and assign categories are not described. Different methods were employed to estimate exposures in earlier and later years when dust data were deemed to be insufficient or not available. Exposures in years prior to 1948 were based on expert assessment from interviews with

employees and company personnel, while those in years following 1966 were extrapolated from the previously measured levels (U.S. EPA, 2020).

The initial publications reported exposure-response analyses based on dust concentrations in mppcf. Some of the later investigations applied conversion factors ranging from approximately 3 to 7 f/cc per mppcf. The basis for these conversion factors, however, is not well described and the reported confidence in these conversion factors also varies. In addition, later examination of dust samples from Quebec mines reported by (Berman, 2010), demonstrated that a third of the structures in samples were not asbestos in PCM and TEM analysis. These findings raise serious doubts about the accuracy of the f/cc estimates of exposure from the Quebec investigations, combined with issues surrounding the selection of an appropriate conversion factor. Ultimately, K_L values were estimated based on modeling with data from Berman and Crump (2008), but because of uncertainties, they were not used in final IUR derivations (U.S. EPA, 2020).

Qinghai, China, Asbestos Mine Cohort

The Qinghai Mine first opened in 1958 and produced raw commercial chrysotile. The examination of workers from this mine included individuals that were on the registry in 1981 and were employed for at least 1 year. They were followed from 1981 to 2006. Periodically between 1984 and 1995, area sampling at specified places was used to measure total dust concentrations, though the number of measurements was not reported. In addition, 28 measurements in 6 different workshops were taken in 2006. Dust concentrations were converted to f/cc using a linear regression model built from 35 paired measurements taken in 1991. Fiber concentrations were determined for each workshop and job description from 1984 to 2006 using a single conversion factor, though the estimation techniques are not fully explained in English-language publications.

In the Part 1 of the Risk Evaluation for Asbestos, K_L values were calculated using data from Wang et al. (2013) and Wang et al. (2014). A strength of the analysis in these studies was the use of continuous exposure variables in log-linear Cox proportional hazards models adjusted for age and smoking. Despite the statistically robust analysis, results from these investigations were not selected for final IUR derivations due to uncertainties in the exposure measurements and assignment.

Balangero, Italy, Mining Cohort

This historical cohort was the subject of four relevant publications (Pira et al., 2017; Pira et al., 2009; Piolatto et al., 1990; Rubino et al., 1979); however, the cohort studies from Balangero, Italy, were omitted due to the models' failure to produce findings when exposure was measured continuously. The Balangero Mine and Mill, was located northwest of Turin, and workers were exposed to chrysotile asbestos. The mine began operations in 1916, expanded to produce an average of 130,000 to 160,000 tons of chrysotile asbestos per year in the 1970s, and shut down in 1990, before all forms of asbestos, including chrysotile, were outlawed in Italy in 1992. The cohort included 952 workers who had each worked at least 30 calendar days between January 1, 1930, and December 31, 1965, and were still living on January 1, 1946. Additionally, a small number of contract workers who were occasionally employed on the Balangero site and subjects who worked for less than a year were not included in the cohort.

The factory's personnel records provided information on employment, and population registrations and copies of death certificates from municipal registration offices provided information on vital status and causes of death for this cohort. Date of birth, employment history, cause of death (including contributing factors for deaths that happened since 1988), job category, and latest information for subjects who were lost to follow-up were all accessible. Since researchers were unable to determine when subjects'

employment ended after December 31, 1987, they used the assumption that those who were still employed at the mine on that day would continue there until production stopped in 1990.

Data on exposure were quantified using the cumulative dose of inhaled fibers reported in fiber-years. This was calculated using environmental observations from 1969 onward and synthetically reconstructed working conditions for earlier times.

In order to determine the cohort's mortality experience through 1975, 98 percent of the cohort was tracked down. Overall, 332 deaths were recorded versus 214.4 predicted, which is an extraordinarily high mortality rate. Nevertheless, non-malignant respiratory disorders, cardiovascular diseases, and accidents accounted for the majority of the extra mortality. Only laryngeal cancer was found to be considerably overrepresented in the entire sample, with the overall SMR for all malignant neoplasms being 106.

Chongqing, China, Asbestos Products Factory

This cohort started with a preliminary study on worker fatalities at a Chongqing, China, facility that manufactured a range of asbestos-containing items. Using plant data, a fixed cohort of 515 males who had been working for at least a year and were active as of January 1, 1972, was formed. Since no women were hired before 1970, none were part of the founding cohort. In later studies, additional analyses based on extensive follow-up were presented. The cohort's 2008 follow-up included 279 more women who had jobs between 1970 and 1972 (U.S. EPA, 2020).

The Chongqing Plant produced a variety of asbestos-containing items including textiles, friction materials, rubber-impregnated commodities, and cement after it first opened in 1939 and then expanded in the 1950s. The plant reportedly used chrysotile asbestos from two mines in Sichuan Province, and it is unlikely that there was amphibole or tremolite contamination.

Techniques of exposure assessment that were reported in this cohort were based on 556 area measurements at 4-year intervals between 1970 and 2006. Fiber concentrations for four activities (processing raw materials, textile carding and spinning, textile weaving and maintenance, and manufacturing rubber and cement) were estimated. Prior to 1999, only total dust was recorded; after that year, measurements of both dust and fibers were done in tandem. In total, there were 223 measurements of fiber concentration made using PCM. To estimate dust to PCM fiber-equivalent concentrations for the period 1970 to 1994, paired dust and fiber samples from 1999 to 2006 was used; however, no information was provided on what operations and jobs these estimations reflect. Cumulative individual fiber exposures were calculated based on the concentration information and the length of time employees spent in each section of the factory, which was generally stable over time (U.S. EPA, 2020).

Several articles have presented exposure-response information for lung cancer in the Chongqing cohort for various time periods of the study, and K_L values were estimated. However, model fitting could not be conducted for the minimal amount of data on mesothelioma. Furthermore, due to potential for exposure misclassification resulting from the low number of exposure measures, the absence of fiber measurements prior to 1999, and the use of area sampling as opposed to personal sampling, this cohort was not selected for use in IUR derivation (U.S. EPA, 2020).

Salonit Anhovo, Slovenia, Asbestos Factory Cohort

This historical cohort was the subject of two relevant publications examining asbestos exposure to workers in asbestos cement factory that included factories producing cement, cement pipes, and corrugated sheets. The factory opened in 1921 and began using asbestos in 1922. In 1996, asbestos was

banned by law in Slovenia. Uniquely, the plant kept record of asbestos use separately for chrysotile and amphibole.

The cohort comprised all 6,714 employees who started working at the Salonit Anhovo factory after December 31, 1946, and who did so for at least 1 day between 1964 and 1994. From the cohort, 58 primary lung cancer cases with histological confirmation and 290 healthy controls were chosen. The working life exposure histories to the asbestos form amphibole (10% exposure) and chrysotile (90% exposure) were estimated independently. Some employees in Salonit Anhovo were also exposed to cement dust, which contains hexavalent chromium (Cr^{6+}), and silica dust, which is free SiO_2. For either silica or chromium, airborne concentration data were not available; nonetheless, each contaminant's presence or absence could be determined for each work and each year.

The facility-maintained records and tracked of the amount of asbestos utilized throughout production (separately for chrysotile and amphibole). Chrysotile was blended with amphiboles in minor but recognized quantities after being primarily acquired from Canada, Rhodesia, Italy, Russia, and then Yugoslavia. The first records of employment are from 1939, when the factory employed 731 people. The total workforce was down to 520 by the end of World War II, although it quickly increased after the war. By 1953, there were more than 1,000 employees, and in 1981, that number peaked at 2,651. Women made up about 30 percent of the employee population. Between 300 and 800 workers were directly exposed to asbestos each year, with the number fluctuating.

From 1961 until 1996, the facility's airborne fiber concentrations were observed for compliance. It was not until 1986 that the workers' exposure conditions significantly changed as a result of the installation of an efficient ventilation system and the introduction of respirators (although they were not used consistently at the time). A total of 1,030 air measurements were taken at the asbestos facility between 1961 and 1995, using a variety of monitoring techniques, including 78 pairs of measurements where the gravimetric and membrane filter methods were utilized side-by-side. Every air sampling measurement was made at a set point that was close to the worker's breathing zone. The side-by-side samples were used to develop conversion factors, which incorporated the information acquired by the various exposure assessment techniques.

Part 1 of the Risk Evaluation considered this cohort for exposure to commercial chrysotile and found that it was uninformative for further consideration because it did not adequately allow exposures to chrysotile and amphibole asbestos forms to be separated. However, this limitation is not relevant to Part 2.

Thus, these studies were considered further for use in dose-response assessment. Additional limitations in the data are available from these cohorts relevant to the criteria described in Section 5.1. Job exposure matrices were constructed based on worker histories and fiber concentrations from area sampling measurements. However, some jobs did not have relevant air sampling data as they moved between or outside of facilities, and in these instances, a consultation group was used to develop exposure matrices. It is unclear what percentage of study participants for which this applied. Another limitation of this cohort for use in dose-response assessment is the use dichotomous exposure or categorical exposures based on the 90th percentile. As described in Section 5.1, preference is for studies with continuous exposure based on individual-level data (Fikfak et al., 2007; Fikfak, 2003).

D.2 Cohorts Included in the IRIS Libby Amphibole Asbestos Assessment

Libby, MT, Vermiculite Mining and Milling Cohort

Several studies are available that examine occupational asbestos exposures to LAA. These studies were conducted in Libby, Montana to assess the mining and milling operations or at a plant in Marysville, Ohio, which received vermiculite mined in Libby, Montana. The Libby vermiculite mine opened in 1923 and remained open until 1990. The operations in the open pit mine produced high dust exposures that were reduced in 1970 with new drilling technology. Vermiculite from the mine was shipped by rail beginning in 1935 and enclosed hoppers were only used beginning in 1960.

The relevant studies examining this occupational cohort are summarized in Table 4-2 of the IRIS LAA Assessment (U.S. EPA, 2014b). The studies were similar in examining asbestos exposure and outcomes in male workers, but varied in the inclusion criteria (*e.g.*, length of employment, employment date), asbestos quantification, and job-exposure classification.

However, in all studies, the asbestos quantification included fiber counts by PCM in later study years and impinger measurements in earlier study years that were converted to f/cc based on analysis of location-specific sampling. Publications on the cohort included various follow-up periods for mortality and pulmonary outcomes, with the longest follow-up in 2006.

For lung cancer and mesothelioma, exposure-response relationships were analyzed to derive an IUR. By 2006, approximately 54 percent of the cohort had died, and a detailed individual-level work history and asbestos exposure measurements were available. As described in Section 6.2.2 of the IRIS LAA Assessment (U.S. EPA, 2014b), the data were fit with various models with a range of exposure metrics because there was not a biological basis for model selection. Ultimately, a subcohort was established that included workers hired after 1959, which improved model fitting. Data prior to 1959 did not include as detailed work history which likely contributed to exposure misclassification in the dataset. This subcohort included 880 workers, of which 26 percent had died at time of follow-up. These model fitting results were retained for consideration in the IUR derivation.

D.3 Cohorts (Mixed-Fiber) Included in the IRIS Asbestos Assessment

Insulation Manufacturing, Paterson, NJ (Amosite)

Between 1941 and 1945, men were recruited to work at an amosite asbestos factory in Paterson, New Jersey, to supply the U.S. Navy with insulation materials for ships in World War II. Seidman et al. (1979) and Seidman (1984) examined the mortality among 820 of these men that met study inclusion criteria, including attaining 5 years of employment at the factory. The cohort was followed through 1982 and mortality data was collected. While no air concentrations were available for the Paterson, New Jersey, plant, fiber counts were available from similar plants located in Tyler, Texas, and Port Allegany, Pennsylvania. Data collection in these other plants was conducted by the U.S. Public Health Service in 1967, 1970, and 1971 and reported in the Asbestos Criteria Document of the National Institute for Occupational Safety and Health. Although the number of samples collected and the methods used for fiber counting are not described, it is known that dust control measures were not in place. Exposure-response analysis was conducted with data for this cohort using SMR based on expected and observed cancer deaths in the population. For this cohort, workers with less than 6 months of history had an abnormally high observed mortality rate; thus, adjustments were made yielding a K_L of 0.043 and a K_M of 3.2×10^{-8} (U.S. EPA, 1986).

Insulation Application, United States (Chrysotile and Amosite)

Selikoff et al. (1979) and Peto et al. (1982) studied the mortality experience in members of the International Association of Heat and Frost Insulators and Asbestos Workers in the New York-New Jersey metropolitan area between 1943 and 1976. The cohort included 623 men employed prior to 1943 and 833 men employed after 1943, the latter group reflecting work experience in post-war conditions. Expected and observed cancer deaths were estimated at follow-up in 1962 and 1976. Asbestos concentrations in these specific work facilities were not measured; however, asbestos air concentration measurements were obtained through study of insulation work facilities by three different laboratories in the United States between 1968 and 1971 using the NIOSH and OSHA method (published in 1979; phase contrast illumination) (Leidel et al., 1979). The average fiber concentration of asbestos dust in insulation work, ranged from roughly 3 to 6 f/mL with 2 to 5 minutes peak concentrations exceeding 100 f/mL. However, it was recognized that asbestos exposures prior to these measurement dates could have been significantly higher due to changes in asbestos products over time (*e.g.*, less asbestos in later years). Because of this, the overall average concentration used was 15 f/mL. For this cohort, a K_L of 0.0075 per fiber/cc was estimated, which included reduction to adjust for death certificate diagnoses rather than best estimates as well as substantial smoking rates in insulation workers. For this cohort, a K_M of 1.5×10^{-8} was estimated (U.S. EPA, 1986; Peto et al., 1982)

Asbestos Products Manufacturing, United States (Chrysotile and Crocidolite)

Henderson and Enterline (1979) studied a cohort of men who had worked in product or maintenance for a U.S. asbestos company. This cohort was established from company records, including those who retired between 1941 and 1967 and were receiving a company pension. The average length of employment in the asbestos industry for these 1,075 men was 25 years. The cohort was followed through 1973, using company records and SSA files for tracing. For this cohort, total dust concentrations were measured in mppcf and no specific conversion factor was available to present air concentrations in f/mL or f/cc. Thus, in U.S. EPA (1986), air concentration data from other relevant studies was considered. It was determined conversion factors from other industrial settings (*i.e.*, cement plants) was useful and a conversion factor of 1.5 f/mL/mppcf was used. In deriving the K_L for this cohort, it was additionally noted that a retrospective analysis starting from retirement would likely underestimate the actual deaths. After adjustment to account for this, a K_L of 0.0049 was presented. (U.S. EPA, 1986).

New Orleans Asbestos Cement Building Material Plants Cohort (Chrysotile and Crocidolite)

In the early 1920s, two asbestos cement building materials plants opened in New Orleans, Louisiana, producing flat shingles and corrugating sheets in one plant, and shingles, pipes, and asphalt flooring materials in the other plant. Overall, products contained between 15 and 28 percent asbestos, predominantly chrysotile with crocidolite and amosite in some products. Weill et al. (1979) studied the mortality experience in 5,645 men who had worked in either or both of these plants that had at least 20 years of follow-up from beginning employment. Plant records included demographic information and complete work history for each person and were mostly complete with the exception of poor records before 1942 in one plant. Tracing of the cohort was done in 1974 through SSA records, and only 75 percent could be verified as deceased or living. While study authors considered the ages and potential occupations of those loss to follow-up, there is likely an underestimation of mortality especially when considering that the deaths prior to 1970, more so for blacks, were not reported to SSA.

Expected and observed mortality rates were used in exposure-response calculations. Exposure data for this cohort consisted of dust measurements collected with impingers, reported in mppcf. Sampling was initiated in the 1950s and impinger measurements were taken at various locations in both plants. Exposure profiles for each workers were developed using impinger sampling data combined with estimated fiber content for each job by month and year. The dose-response modeling of this data

resulted in a K_L of 0.0053, which included adjustment for loss to follow-up and application of a fiber-particle conversion factor of 1.4.

Ontario, Canada, Asbestos Cement Factory Cohort (Chrysotile and Crocidolite)

An Ontario asbestos-cement factory that began production in 1948 was the manufacturing site for a variety of product including cement board and insulation materials made with both chrysotile and crocidolite. Finkelstein (1983) examined mortality in a cohort of men hired before 1960 and who had been employed for nine or more years. The cohort included production and maintenance workers in asbestos operations as well as workers in rock wool operations that had minimal asbestos exposure. Workers who could not be classified based on work history were excluded from the cohort.

Air measurements were collected in the factory using impingers for area sampling from 1949 through the 1960s and membrane filters in personal sampling starting in 1969. Based on crude analysis of the impinger data, fiber concentrations from 1955 to 1961 were assumed to be 30 percent higher and from 1948 to 1954 twice as high. These exposure estimates were matched with detailed work history for each workers based on company records to calculate an annual exposure concentration; however, extrapolations were used for maintenance workers. Even with these uncertainties, exposure estimates were assumed to be accurate to within a factor of 3 to 5. Exposure-response analysis was conducted based on individual-level cumulative exposures over an 18-year period with follow-up through 1980. Local tracing and Statistic Canada were used to determine confirm the deceased and living. Of note, only 2 to 7 percent of the cohort were lost to follow-up and smoking status was obtained for 70 percent of men. Calculations resulted in a K_L of 0.067 and K_M of 1.2×10^{-7} (U.S. EPA, 1986).

D.4 Cohorts Not Included in Existing EPA Assessments

Wittenoom, Australia, Residents Cohort

From 1937 to 1966, crocidolite (blue asbestos) was mined in Western Australia's Wittenoom Gorge. A single proprietor, the Australian Blue Asbestos firm, which employed about 7,000 people during that time period, owned the plant. The township of Wittenoom was established in 1946 and initially situated just 1.6 km from the mine but was relocated to 12 km away in 1947. Tailings from the mine were high in crocidolite fibers and distributed throughout the town for a variety of uses through the 1960s.

The Wittenoom, Australia, Residents Cohort comprised all individuals residing within the town for at least a month between 1943 and 1992 and were not employed in asbestos work. Of the 4,659 former residents in the cohort, follow-up by questionnaire in 1993 resulted in 2,173 responses, confirmed 460 deaths and 549 that could not be traced. By 1993, there only 45 residents remained in the town.

The Mines Department of Western Australia used a konimeter to measure dust levels in the mine and mill on a number of occasions between 1948 and 1958. A Casella long running thermal precipitator was used to conduct the first fiber count of the mine, mill, and Wittenoom area in 1966. Using a combination of personal and fixed positional monitors, additional monitoring was conducted in and around the township in 1973, 1977, 1978, 1980, 1984, 1986, and 1992. Based on the monitoring conducted in 1966, inhabitants were allocated an intensity of exposure of 0.5 fiber/milliliter (f/mL) of air between 1958 and 1966, when the mine closed. In light of the assumption that fiber levels were roughly twice as high when the original mill was in operation, a level of 1.0 f/mL was assigned for the period 1943 to 1957. Exposures were interpolated from 0.5 f/ml in 1966 to 0.01 f/mL in 1992 based on dust surveys that employed personal monitors. The product of the fiber content for each year and the amount of time spent in Wittenoom during that year was multiplied by the number of years each resident lived there to determine their cumulative exposure, adjusted to account for a continuous 24-hour exposure. By

demonstrating concordance with lung fiber burdens, the estimations of asbestos exposure have been internally validated.

The earliest identified publication on the cohort was conducted by Hansen et al. (1998) and demonstrated a strong relationship between mesothelioma mortality that increased with time from first exposure and duration of exposure. Additional publications examined differences between age and sex in mesothelioma mortality in the cohort (Reid et al., 2007), mortality observed only in women and girls in the cohort (Reid et al., 2008), as well as childhood exposures and adult mortality (Reid et al., 2013).

Appendix E LITERATURE INVENTORY FORM

Asbestos Human Lit Inventory Distiller Form

Is this study a candidate for re-screening? (*i.e.*, PECO-relevance related issues) If yes, please stop inventorying.

- Case-only, case-case, or other case-report
- No quantitative exposure concentration
- Other

Exposure routes (check all that apply)

- Inhalation
- Dermal
- Oral

Endpoints analyzed (check all that apply)

- Cancer (check all that apply)
  - Mesothelioma (ICD-9: 163)
  - Lung (ICD-9: 162)
  - Laryngeal (ICD-9: 161)
  - Ovarian
  - Other
- Non-cancer (check all that apply)
  - Pleural Plaques
  - Asbestosis
- Other Respiratory (check all that apply)
  - Spirometry (forced expiratory volume [FEV], total liquid ventilation [TLV], FVC, etc.)
  - Chest x-ray
  - Asthma/wheeze
  - Chronic obstructive pulmonary disease (COPD)
  - Other
- Non-respiratory

Study type (focus on the study population)

- Occupational
  - Study Design
    - Prospective Cohort
      - Study Identifiers
        - Cohort/Study Name: _____
        - Cohort/Study Location: _____
    - Retrospective Cohort
      - Study Identifiers
        - Cohort/Study Name: _____
        - Cohort/Study Location: _____
    - Case-control
    - Other
- Other

- Study Design
  - Prospective Cohort
    - Study Identifiers
      - Cohort/Study Name: _____
      - Cohort/Study Location: _____
  - Retrospective Cohort
    - Study Identifiers
      - Cohort/Study Name: _____
      - Cohort/Study Location: _____
  - Case-control
  - Other

Analysis characterization

- SMR studies
- Incidence rate or number of cases of the outcome and person-years for each interval - Are the incidence rates broken out by? (check all that apply)
  - Interval of time since first exposure (TSFE)
  - Cumulative exposure
  - Duration of employment or exposure
  - Other
- Regression analyses – What was the unit of analysis for the regression (*i.e.*, form of the exposure term)? (check all that apply)
  - Analyzed by intervals of times since first exposure (TSFE)
  - Analyzed by intervals of cumulative exposure
  - Analyzed by duration of employment/exposure
  - Other
- Other

Appendix F POPULATIONS, EXPOSURES, COMPARATORS, AND OUTCOMES (PECO) CRITERIA FOR PART 2 OF THE RISK EVALUATION FOR ASBESTOS

Table_Apx F-1. PECO Criteria for Asbestos Part 2 (Legacy Uses and Associated Disposals)

PECO Element	Evidence
P	**Human:** Any population and lifestage (*e.g.*, occupational or general population, including children and other sensitive populations). **Animal:** Aquatic and terrestrial species (live, whole organism) from any lifestage (*e.g.*, preconception, in utero, lactation, peripubertal, and adult stages). Animal models will be inventoried according to the categorization below: • Ecotoxicological models: invertebrates (*e.g.*, insects, spiders, crustaceans, mollusks, and worms) and vertebrates (*e.g.*, mammals and all amphibians, birds, fish, and reptiles). **Plants:** All aquatic and terrestrial species (live), including algal, moss, lichen, and fungi species. **Screener notes:** • All non-human animal (*e.g.*, rodents, rabbits, hens, amphibians, fish, insects) and plant models listed above are relevant as an ecotoxicological model. • PECO considerations should be directed toward effects on target species only and not on the indirect effects expressed in taxa as a result of chemical treatment (*e.g.*, substance is lethal to a targeted pest species leading to positive effects on plant growth due to diminished presence of the targeted pest species). Tests of single toxicants in *in vitro* and *ex vivo* systems or on gametes, embryos, or plant or fungal sections capable of forming whole, new organisms will be tagged as potentially supplemental (mechanistic studies). Bacteria and yeast studies specific for assessing genotoxicity or mutagenicity (*e.g.*, Ames assay) will also be tagged as potentially supplemental (mechanistic studies) but are otherwise excluded. Studies on viruses will be excluded.
E	**Relevant forms:** Asbestos, as defined by the following fiber types (or mixtures of fiber types): • Asbestos: 1332-21-4 • Chrysotile (serpentine): 12001-29-5 • Crocidolite (riebeckite): 12001-28-4 • Amosite (grunerite): 12172-73-5 • Anthophyllite: 17068-78-9 • Tremolite: 14567-73-8 • Actinolite: 12172-67-7 • Winchite: 12425-92-2 • Richterite: 17068-76-7 • Libby amphibole: 1318-09-8 • Exposure reported as PCM or TEM (including conversion factors for dust) • Talc (or magnesium silicate) contaminated with asbestos For **synonyms** see and a list of validated synonyms on the EPA Chemistry Dashboard. **Human:** Any exposure to one or more of the nine asbestos fiber types, singularly or mixed, that meets the following conditions: • Exposure based on **quantitative** (measured or estimated) concentrations of asbestos, such as exposure biomonitoring data (*e.g.*, lung tissue specimens), environmental or occupational monitoring data (*e.g.*, ambient air levels). This may be combined with estimates of duration of exposure. (Generally, studies with quantitative exposure data are included; however, studies that included a quantitative measurement of exposure but did not use that

PECO Element	Evidence
E	quantitative measurement in the analysis of the association between exposure and outcome are excluded.) • For categorical exposures, a minimum of two exposure groups (referent group + 1) **Eco Animal:** Any **<u>oral exposure</u>** to one or more of the nine asbestos fiber types, regardless of the exposure media (*e.g.*, water, diet, soil, sediment), singularly or mixed. All other exposure pathways (*e.g.*, dermal, inhalation, injection) are designated as not meeting screening criteria (please select the correct supplemental tag: apical/mechanistic and the non-oral exposure pathway). **For organism exposures to asbestos or PECO-relevant asbestos fibers where oral exposures cannot be discerned from other exposure pathways that are more characteristic of mammalian and avian studies, please select include (*e.g.*, fish or invertebrates exposed to asbestos in surface water, sediment, and/or soil.** **Plants:** Any exposure to one or more of the 9 asbestos fiber types, regardless of the exposure media (*e.g.*, water, soil, sediment), singularly or mixed **<u>Screener notes</u>:** • Field studies with media concentrations (*e.g.*, surface water, interstitial water, soil, sediment) and/or body/tissue concentrations of animals or plants are to be identified as **<u>Supplemental</u>** if any biological effects are reported. • Controlled outdoor experimental studies (*e.g.*, controlled crop/greenhouse studies, mesocosm studies, artificial stream studies) are considered to be laboratory studies (*not field studies*) because there is a known and prescribed exposure dose(s) and an evaluation of hazardous effect(s). Whereas field studies (*e.g.*, biomonitoring) where there is no prescribed exposure dose(s) do not meet screening criteria if there is no evaluated hazardous effect, and tagged as **<u>Supplemental</u>** field, if there is an evaluated hazardous effect. Papers reporting exposure to "asbestos" generally and not specific fiber type of asbestos will be included for further consideration.
C	**Human:** The source meets either of the following conditions: • Contains a comparison or referent population exposed to lower levels (or no exposure/exposure below detection limits) of asbestos, and other relevant forms listed above. **Eco Animal and Plants:** A concurrent control group exposed to vehicle-only treatment and/or untreated control (control could be a baseline measurement). **<u>Screener note</u>:** • If no control group is explicitly stated or implied (*e.g.*, by mention of statistical results that could only be obtained if a control group was present), the study will be marked as ***Unclear*** during TIAB screening.
O	**Human:** Health outcomes including cancer (*e.g.*, lung cancer, mesothelioma, laryngeal cancer, ovarian cancer) and all non-cancer endpoints at the organ level (*e.g.*, immune, cardiovascular, respiratory) or higher. **Eco Animal and Plants:** All apical biological effects (effects measured at the organ level or higher) and bioaccumulation from laboratory studies with concurrently measured media and/or tissue concentrations. Apical endpoints include but are not limited to reproduction, survival, and growth. **<u>Screener notes</u>:** • For ActiveScreener only: INCLUDE Supplemental references: mechanistic (including *in vitro*/*in silico* studies and studies with genotoxicity/mutagenicity assays in yeast/bacteria); absorption, distribution, metabolism, and excretion (ADME)/physiologically based pharmacokinetic (PBPK)/toxicokinetic; case reports or case series; susceptible populations

PECO Element	Evidence
	(with no health outcome; only at full text screening); mixture studies (tagged separately for human health animal and eco animal/plant studies); non-English records, records with no original data (*e.g.*, reviews, editorials, commentaries, assessments); conference abstracts; field studies. • For citations with no abstract, use the following to screen: title relevance and page numbers (articles two pages in length or less are assumed to be conference reports, editorials, or letters and can be tagged as supplemental material). Reviews that do not suggest a specific focus on the chemical of interest can be excluded rather than marked as supplemental material.

Table_Apx F-2. Major Categories of "Potentially Relevant Supplemental Material"

Category	Evidence
Mechanistic studies	All studies that report results at the cellular level and lower in both mammalian and non-mammalian model systems, including *in vitro*, *in vivo*, *ex vivo*, and *in silico* studies. These studies include assays for genotoxicity or mutagenicity using bacteria or yeast.
ADME, PBPK, and toxicokinetic	Studies designed to capture information regarding ADME, toxicokinetic studies, or PBPK models.
Case reports, case series, case-case, or case-only study designs	Case reports, case series, case-case, and case-only study designs will be tracked as potentially relevant supplemental information. (Does NOT include case-control, case-referent, or case-crossover study designs, which would be PECO includes if they meet criteria).
Susceptible populations (no health outcome)	Studies that identify potentially susceptible subgroups; for example, studies that focus on a specific demographic, lifestage, or genotype. This tag applies primarily during full text screening. **Screener note:** • If biological susceptibility issues are clearly present or *strongly* implied in the title/abstract, this supplemental tag may be applied at the title/abstract level. If uncertain at title/abstract, do not apply this tag to the reference during title/abstract screening.
Non-English records	Non-English records will be tracked as potentially relevant supplemental information.
Records with no original data	Records that do not contain original data, such as other agency assessments, informative scientific literature reviews, editorials, or commentaries.
Conference abstracts	Records that do not contain sufficient documentation to support study evaluation and data extraction.
Field Studies	Field studies with media concentrations (*e.g.*, surface water, interstitial water, soil, sediment) and/or body/tissue concentrations of animals or plants if biological effects reported
Other relevant structures	If another asbestos fiber type or talc/magnesium silicate are mentioned with resulting biological effects reported. However, please exclude synthetic magnesium silicate (lab-synthesized and thus, not asbestos-relevant) or synthetic magnesium silicate-products.

Appendix G DATA QUALITY EVALUATION CRITERIA

As described above in Appendix Section B.3, data quality evaluation forms originally used in Part 1 of the Risk Evaluation for Asbestos were updated and used to evaluate references containing epidemiological data for Part 2. In short, the mesothelioma data quality evaluation form used in Part 1, with updates based on calibration, was used for mesothelioma studies in Part 2. The lung cancer data quality evaluation form from Part 1 was modified to include considerations of other cancer and non-cancer outcomes for Part 2. Additional description of the updates to the data quality evaluation forms will be provided in the forthcoming *Draft Risk Evaluation for Asbestos Part 2: Supplemental Evaluation including Legacy Uses and Associated Disposals of Asbestos – Systematic Review Protocol*.

Table_Apx G-1. Mesothelioma Criteria

Data Quality Rating	Description
Domain 1. Study Participation	
Metric 1. Participant Selection (selection, performance biases)	
High	***For all study types:*** - All key elements of the study design are reported (*e.g.*, setting, participation rate described at all steps of the study, inclusion and exclusion criteria, and methods of participant selection or case ascertainment) **AND** - The reported information indicates that participant selection in or out of the study (or analysis sample) and participation was not likely to be biased (*i.e.*, the exposure-outcome distribution of the participants is likely representative of the exposure-outcome distributions in the population of persons eligible for inclusion in the study.)
Medium	***For all study types:*** - Some key elements of the study design were not present but available information indicates a low risk of selection bias (*i.e.*, the exposure-outcome distribution of the participants is likely representative of the exposure-outcome distributions in the population of persons eligible for inclusion in the study.)
Low	***For all study types:*** - Key elements of the study design and information on the population (*e.g.*, setting, participation rate described at most steps of the study, inclusion and exclusion criteria, and methods of participant selection or case ascertainment) are not reported (STROBE checklist 4, 5 and 6 (Von Elm et al., 2008)). -If the study provides little to no information about selection criteria, then rate this metric as Low.
Critically Deficient	***For all study types:*** The reported information indicates that selection in or out of the study (or analysis sample) and participation was likely to be significantly biased (*i.e.*, the exposure-outcome distribution of the participants is likely not representative of the exposure-outcome distributions of the population of persons eligible for inclusion in the study).
Not Rated/Not Applicable	- Do not select for this metric.
Reviewer's Comments	Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance.

Data Quality Rating	Description
Metric 2. Attrition (missing data/attrition/exclusion, reporting biases)	
High	***For cohort studies:*** - There was minimal subject loss to follow up during the study (or exclusion from the analysis sample) and outcome and exposure data were largely complete. **OR** - Any loss of subjects (*i.e.*, incomplete outcome data) or missing exposure and outcome data were adequately* addressed (as described below) and reasons were documented when human subjects were removed from a study (NTP, 2015). **OR** - Missing data have been imputed using appropriate methods (*e.g.*, multiple imputation methods), and characteristics of subjects lost to follow up or with unavailable records are not significantly different from those of the study participants (NTP, 2015). ***For case-control studies and cross-sectional studies:*** - There was minimal subject withdrawal from the study (or exclusion from the analysis sample) and outcome data and exposure were largely complete. **OR** - Any exclusion of subjects from analyses was adequately* addressed (as described below), and reasons were documented when subjects were removed from the study or excluded from analyses (NTP, 2015). ***NOTE for all study types:*** Adequate handling of subject attrition can include: Use of imputation methods for missing outcome and exposure data; reasons for missing subjects unlikely to be related to outcome (for survival data, censoring was unlikely to introduce bias); missing outcome data balanced in numbers across study groups, with similar reasons for missing data across groups.
Medium	***For cohort studies:*** - There was moderate subject loss to follow up during the study (or exclusion from the analysis sample) or outcome and exposure data were nearly complete. **AND** - Any loss or exclusion of subjects was adequately addressed (as described in the acceptable handling of subject attrition in the high confidence category) and reasons were documented when human subjects were removed from a study. ***For case-control studies and cross-sectional studies:*** - There was moderate subject withdrawal from the study (or exclusion from the analysis sample), but outcome and exposure data were largely complete **AND** - Any exclusion of subjects from analyses was adequately addressed (as described above), and reasons were documented when subjects were removed from the study or excluded from analyses (NTP, 2015).

Data Quality Rating	Description
Low	***For cohort studies:*** - The loss of subjects (*e.g.*, loss to follow up, incomplete outcome or exposure data) was moderate and unacceptably handled (as described below in the unacceptable confidence category) (Source: OHAT). **OR** - Numbers of individuals were not reported at important stages of study (*e.g.*, numbers of eligible participants included in the study or analysis sample, completing follow-up, and analyzed). Reasons were not provided for non-participation at each stage (STROBE Checklist Item 13 (Von Elm et al., 2008)). ***For case-control and cross-sectional studies:*** - The exclusion of subjects from analyses was moderate and unacceptably handled (as described below in the unacceptable confidence category). **OR** - Numbers of individuals were not reported at important stages of study (*e.g.*, numbers of eligible participants included in the study or analysis sample, completing follow-up, and analyzed). Reasons were not provided for non-participation at each stage (STROBE Checklist Item 13 (Von Elm et al., 2008)).
Critically Deficient	***For cohort studies:*** - There was large subject attrition during the study (or exclusion from the analysis sample). **OR** - Unacceptable handling of subject attrition: reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across study groups; or potentially inappropriate application of imputation (Source: OHAT). ***For case-control and cross-sectional studies:*** - There was large subject withdrawal from the study (or exclusion from the analysis sample). **OR** - Unacceptable handling of subject attrition: reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across study groups; or potentially inappropriate application of imputation.
Not Rated/Not Applicable	- Do not select for this metric.
Reviewer's Comments	Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance.

Data Quality Rating	Description
Metric 3. Comparison Group (selection, performance biases)	
High	***For ALL study types:*** - Any differences in baseline characteristics of groups were considered as potential confounding or stratification variables and were thereby controlled by statistical analysis (Source: OHAT). **OR** ***For cohort and cross-sectional studies:*** - Key elements of the study design are reported (*i.e.*, setting, inclusion and exclusion criteria, and methods of participant selection), and indicate that subjects were similar (*e.g.*, recruited from the same eligible population with the same method of ascertainment and within the same time frame using the same inclusion and exclusion criteria, and were of similar age and health status) (NTP, 2015). ***For case-control studies:*** - Key elements of the study design are reported indicate that that cases and controls were similar (*e.g.*, recruited from the same eligible population with the number of controls described, and eligibility criteria and are recruited within the same time frame (NTP, 2015). ***For studies reporting Standardized Mortality Ratios (SMRs) or Standardized Incidence Ratios (SIRs):*** - Age, sex (if applicable), and race (if applicable) adjustment or stratification is described and choice of reference population (*e.g.*, general population) is reported.
Medium	***For cohort studies and cross-sectional studies:*** - There is only indirect evidence (*e.g.*, stated by the authors without providing a description of methods) that groups are similar (as described above for the high confidence rating). **OR** - If there is potential for healthy worker effect. ***For case-control studies:*** - There is indirect evidence (*i.e.*, stated by the authors without providing a description of methods) that cases and controls are similar (as described above for the high confidence rating). ***For studies reporting SMRs or SIRs:*** - Age, sex (if applicable), and race (if applicable) adjustment or stratification is not specifically described in the text, but results tables are stratified by age and/or sex (*i.e.*, indirect evidence); choice of reference population (*e.g.*, general population) is reported.
Low	***For cohort and cross-sectional studies:*** - There is indirect evidence (*i.e.*, stated by the authors without providing a description of methods) that groups were not similar (as described above for the high confidence rating). **AND** - Differences between the exposure groups are not adequately controlled for in the statistical analysis. ***For case-control studies:***

Data Quality Rating	Description
	- There is indirect evidence (*i.e.*, stated by the authors without providing a description of methods) that cases and controls were not similar (as described above for the high confidence rating). **AND** - The characteristics of cases and controls are not reported (NTP, 2015). **AND** - Differences in groups is not adequately controlled for in the statistical analysis. ***For studies reporting SMRs or SIRs:*** - Indirect evidence of a lack of adjustment or stratification for age or sex (if applicable); indirect evidence that choice of reference population (*e.g.*, general population) is inappropriate.
Critically Deficient	***For cohort studies:*** - Subjects in all exposure groups were not similar. **OR** - Information was not reported to determine if participants in all exposure groups were similar (STROBE Checklist 6 (Von Elm et al., 2008)). **AND** - Potential differences in exposure groups were for a factor that was related to the outcome and not controlled for in the statistical analysis. **OR** - Subjects in the exposure groups had very different participation/response rates (NTP, 2015). **AND** - Participation rates were related to exposure and outcome ***For case-control studies:*** -Controls were drawn from a very dissimilar population than cases or recruited within very different time frames (NTP, 2015). **AND** -Potential differences in the case and control groups were not controlled for in the statistical analysis. **OR** - Rationale and/or methods for case and control selection, matching criteria including number of controls per case (if relevant) were not reported (STROBE Checklist 6 (Von Elm et al., 2008)). ***For cross-sectional studies:*** - Subjects in all exposure groups were not similar, recruited within very different time frames, or had very different participation/response rates (NTP, 2015). **AND** - Potential differences in exposure groups were not controlled for in the statistical analysis. **OR** - Sources and methods of selection of participants in all exposure groups were not reported (STROBE Checklist Item 13 (Von Elm et al., 2008)). ***For studies reporting SMRs or SIRs:*** - Lack of adjustment or stratification for both age and sex (if applicable), race (if applicable), and calendar time or choice of reference population (*e.g.*, general population) is not reported.

Data Quality Rating	Description
Not Rated/Not Applicable	- For mesothelioma studies, a comparison population is not required, as EPA's interest is in the absolute risk and not the relative risk. **All studies of mesothelioma allowing for evaluation of absolute risk should be labeled as "Not rated/not applicable"** -Only rate as NA if there is no mesothelioma comparison group. Otherwise, if the study includes a comparison group, rate this metric H, M, L, or U.
Reviewer's Comments	Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance.
Domain 2. Exposure Characterization	
Metric 4. Measurement of Exposure (detection/measurement/information, performance biases)	
High	***For all study types:*** - Quantitative estimates of exposure were consistently assessed (*i.e.*, using the same method and sampling timeframe) during multiple time periods and using either PCM or TEM. **OR** - A combination of methods were used over time (*i.e.*, midget impinger, PCM or TEM), but side by side sampling and analyses were conducted to develop appropriate conversion criteria. **AND** - For an occupational population, contains detailed employment records and quantitative estimates of exposure using either PCM or TEM which allows for construction of job-matrix for entire work history of exposure (*i.e.*, Cumulative or peak exposures, and time since first exposure).
Medium	***For all study types:*** - (Exposure was assessed during one time period but this time period is judged to be reasonably representative of the entire study time period. **AND** - Exposure was assessed using a combination of midget impingers, PCM, and/or TEM measurements, but side by side sampling and analyses were not conducted for all operations and thus there is a lack of confidence in the conversion factors.) **OR** - For an occupational study population, contains detailed employment records and quantitative estimates of exposure using a combination of midget impingers and PCM or TEM measurements 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.
Low	***For all study types:*** -Exposure was estimated solely using professional judgement. **OR** -The method of quantifying/counting fibers was not specified. **OR** - Exposure was directly measured (*e.g.*, midget impinger) and assessed using a quantitative method other than PCM or TEM and conversion factors were not determined.

Data Quality Rating	Description
Critically Deficient	***For all study types:*** - Methods used to quantify the exposure were not well defined, and sources of data and detailed methods of exposure assessment were not reported (STROBE Checklist 7 and 8 (Von Elm et al., 2008)). **OR** - There was no quantitative measure or estimate of exposure. **OR** - There is evidence of substantial exposure misclassification that would significantly bias the results.
Not Rated/Not Applicable	- Do not select for this metric.
Reviewer's Comments	Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance.
Metric 5. Exposure Levels (detection/measurement/information biases)	
High	- Do not select for this metric
Medium	***For all study types:*** - The range and distribution of exposure is sufficient or adequate to develop an exposure-response estimate (Cooper et al., 2016).
Low	***For all study types:*** - The range of exposure in the population is limited
Critically Deficient	***For all study types:*** - The range and distribution of exposure are not adequate to determine an exposure-response relationship (Cooper et al., 2016). **OR** - No description is provided on the levels or range of exposure.
Not Rated/Not Applicable	- Do not select for this metric.
Reviewer's Comments	Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance.
Metric 6. Temporality	
High	***For all study types:*** - The study presents an appropriate temporality between exposure and outcome (*i.e.*, the exposure precedes the disease). **AND** - The interval between the exposure (or reconstructed exposure) and the outcome is sufficiently long considering the latency of the disease (*i.e.*, study follow-up is more than 20 years for mesothelioma) (LaKind et al., 2014).
Medium	***For all study types except cross-sectional studies:*** - Temporality is established, but it is unclear whether there is adequate follow-up for consideration of latency (*i.e.*, only 15–20 years of follow-up) (LaKind et al., 2014).
Low	***For all study types:*** - The temporality of exposure and outcome is uncertain (10-15 years). **OR** - There is inadequate follow-up of the cohort considering the latency period.

Data Quality Rating	Description
Critically Deficient	***For all study types*:** - Study lacks an established time order, such that exposure is not likely to have occurred prior to outcome (LaKind et al., 2014). **OR** - There was inadequate follow-up of the cohort for the expected latency period (<10 years). **OR** - Sources of data and details of methods of assessment were not sufficiently reported (*e.g.*, duration of follow-up, periods of exposure, dates of outcome ascertainment, etc.) (Source: STROBE Checklist 8 (Von Elm et al., 2008)).
Not Rated/Not Applicable	- Do not select for this metric.
Reviewer's Comments	Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance.
Domain 3. Outcome Assessment	
Metric 7. Outcome Measurement or Characterization (detection/measurement/information, performance, reporting biases)	
High	***For all study types*:** The outcome was assessed using one or a combination of the following well-established methods: - Mesothelioma cases confirmed by histological or cytological means (including subtypes of mesothelioma) and/or - ICD-10 codes (3-digit) C45 or (4-digit) C45.x (C45.0, C45.1, C45.2, C45.7, C45.9) - All fields on the death certificates of cohort searched for 'mesothelioma' - Appropriate Pre-ICD 10 codes supplemented by additional evidence (*e.g.*, pathology/autopsy) see Table 1 of (Kopylev et al., 2011) - International Classification of Diseases for Oncology Third Edition (ICD-O-3) and Second Edition (ICD-O-2) codes are acceptable because ICD-O-3 and ICD-O-2 include mesothelioma-specific codes. - ICD-O-3 and ICD-O-2 codes 9050-9055 (note if designated as benign or malignant) are acceptable.
Medium	***For all study types*:** - Examined death certificates searched for mesothelioma for pre-ICD-10 codes that include pleura, peritoneum and site unspecified (ICD code 199)
Low	- Do not select for this metric.
Critically Deficient	***For all study types*:** - Numbers of outcome events or summary measures were not reported (Source: STROBE Checklist 15 (Von Elm et al., 2008) **OR** - Only pre ICD-10 codes (without additional information) were used for ascertainment of mesothelioma. **OR** - Examined death certificates searched for mesothelioma for codes that included only pleura and/or peritoneum **OR** - Study lacks individual assessment of mesothelioma (i.e, mesothelioma is assessed as a combination with other cancer types, excluding lung and bronchus or trachea) **OR** - Any self-reported information

Data Quality Rating	Description
Not Rated/Not Applicable	- Do not select for this metric.
Reviewer's Comments	Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance.
Metric 8. Reporting Bias	
High	***For all study types:*** - Mesothelioma findings are reported in the abstract, results or discussion. Effect estimates are reported with confidence intervals and/or standard errors, number of cases/controls or exposed/unexposed reported for each analysis, to be included in exposure-response analysis or fully tabulated during data extraction and analyses (NTP, 2015).
Medium	***For all study types:*** - All of the study's findings (primary and secondary) outlined in the abstract, results or discussion (that are relevant for the evaluation) are reported but not in a way that would allow for detailed extraction (*e.g.*, results were discussed in the text but accompanying data were not shown).
Low	***For all study types:*** - Mesothelioma outcomes outlined in the methods, abstract, and/or introduction (that are relevant for the evaluation) have not been reported (NTP, 2015).
Critically Deficient	- Do not select for this metric.
Not Rated/Not Applicable	- Do not select for this metric.
Reviewer's Comments	Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance.
Domain 4. Potential Confounding/Variability Control[a]	
Metric 9. Covariate Adjustment (confounding)	
High	***For all study types:*** - Appropriate adjustments or explicit considerations were made for potential confounders (*e.g.*, age, sex, SES, race, etc.) (excluding co-exposures, which are evaluated in metric 11) in the final analyses through the use of statistical models to reduce research-specific bias, including matching, adjustment in multivariate models, stratification, or other methods that were appropriately justified (NTP, 2015). ***For studies reporting SMRs or SIRs:*** - Adjustments are described and results are age-, race-, and sex-adjusted (or stratified) if applicable.

Data Quality Rating	Description
Medium	***For all study types:*** - There is indirect evidence that appropriate adjustments were made (*i.e.,* considerations were made for primary covariates (excluding co-exposures) and potential confounders adjustment) without providing a description of methods. **OR** - The distribution of potential confounders (excluding co-exposures) did not differ significantly between exposure groups or between cases and controls. **OR** - The major potential confounders (excluding co-exposures) were appropriately adjusted and any not adjusted for are considered not to appreciably bias the results (*e.g.*, smoking rates in an occupational cohort are expected to be generally similar in different departments and thus confounding by smoking is unlikely when internal analyses are applied). ***For studies reporting SMRs or SIRs:*** - Results are adjusted (or stratified) for age and sex, unless adjustment or stratification is not necessary because the exposed and control groups are sufficiently similar on the particular demographic variable.
Low	***For all study types:*** - There is indirect evidence (*i.e.,* no description is provided in the study) that considerations were not made for potential confounders adjustment in the final analyses (NTP, 2015). **AND** - The distribution of primary covariates (excluding co-exposures) and potential confounders was not reported between the exposure groups or between cases and controls (NTP, 2015). ***For studies reporting SMRs or SIRs:*** - Results are adjusted or stratified for age, race, **OR** sex (any one of the three), unless adjustment or stratification is not necessary because the exposed and control groups are sufficiently similar on the particular demographic variable.
Critically Deficient	***For all study types:*** - The distribution of potential confounders differed significantly between the exposure groups. **AND** - Confounding was demonstrated and was not appropriately adjusted for in the final analyses (NTP, 2015). ***For studies reporting SMRs or SIRs:*** - No discussion of adjustments. Results are not adjusted for both age and sex (or stratified) if applicable.
Not Rated/Not Applicable	- Rate this metric as "N/A" if no analyses of the association between exposure and outcome were performed or if there are no potential confounders.
Reviewer's Comments	Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance.

Data Quality Rating	Description
Metric 10. Covariate Characterization (measurement/information, confounding biases) For occupational studies, it can be assumed that personnel records were used to obtain covariate data if not otherwise specified.	
High	***For all study types:*** - Potential confounders (excluding co-exposures; *e.g.*, age, sex, SES) were assessed using valid and reliable methodology where appropriate (*e.g.*, validated questionnaires, biomarker).
Medium	***For all study types:*** - A less-established method was used to assess confounders (excluding co-exposures) and no method validation was conducted against well-established methods, but there was little to no evidence that that the method had poor validity and little to no evidence of confounding.
Low	***For all study types:*** - The confounder assessment method is an insensitive instrument or measure or a method of unknown validity.
Critically Deficient	***For all study types:*** - Confounders were assessed using a method or instrument known to be invalid.
Not Rated/Not Applicable	***For all study types:*** - Covariates were not assessed. **OR** - Metric 9 is rated "Not applicable"
Reviewer's Comments	Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance.
Metric 11. Co-exposure Reliability (measurement/information, confounding biases)	
High	- Do not select for this metric.
Medium	***For all study types:*** - Any co-exposures to pollutants that are not the target exposure that would likely bias the results were not likely to be present. **OR** - Co-exposures to pollutants were appropriately measured or either directly or indirectly adjusted for. - *Example:* There is confirmation of the likely absence of known co-exposures via mechanisms such as engineering controls (closed systems) for co-pollutants or confirmation of the absence of co-pollutants through monitoring.
Low	***For cohort and cross-sectional studies:*** - There is direct evidence that there was an unbalanced provision of additional co-exposures across the primary study groups, which were not appropriately adjusted for. ***For case-control studies:*** - There is direct evidence that there was an unbalanced provision of additional co-exposures across cases and controls, which were not appropriately adjusted for, and significant indication a biased exposure-outcome association. **OR** ***For all study types:*** In an occupational setting, potential co-exposures are not discussed.
Critically Deficient	- Do not select for this metric.

Data Quality Rating	Description
Not Rated/Not Applicable	- For mesothelioma studies, evaluations of potential confounders are not required as there are few other causes of mesothelioma (zeolites, viruses, therapeutic or diagnostic radiation) and none that are likely to be correlated in a dose-dependent manner with asbestos. **Evaluation of potential confounding in mesothelioma studies should be labeled as "Not rated/applicable" unless there is substantial information to indicate otherwise**.
Reviewer's Comments	Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance.
Domain 5. Analysis	
Metric 12. Study Design and Methods	
High	- Do not select for this metric.
Medium	***For all study types:*** - The study design chosen was appropriate for the research question. **OR** - The study uses an appropriate statistical method to address the research question(s) (*e.g.*, Cox and Poisson regression for cohort studies and logistic regression analysis for case-control studies.
Low	- Do not select for this metric.
Critically Deficient	***For all study types:*** - The study design chosen was not appropriate for the research question.
Not Rated/Not Applicable	- Do not select for this metric.
Reviewer's Comments	Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance.
Metric 13. Statistical Power (sensitivity)	
High	- Do not select for this metric.
Medium	***For cohort and cross-sectional studies:*** - The number of participants are adequate to detect an effect in the exposed population and/or subgroups of the total population. **OR** - The paper reported statistical power is high enough (≥ 80%) to detect an effect in the exposure population and/or subgroups of the total population. ***For case-control studies:*** - The number of cases and controls are adequate to detect an effect in the exposed population and/or subgroups of the total population. **OR** - The paper reported statistical power is high enough (≥ 80%) to detect an effect in the exposure population and/or subgroups of the total population.
Low	- Do not select for this metric.
Critically Deficient	***For cohort and cross-sectional studies:*** - The number of participants is inadequate to detect an effect in the exposed population and/or subgroups of the total population and the study was negative. ***For case-control studies:*** - The number of cases and controls are inadequate to detect an effect in the exposed population and/or subgroups of the total population and the study was negative.

Data Quality Rating	Description
Not Rated/Not Applicable	- For mesothelioma, EPA is primarily interested in the presentation of data collected in the study, rather than the statistical analysis. EPA will pool data across asbestos studies to conduct for the analysis of mesothelioma risk. Therefore, the power of individual studies will not be considered. This metric may be marked as not rated/applicable. - Mark as NA if there were no statistical analyses or models for mesothelioma. If no analyses were performed because (whether stated or implied) there wasn't sufficient statistical power to do analyses, be sure to note this in the comments.
Reviewer's Comments	Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance.
Metric 14. Reproducibility of Analyses (adapted from Blettner et al. (2001))	
High	- Do not select for this metric.
Medium	***For all study types:*** - The description of the analysis is sufficient to understand how to conceptually reproduce the analysis with access to the analytic data.
Low	***or all study types:*** - The description of the analysis is insufficient to understand what has been done and to be reproducible OR a description of analyses are not present (*e.g.*, statistical tests and estimation procedures were not described, variables used in the analysis were not listed, transformations of continuous variables (*e.g.*, logarithmic) were not explained, rules for categorization of continuous variables were not presented, exclusion of outliers was not elucidated and how missing values are dealt with was not mentioned).
Critically Deficient	- Do not select for this metric.
Not Rated/Not Applicable	- For mesothelioma, EPA is primarily interested in the presentation of data collected in the study, rather than the statistical analysis. If individual data elements (*e.g.*, time since first exposure, number of person-years, etc.) are present in the study that will allow EPA to conduct its own analysis, this metric may be marked as not rated/applicable. - Mark as NA if there were no statistical analyses or models for mesothelioma.
Reviewer's Comments	Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance.
Metric 15. Statistical Models (confounding bias)	
High	- Do not select for this metric.
Medium	***For all study types:*** - The model or method for calculating the risk estimates (*e.g.*, odds ratios, SMRs, SIR) is transparent (*i.e.*, it is stated how/why variables were included or excluded).
Low	***For all study types:*** - The statistical model building process is not fully appropriate **OR** model assumptions were not met **OR** a description of analyses and assumptions are not present (STROBE Checklist 12e (Von Elm et al., 2008)).
Critically Deficient	- Do not select for this metric.
Not Rated/Not Applicable	- For mesothelioma, EPA is primarily interested in the presentation of data collected in the study, rather than the statistical analysis. If individual data elements (*e.g.*, time since first exposure, number of person-years, etc.) are present in the study that will allow EPA to conduct its own analysis, this metric may be marked as not rated/applicable. - Mark as NA if there were no statistical analyses or models for mesothelioma.
Reviewer's Comments	Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance.

Data Quality Rating	Description
Domain 6. Other (if applicable) Considerations for Biomarker Selection and Measurement (LaKind et al., 2014)	
Metric 16. Use of Biomarker of Exposure (detection/measurement/information biases)	
High	- Biomarker in a specified matrix has accurate and precise quantitative relationship with external exposure, internal dose, or target dose. **AND** - Biomarker is derived from exposure to one parent chemical.
Medium	- Biomarker in a specified matrix has accurate and precise quantitative relationship with external exposure, internal dose, or target dose. **AND** - Biomarker is derived from multiple parent chemicals.
Low	- Evidence exists for a relationship between biomarker in a specified matrix and external exposure, internal dose or target dose, but there has been no assessment of accuracy and precision or none was reported.
Critically Deficient	- Biomarker in a specified matrix is a poor surrogate (low accuracy, specificity, and precision) for exposure/dose.
Not Rated/Not Applicable	- Select "N/A" if no human biological samples were assessed or if the only biomarkers assessed were biomarkers of effect or biomarkers of susceptibility.
Reviewer's Comments	Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance.
Metric 17. Effect Biomarker (detection/measurement/information biases)	
High	- Effect biomarker measured is an indicator of a key event in an adverse outcome pathway (AOP).
Medium	- Biomarkers of effect shown to have a relationship to health outcomes using well validated methods, but the mechanism of action is not understood.
Low	- Biomarkers of effect shown to have a relationship to health outcomes, but the method is not well validated and mechanism of action is not understood.
Critically Deficient	- Biomarker has undetermined consequences (*e.g.*, biomarker is not specific to a health outcome).
Not Rated/Not Applicable	- Select "N/A" if no human biological samples were assessed or if the only biomarkers assessed were biomarkers of exposure or biomarkers of susceptibility.
Reviewer's Comments	Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance.
Metric 18. Method Sensitivity (detection/measurement/information biases)	
High	- Do not select for this metric.
Medium	- Limits of detection are low enough to detect chemicals in a sufficient percentage of the samples to address the research question. Analytical methods measuring biomarker are adequately reported. The limit of detection (LOD) and limit of quantification (LOQ) (value or %) are reported.
Low	- Frequency of detection too low to address the research hypothesis. **OR** - LOD/LOQ (value or %) are not stated.
Critically Deficient	- Do not select for this metric.
Not Rated/Not Applicable	- Do not select "N/A" for this metric if the study assessed biomarkers. If LOD/LOQ are not stated then select Low.

Data Quality Rating	Description
Reviewer's Comments	Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance.
Metric 19. Biomarker Stability (detection/measurement/information biases)	
High	- Samples with a known storage history and documented stability data or those using real-time measurements.
Medium	- Samples have known losses during storage, but the difference between low and high exposures can be qualitatively assessed.
Low	- Samples with either unknown storage history and/or no stability data for target analytes and high likelihood of instability for the biomarker under consideration.
Critically Deficient	- Do not select for this metric.
Not Rated/Not Applicable	- Do not select "N/A" for this metric if the study assessed biomarkers.
Reviewer's Comments	Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance.
Metric 20. Sample Contamination (detection/measurement/information biases)	
High	- Samples are contamination-free from the time of collection to the time of measurement (*e.g.,* by use of certified analyte free collection supplies and reference materials, and appropriate use of blanks both in the field and lab). **AND** - Documentation of the steps taken to provide the necessary assurance that the study data are reliable is included.
Medium	- Samples are stated to be contamination-free from the time of collection to the time of measurement. **AND** - There is incomplete documentation of the steps taken to provide the necessary assurance that the study data are reliable. **OR** - Samples are known to have contamination issues, but steps have been taken to address and correct contamination issues. **OR** - There is no information included about contamination (only allowed for biomarker samples not susceptible to contamination).
Low	- Samples are known to have contamination issues, but steps have been taken to address and correct contamination issues. **OR** - Samples are stated to be contamination-free from the time of collection to the time of measurement, but there is no use or documentation of the steps taken to provide the necessary assurance that the study data are reliable.
Critically Deficient	- There are known contamination issues (*e.g.,* phthalate study that used plastic sample collection vials) and no documentation that the issues were addressed.
Not Rated/Not Applicable	- Do not select "N/A" for this metric if the study assessed biomarkers.
Reviewer's Comments	Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance.

Data Quality Rating	Description
Metric 21. Method Requirements (detection/measurement/information biases)	
High	- Instrumentation that provides unambiguous identification and quantitation of the biomarker at the required sensitivity (*e.g.*, gas chromatography/high-resolution mass spectrometry [GC–HRMS]; gas chromatography with tandem mass spectrometry [GC–MS/MS]; liquid chromatography with tandem mass spectrometry [LC–MS/MS]).
Medium	- Instrumentation that allows for identification of the biomarker with a high degree of confidence and the required sensitivity (*e.g.*, gas chromatography mass spectrometry [GC–MS], gas chromatography with electron capture detector [GC–ECD]).
Low	- Instrumentation that only allows for possible quantification of the biomarker, but the method has known interferants (*e.g.*, gas chromatography with flame-ionization detection [GC–FID], spectroscopy).
Critically Deficient	- Do not select for this metric.
Not Rated/Not Applicable	- Do not select "N/A" for this metric if the study assessed biomarkers.
Reviewer's Comments	Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance.
Metric 22. Matrix Adjustment (detection/measurement/information biases)	
High	- If applicable for the biomarker under consideration, study provides results, either in the main publication or as a supplement, for both adjusted and unadjusted matrix concentrations (*e.g.*, creatinine-adjusted or specific gravity-adjusted and non-adjusted urine concentrations) and reasons are given for adjustment approach.
Medium	- If applicable for the biomarker under consideration, study only provides results using one method (matrix-adjusted or not).
Low	- If applicable for the biomarker under consideration, no established method for matrix adjustment was conducted.
Critically Deficient	- Do not select for this metric.
Not Rated/Not Applicable	- If metrics 16 and 17 are both NA, then the remaining biomarker metrics are automatically not rated. Otherwise: Select "N/A" if matrix adjustment is not required for assessment of the biomarker.
Reviewer's Comments	Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance.

Table_Apx G-2. Other Outcomes Data Quality Evaluation Criteria

Data Quality Rating	Description
Domain 1. Study Participation	
Metric 1. Participant Selection (selection, performance biases)	
High	***For all study types:*** - All key elements of the study design are reported (*e.g.*, setting, participation rate described at all steps of the study, inclusion and exclusion criteria, and methods of participant selection or case ascertainment) **AND** - The reported information indicates that participant selection in or out of the study (or analysis sample) and participation was not likely to be biased (*i.e.*, the exposure-outcome distribution of the participants is likely representative of the exposure-outcome distributions in the population of persons eligible for inclusion in the study.)

Data Quality Rating	Description
Medium	***For all study types:*** - Some key elements of the study design were not present but available information indicates a low risk of selection bias (*i.e.*, the exposure-outcome distribution of the participants is likely representative of the exposure-outcome distributions in the population of persons eligible for inclusion in the study.)
Low	***For all study types:*** - Key elements of the study design and information on the population (*e.g.*, setting, participation rate described at most steps of the study, inclusion and exclusion criteria, and methods of participant selection or case ascertainment) are not reported (STROBE Checklist 4, 5, and 6 (Von Elm et al., 2008)). - If the study provides little to no information about selection criteria, then rate this metric as Low.
Critically Deficient	***For all study types:*** The reported information indicates that selection in or out of the study (or analysis sample) and participation was likely to be significantly biased (*i.e.*, the exposure-outcome distribution of the participants is likely not representative of the exposure-outcome distributions of the population of persons eligible for inclusion in the study).
Not Rated/Not Applicable	- Do not select for this metric.
Reviewer's Comments	Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance.
Metric 2. Attrition (missing data/attrition/exclusion, reporting biases)	
High	***For cohort studies:*** - There was minimal subject loss to follow up during the study (or exclusion from the analysis sample) and outcome and exposure data were largely complete. **OR** - Any loss of subjects (*i.e.*, incomplete outcome data) or missing exposure and outcome data were adequately* addressed (as described below) and reasons were documented when human subjects were removed from a study (NTP, 2015). **OR** - Missing data have been imputed using appropriate methods (*e.g.*, multiple imputation methods), and characteristics of subjects lost to follow up or with unavailable records are not significantly different from those of the study participants (NTP, 2015). ***For case-control studies and cross-sectional studies:*** - There was minimal subject withdrawal from the study (or exclusion from the analysis sample) and outcome data and exposure were largely complete. **OR** - Any exclusion of subjects from analyses was adequately* addressed (as described below), and reasons were documented when subjects were removed from the study or excluded from analyses (NTP, 2015). ***NOTE for all study types:** Adequate handling of subject attrition can include: Use of imputation methods for missing outcome and exposure data; reasons for missing subjects unlikely to be related to outcome (for survival data, censoring was unlikely to introduce bias); missing outcome data balanced in numbers across study groups, with similar reasons for missing data across groups.
Medium	***For cohort studies:*** - There was moderate subject loss to follow up during the study (or exclusion from the analysis sample) or outcome and exposure data were nearly complete.

Data Quality Rating	Description
	AND - Any loss or exclusion of subjects was adequately addressed (as described in the acceptable handling of subject attrition in the high confidence category) and reasons were documented when human subjects were removed from a study. ***For case-control studies and cross-sectional studies:*** - There was moderate subject withdrawal from the study (or exclusion from the analysis sample), but outcome and exposure data were largely complete **AND** - Any exclusion of subjects from analyses was adequately addressed (as described above), and reasons were documented when subjects were removed from the study or excluded from analyses (NTP, 2015).
Low	***For cohort studies:*** - The loss of subjects (*e.g.*, loss to follow up, incomplete outcome or exposure data) was moderate and unacceptably handled (as described below in the unacceptable confidence category) (Source: OHAT). **OR** - Numbers of individuals were not reported at important stages of study (*e.g.*, numbers of eligible participants included in the study or analysis sample, completing follow-up, and analyzed). Reasons were not provided for non-participation at each stage (STROBE Checklist Item 13 (Von Elm et al., 2008)). ***For case-control and cross-sectional studies:*** - The exclusion of subjects from analyses was moderate and unacceptably handled (as described below in the unacceptable confidence category). **OR** - Numbers of individuals were not reported at important stages of study (*e.g.*, numbers of eligible participants included in the study or analysis sample, completing follow-up, and analyzed). Reasons were not provided for non-participation at each stage (STROBE Checklist Item 13 (Von Elm et al., 2008)).
Critically Deficient	***For cohort studies:*** There was large subject attrition during the study (or exclusion from the analysis sample). **OR** - Unacceptable handling of subject attrition: reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across study groups; or potentially inappropriate application of imputation (Source: OHAT). ***For case-control and cross-sectional studies:*** - There was large subject withdrawal from the study (or exclusion from the analysis sample). **OR** - Unacceptable handling of subject attrition: reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across study groups; or potentially inappropriate application of imputation.
Not Rated/Not Applicable	- Do not select for this metric.
Reviewer's Comments	Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance.

Data Quality Rating	Description
Metric 3. Comparison Group (selection, performance biases)	
High	***For ALL study types:*** - Any differences in baseline characteristics of groups were considered as potential confounding or stratification variables and were thereby controlled by statistical analysis (Source: OHAT). **OR** ***For cohort and cross-sectional studies:*** - Key elements of the study design are reported (*i.e.*, setting, inclusion and exclusion criteria, and methods of participant selection), and indicate that subjects were similar (*e.g.*, recruited from the same eligible population with the same method of ascertainment and within the same time frame using the same inclusion and exclusion criteria, and were of similar age and health status) (NTP, 2015). ***For case-control studies:*** - Key elements of the study design are reported indicate that that cases and controls were similar (*e.g.*, recruited from the same eligible population with the number of controls described, and eligibility criteria and are recruited within the same time frame (NTP, 2015). ***For studies reporting SMRs or SIRs:*** - Age, sex (if applicable), and race (if applicable) adjustment or stratification is described and choice of reference population (*e.g.*, general population) is reported.
Medium	-If there is substantial potential for healthy worker effect. **OR** ***For cohort studies and cross-sectional studies:*** - There is only indirect evidence (*e.g.*, stated by the authors without providing a description of methods) that groups are similar (as described above for the high confidence rating). ***For case-control studies:*** - There is indirect evidence (*i.e.*, stated by the authors without providing a description of methods) that cases and controls are similar (as described above for the high confidence rating). ***For studies reporting SMRs or SIRs:*** - Age, sex (if applicable), and race (if applicable) adjustment or stratification is not specifically described in the text, but results tables are stratified by age and/or sex (*i.e.*, indirect evidence); choice of reference population (*e.g.*, general population) is reported.

Data Quality Rating	Description
Low	***For cohort and cross-sectional studies:*** - There is indirect evidence (*i.e.*, stated by the authors without providing a description of methods) that groups were not similar (as described above for the high confidence rating). **AND** - Differences between the exposure groups are not adequately controlled for in the statistical analysis. ***For case-control studies:*** - There is indirect evidence (*i.e.*, stated by the authors without providing a description of methods) that cases and controls were not similar (as described above for the high confidence rating). **AND** - The characteristics of cases and controls are not reported (NTP, 2015). **AND** - Differences in groups is not adequately controlled for in the statistical analysis. ***For studies reporting SMRs or SIRs:*** - Indirect evidence of a lack of adjustment or stratification for age or sex (if applicable); indirect evidence that choice of reference population (*e.g.*, general population) is inappropriate.
Critically Deficient	***For cohort studies:*** - Subjects in all exposure groups were not similar. **OR** - Information was not reported to determine if participants in all exposure groups were similar (STROBE Checklist 6 (Von Elm et al., 2008)). **AND** - Potential differences in exposure groups were for a factor that was related to the outcome and not controlled for in the statistical analysis. **OR** - Subjects in the exposure groups had very different participation/response rates (NTP, 2015). **AND** - Participation rates were related to exposure and outcome ***For case-control studies:*** -Controls were drawn from a very dissimilar population than cases or recruited within very different time frames (NTP, 2015). **AND** -Potential differences in the case and control groups were not controlled for in the statistical analysis. **OR** - Rationale and/or methods for case and control selection, matching criteria including number of controls per case (if relevant) were not reported (STROBE Checklist 6 (Von Elm et al., 2008)). ***For cross-sectional studies:*** - Subjects in all exposure groups were not similar, recruited within very different time frames, or had very different participation/response rates (NTP, 2015). **AND** - Potential differences in exposure groups were not controlled for in the statistical analysis.

Data Quality Rating	Description
	OR - Sources and methods of selection of participants in all exposure groups were not reported (STROBE Checklist 6 (Von Elm et al., 2008)). ***For studies reporting SMRs or SIRs:*** - Lack of adjustment or stratification for both age and sex (if applicable), race (if applicable), and calendar time or choice of reference population (*e.g.*, general population) is not reported.
Not Rated/Not Applicable	- Do not select for this metric.
Reviewer's Comments	Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance.
Domain 2. Exposure Characterization	
Metric 4. Measurement of Exposure (detection/measurement/information, performance biases)	
High	***For all study types:*** - Quantitative estimates of exposure were consistently assessed (*i.e.*, using the same method and sampling timeframe) during multiple time periods and using either PCM or TEM. **OR** - A combination of methods were used over time (*i.e.*, midget impinger, PCM or TEM), but side by side sampling and analyses were conducted to develop appropriate conversion criteria. **AND** - For an occupational population, contains detailed employment records and quantitative estimates of exposure using either PCM or TEM which allows for construction of job-matrix for entire work history of exposure (*i.e.*, Cumulative or peak exposures, and time since first exposure).
Medium	***For all study types:*** - (Exposure was assessed during one time period but this time period is judged to be reasonably representative of the entire study time period. **AND** - Exposure was assessed using a combination of midget impingers, PCM, and/or TEM measurements, but side by side sampling and analyses were not conducted for all operations and thus there is a lack of confidence in the conversion factors.) **OR** - For an occupational study population, contains detailed employment records and quantitative estimates of exposure using a combination of midget impingers and PCM or TEM measurements 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.
Low	***For all study types:*** -Exposure was estimated solely using professional judgement. **OR** - Exposure was directly measured and assessed using a quantitative method other than PCM or TEM and conversion factors were not determined. **OR** -The method of quantifying/counting fibers was not specified (PCM, TEM, or other method not specified)

Data Quality Rating	Description
Critically Deficient	***For all study types:*** - Methods used to quantify the exposure were not well defined, and sources of data and detailed methods of exposure assessment were not reported (STROBE Checklist 7 and 8 (Von Elm et al., 2008)). **OR** - There was no quantitative measure or estimate of exposure. **OR** - There is evidence of substantial exposure misclassification that would significantly bias the results.
Not Rated/Not Applicable	- Do not select for this metric.
Reviewer's Comments	Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance.
Metric 5. Exposure Levels (detection/measurement/information biases)	
High	- Do not select for this metric
Medium	***For all study types:*** - The range and distribution of exposure is sufficient or adequate to develop an exposure-response estimate (Cooper et al., 2016). **AND** - Reports 3 or more levels of exposure (*i.e.*, referent group +2 or more) or an exposure-response model using a continuous measure of exposure.
Low	***For all study types:*** - The range of exposure in the population is limited **OR** - Reports 2 levels of exposure (*e.g.*, exposed/unexposed)) (Cooper et al., 2016) (Source: IRIS)
Critically Deficient	***For all study types:*** - The range and distribution of exposure are not adequate to determine an exposure-response relationship (Cooper et al., 2016). **OR** - No description is provided on the levels or range of exposure.
Not Rated/Not Applicable	- Do not select for this metric.
Reviewer's Comments	Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance.
Metric 6. Temporality (detection/measurement/information biases)	
High	***For all study types:*** - The study presents an appropriate temporality between exposure and outcome (*i.e.*, the exposure precedes the disease). **AND** - The interval between the exposure (or reconstructed exposure) and the outcome is sufficiently long considering the latency of the disease (*i.e.*, study follow-up is more than 15 years for lung cancer) (LaKind et al., 2014).
Medium	***For all study types except cross-sectional studies:*** - Temporality is established, but it is unclear whether there is adequate follow-up for consideration of latency (*i.e.*, only 10 years of follow-up) (LaKind et al., 2014).
Low	***For all study types:*** - The temporality of exposure and outcome is uncertain.

Data Quality Rating	Description
	OR - There is inadequate follow-up of the cohort considering the latency period (5-10 years of follow-up).
Critically Deficient	***For all study types*:** - Study lacks an established time order, such that exposure is not likely to have occurred prior to outcome (LaKind et al., 2014). **OR** - There was inadequate follow-up of the cohort for the expected latency period (<5 years). **OR** - Sources of data and details of methods of assessment were not sufficiently reported (*e.g.*, duration of follow-up, periods of exposure, dates of outcome ascertainment, etc.) (Source: STROBE Checklist 8 (Von Elm et al., 2008)).
Not Rated/Not Applicable	- Do not select for this metric.
Reviewer's Comments	Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance.
Domain 3. Outcome Assessment	
Each of the following outcomes has separate criteria for Metric 7: Lung Cancer, Ovarian Cancer, Laryngeal Cancer, Other Cancer(s), Asbestosis, Pulmonary Function/Spirometry Results, Pleural Plaques, and Other Non-cancer Outcomes (Mesothelioma criteria are on the Mesothelioma Form)	
Metric 7. Outcome Measurement or Characterization (detection/measurement/information, performance, reporting biases): **Lung Cancer**	
High	***For all study types*:** - The outcome was assessed using one or a combination of the following well-established methods: o Lung cancer cases confirmed by histological or cytological means (including subtypes of lung cancer) o ICD-10 C34 (lung and bronchus with or without C33 (trachea) o ICD-9 (5-digit code) 162.2-162.9 or o ICD-8 (4-digit code) 162.1 or o ICD-7 (4-digit code) 162.1 and 163 o ICD-9 (3-digit code) 162 o ICD-8 (3-digit code) 162 o ICD-7 (3-digit code) 162 and 163
Medium	***For all study types*:** - Although authors state they identified lung cancer cases they did not use or report the ICD codes or cases were not confirmed by histological or cytological means.
Low	- Do not select for this metric
Critically Deficient	***For all study types*:** - Any self-reported information. OR - Study lacks individual assessment of lung cancer (*i.e.*, lung cancer is assessed as a combination of cancer types, excluding lung and bronchus or trachea).
Not Rated/Not Applicable	- The study did not assess lung cancer.
Reviewer's Comments	Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance.

Data Quality Rating	Description
Metric 7. Outcome Measurement or Characterization (detection/measurement/information, performance, reporting biases): **Ovarian Cancer**	
High	***For all study types:*** -The outcome was assessed using one or a combination of the following well-established methods: o Ovarian cancer cases confirmed by tissue biopsy o ICD-11 2C73 Malignant neoplasm of ovary o ICD-10 C56 Malignant neoplasm of ovary o ICD-9 183 Malignant neoplasm of ovary o ICD-8 183 Malignant neoplasm of ovary, fallopian tube and broad ligament, supplemented by additional information to validate a diagnosis of ovarian cancer. o Pre-ICD-8 codes supplemented by additional information to validate a diagnosis of ovarian cancer. o All fields on the death certificate were searched for a diagnosis of ovarian cancer.
Medium	***For all study types:*** - Other diagnostic methods such as imaging tests (ultrasound or CT scan) or CA-125 blood tests were used without confirmation by tissue biopsy. OR - The study reports a doctor diagnosis without additional details or validation.
Low	- Do not select for this metric
Critically Deficient	***For all study types:*** - The only included information is a self-reported diagnosis of ovarian cancer without any additional validation.
Not Rated/Not Applicable	- The study did not assess ovarian cancer.
Reviewer's Comments	Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance.

Data Quality Rating	Description
Metric 7. Outcome Measurement or Characterization (detection/measurement/information, performance, reporting biases): **Laryngeal Cancer**	
High	***For all study types:*** - The outcome was assessed using one or a combination of the following well-established methods: o Laryngeal cancer cases confirmed by tissue biopsy. o ICD-11 2C23 Malignant neoplasm of larynx o ICD-10 C32 Malignant neoplasm of larynx o ICD-9 161 Malignant neoplasm of larynx o ICD-8 132 Malignant neoplasm of larynx o ICD-7 161 Malignant neoplasm of larynx o Pre-ICD-7 codes supplemented by additional information to validate a diagnosis of laryngeal cancer. o All fields on the death certificate were searched for a diagnosis of laryngeal cancer.
Medium	***For all study types:*** - Other diagnostic methods were used without confirmation by tissue biopsy. **OR** - Doctor diagnosis without additional details or validation.
Low	- Do not select for this metric
Critically Deficient	***For all study types:*** - The only included information is a self-reported diagnosis of laryngeal cancer without any additional validation.
Not Rated/Not Applicable	- The study did not assess laryngeal cancer.
Reviewer's Comments	Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance.
Metric 7. Outcome Measurement or Characterization (detection/measurement/information, performance, reporting biases): **Other Cancer Outcomes**	
High	***For all study types:*** - The cancer was assessed using well-established methods, such as one or a combination of the following: specific ICD Codes cases confirmed using histological or cytological methods, other lab tests, or diagnostic imaging. **OR** - All fields on the death certificate were searched for the specific diagnosis.
Medium	***For all study types:*** - The authors state that they identified a specific health outcome, but less-established methods were used and they did not conduct method validation. **AND** - There is little to no evidence that the method had poor validity and little to no evidence of outcome misclassification. **OR** - There was a doctor's report or diagnosis, but no ICD code and no additional confirmation or validation of the diagnosis.
Low	- Do not select for this metric
Critically Deficient	***For all study types:*** - The study lacks individual assessment of specific cancer types (*i.e.*, the specific cancer is assessed as a combination with other cancer types).

Data Quality Rating	Description
	OR - Only self-reported information was included, without any validation.
Not Rated/Not Applicable	- The study did not assess other cancer outcomes.
Reviewer's Comments	Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance.
Metric 7. Outcome Measurement or Characterization (detection/measurement/information, performance, reporting biases): **Asbestosis**	
High	***For all study types:*** - The outcome was assessed using one or a combination of the following well-established methods: Diagnostic imaging tests (such as chest x-rays or computed tomography (CT) scans) showing pulmonary fibrosis or scarring of the lung tissue. ICD-11 code CA60.2 Pneumoconiosis due to mineral fibers including asbestos o ICD-10 Code J61 Pneumoconiosis due to asbestos and other mineral fibers o ICD-9 Code 501 Asbestosis o ICD-8 515.2 Asbestosis o Pre-ICD-8 codes supplemented by additional information to validate a diagnosis of asbestosis o All fields on the death certificate were searched for a diagnosis of asbestosis.
Medium	***For all study types:*** - The authors report doctor-diagnosed asbestosis but do not report specific evidence of lung tissue scarring or ICD codes.
Low	- A less valid method was used to diagnose asbestosis without confirmation using imaging tests.
Critically Deficient	***For all study types:*** - The only included information is a self-reported diagnosis of asbestosis without any additional validation.
Not Rated/Not Applicable	- The study did not assess asbestosis.
Reviewer's Comments	Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance.
Metric 7. Outcome Measurement or Characterization (detection/measurement/information, performance, reporting biases): **Pulmonary Function/Spirometry Testing Results**	
High	***For all study types:*** - The outcome was assessed using well established methods that include standardized spirometric measurements (FEV1, FVC) and/or diffusing capacity of the lungs for carbon monoxide (DLCO) measurements. Forced expiratory Volume in 1s (FEV1) and Forced Vital Capacity (FVC) (Finnish Institute of Occupational Health, 2014).
Medium	***For all study types:*** - Use of less sensitive and standard methods such as low scanning electron microscopy (SEM), which lacks sensitivity and standardization as it relates to pulmonary function. - There is little to no evidence that the method had poor validity and little to no evidence of outcome misclassification.
Low	- Do not select for this metric

Data Quality Rating	Description
Critically Deficient	***For all study types*:** - Any self-reported information without additional validation. - Study lacks individual assessment of pulmonary function and does not use spirometry testing
Not Rated/Not Applicable	- The study did not assess pulmonary function.
Reviewer's Comments	Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance.
Metric 7. Outcome Measurement or Characterization (detection/measurement/information, performance, reporting biases): **Pleural Abnormalities, Pleural Plaques, or Parenchymal Opacities**	
High	***For all study types*:** - The outcome was assessed using well-established methods such as x-rays or high-resolution computed tomography (HRCT), with cases defined based on consensus of two or more B-readers* (blinded) for any pleural abnormality or parenchymal opacities (ILO, 2000). **OR** ○ ICD-11 Code CB20 Pleural Plaque ○ ICD-10 Code CM J92 Pleural Plaque **OR** ○ All fields on the death certificate were searched for the specific diagnosis.
Medium	***For all study types*:** - The outcome was assessed using x-rays or HRCT methods: cases defined as one B-reader assessment (with either blinding reported or not) for any pleural abnormality or parenchymal opacities. **OR** - There was a doctor's report or diagnosis but using other less-established methods.
Low	- Do not select for this metric
Critically Deficient	***For all study types*:** - The study lacks assessment of any of the specific pleural abnormality types (*i.e.*, costophrenic angle obliteration or diffuse pleural thickening) or parenchymal opacities (*i.e.*, small opacities or large opacities). **OR** - Only self-reported information without any validation.
Not Rated/Not Applicable	- The study did not assess pleural abnormalities, pleural plaques, or parenchymal opacities.
Reviewer's Comments	Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance.

Data Quality Rating	Description
Metric 7. Outcome Measurement or Characterization (detection/measurement/information, performance, reporting biases): **Other Non-cancer Outcomes**	
High	***For all study types:*** - The outcome was assessed using well-established methods, such as one or a combination of the following: specific ICD Codes, cases confirmed using histological or cytological methods, other lab tests, or diagnostic imaging. **OR** - All fields on the death certificate were searched for the specific diagnosis.
Medium	***For all study types:*** - The authors state that they identified a specific health outcome, but less-established methods were used and they did not conduct method validation. **AND** - There is little to no evidence that the method had poor validity and little to no evidence of outcome misclassification. **OR** - There was a doctor's report or diagnosis, but no ICD code and no additional confirmation or validation of the diagnosis.
Low	- Do not select for this metric
Critically Deficient	***For all study types:*** - Only self-reported information was included, without any validation.
Not Rated/Not Applicable	- The study did not assess other non-cancer outcomes.
Reviewer's Comments	Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance.
Metric 8. Reporting Bias	
High	***For all study types:*** - Findings are reported in the abstract, results or discussion. Effect estimates are reported with confidence intervals and/or standard errors, number of cases/controls or exposed/unexposed reported for each analysis, to be included in exposure-response analysis or fully tabulated during data extraction and analyses (NTP, 2015).
Medium	***For all study types:*** - All of the study's findings (primary and secondary) outlined in the abstract, results or discussion (that are relevant for the evaluation) are reported but not in a way that would allow for detailed extraction (*e.g.*, results were discussed in the text but accompanying data were not shown).
Low	***For all study types:*** - Outcomes outlined in the methods, abstract, and/or introduction (that are relevant for the evaluation) have not been reported (NTP, 2015).
Critically Deficient	- Do not select for this metric
Not Rated/Not Applicable	- Do not select for this metric.
Reviewer's Comments	Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance.

Data Quality Rating	Description
Domain 4. Potential Confounding/Variability Control[a]	
Metric 9. Covariate Adjustment (confounding)	
High	***For all study types:*** - Appropriate adjustments or explicit considerations were made for potential confounders (*e.g.*, age, sex, SES, race, etc.) (excluding co-exposures, which are evaluated in metric 11) in the final analyses through the use of statistical models to reduce research-specific bias, including matching, adjustment in multivariate models, stratification, or other methods that were appropriately justified (NTP, 2015). ***For studies reporting SMRs or SIRs:*** - Adjustments are described and results are age-, race-, and sex-adjusted (or stratified) if applicable.
Medium	***For all study types:*** - There is indirect evidence that appropriate adjustments were made (*i.e.*, considerations were made for primary covariates (excluding co-exposures) and potential confounders adjustment) without providing a description of methods. **OR** - The distribution of potential confounders (excluding co-exposures) did not differ significantly between exposure groups or between cases and controls. **OR** - The major potential confounders (excluding co-exposures) were appropriately adjusted (*e.g.*, SMRs, SIRs, etc.) and any not adjusted for are considered not to appreciably bias the results (*e.g.*, smoking rates in an occupational cohort are expected to be generally similar in different departments and thus confounding by smoking is unlikely when internal analyses are applied). ***For studies reporting SMRs or SIRs:*** - Results are adjusted (or stratified) for age and sex, unless adjustment or stratification is not necessary because the exposed and control groups are sufficiently similar on the particular demographic variable.
Low	***For all study types:*** - There is indirect evidence (*i.e.*, no description is provided in the study) that considerations were not made for potential confounders adjustment in the final analyses (NTP, 2015). **AND** - The distribution of primary covariates (excluding co-exposures) and potential confounders was not reported between the exposure groups or between cases and controls (NTP, 2015). ***For studies reporting SMRs or SIRs:*** - Results are adjusted or stratified for age, race, **OR** sex (any one of the three), unless adjustment or stratification is not necessary because the exposed and control groups are sufficiently similar on the particular demographic variable.
Critically Deficient	***For all study types:*** - The distribution of potential confounders differed significantly between the exposure groups. **AND** - Confounding was demonstrated and was not appropriately adjusted for in the final analyses (NTP, 2015). ***For studies reporting SMRs or SIRs:*** - No discussion of adjustments. Results are not adjusted for both age and sex (or stratified) if applicable.

Data Quality Rating	Description
Not Rated/Not Applicable	- Do not select for this metric
Reviewer's Comments	Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance.
Metric 10. Covariate Characterization (measurement/information, confounding biases)	
High	***For all study types:*** - Potential confounders (*e.g.*, age, sex, SES), excluding co-exposures, were assessed using valid and reliable methodology where appropriate (*e.g.*, validated questionnaires, biomarker).
Medium	***For all study types:*** - A less-established method was used to assess confounders (excluding co-exposures) and no method validation was conducted against well-established methods, but there was little to no evidence that that the method had poor validity and little to no evidence of confounding.
Low	***For all study types:*** - The confounder assessment method is an insensitive instrument or measure or a method of unknown validity.
Critically Deficient	***For all study types:*** - Confounders were assessed using a method or instrument known to be invalid.
Not Rated/Not Applicable	***For all study types:*** - Covariates were not assessed.
Reviewer's Comments	Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance.
Metric 11. Co-exposure Confounding (measurement/information, confounding biases)	
High	- Do not select for this metric.
Medium	***For all study types:*** - Any co-exposures to pollutants that are not the target exposure that would likely bias the results were not likely to be present. **OR** - Co-exposures to pollutants were appropriately measured and either directly or indirectly adjusted for. - *Example*: There is confirmation of the likely absence of known co-exposures via mechanisms such as engineering controls (closed systems) for co-pollutants or confirmation of the absence of co-pollutants through monitoring.
Low	***For cohort and cross-sectional studies:*** - There is direct evidence that there was an unbalanced provision of additional co-exposures across the primary study groups, which were not appropriately adjusted for. ***For case-control studies:*** - There is direct evidence that there was an unbalanced provision of additional co-exposures across cases and controls, which were not appropriately adjusted for, and significant indication a biased exposure-outcome association. **OR** ***For all study types*:** - In an occupational setting, potential co-exposures are not discussed.
Critically Deficient	- Do not select for this metric
Not Rated/Not Applicable	- Enter "N/A" and do not score this metric.

Data Quality Rating	Description
Reviewer's Comments	Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance.
Domain 5. Analysis	
Metric 12. Study Design and Methods	
High	- Do not select for this metric.
Medium	***For all study types:*** - The study design chosen was appropriate for the research question. **OR** - The study uses an appropriate statistical method to address the research question(s) (*e.g.*, Cox and Poisson regression for cohort studies and logistic regression analysis for case-control studies.
Low	- Do not select for this metric.
Critically Deficient	***For all study types:*** - The study design chosen was not appropriate for the research question. **OR** - Inappropriate statistical analyses were applied to assess the research questions.
Not Rated/Not Applicable	- Do not select for this metric.
Reviewer's Comments	Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance.
Metric 13. Statistical Power (sensitivity)	
High	- Do not select for this metric.
Medium	***For cohort and cross-sectional studies:*** - The number of participants are adequate to detect an effect in the exposed population and/or subgroups of the total population. **OR** - The paper reported statistical power is high enough (≥ 80%) to detect an effect in the exposure population and/or subgroups of the total population. ***For case-control studies:*** - The number of cases and controls are adequate to detect an effect in the exposed population and/or subgroups of the total population. **OR** - The paper reported statistical power is high enough (≥80%) to detect an effect in the exposure population and/or subgroups of the total population.
Low	- Do not select for this metric.
Critically Deficient	***For cohort and cross-sectional studies:*** - The number of participants is inadequate to detect an effect in the exposed population and/or subgroups of the total population and the study was negative. ***For case-control studies:*** - The number of cases and controls are inadequate to detect an effect in the exposed population and/or subgroups of the total population and the study was negative.
Not Rated/Not Applicable	- Do not select for this metric.
Reviewer's Comments	Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance

Data Quality Rating	Description
Metric 14. Reproducibility of Analyses (adapted from Blettner et al. (2001))	
High	- Do not select for this metric.
Medium	***For all study types:*** - The description of the analysis is sufficient to understand how to conceptually reproduce the analysis with access to the analytic data.
Low	***For all study types:*** - The description of the analysis is insufficient to understand what has been done and to be reproducible OR a description of analyses are not present (*e.g.*, statistical tests and estimation procedures were not described, variables used in the analysis were not listed, transformations of continuous variables (*e.g.*, logarithmic) were not explained, rules for categorization of continuous variables were not presented, exclusion of outliers was not elucidated and how missing values are dealt with was not mentioned).
Critically Deficient	- Do not select for this metric.
Not Rated/Not Applicable	- Do not select for this metric
Reviewer's Comments	Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance.
Metric 15. Statistical Models (confounding bias)	
High	- Do not select for this metric.
Medium	***For all study types:*** - The model or method for calculating the risk estimates (*e.g.*, odds ratios, SMRs, SIR) is transparent (*i.e.*, it is stated how/why variables were included or excluded). **AND** - Model assumptions were met.
Low	***For all study types:*** - The statistical model building process is not fully appropriate **OR** model assumptions were not met **OR** a description of analyses and assumptions are not present (STROBE Checklist 12e (Von Elm et al., 2008)).
Critically Deficient	- Do not select for this metric.
Not Rated/Not Applicable	- Enter "N/A" if the study did not use a statistical model.
Reviewer's Comments	Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance.
Domain 6. Other (if applicable) Considerations for Biomarker Selection and Measurement (LaKind et al., 2014)	
Metric 16. Use of Biomarker of Exposure (detection/measurement/information biases)	
High	- Biomarker in a specified matrix has accurate and precise quantitative relationship with external exposure, internal dose, or target dose. **AND** - Biomarker is derived from exposure to one parent chemical.
Medium	- Biomarker in a specified matrix has accurate and precise quantitative relationship with external exposure, internal dose, or target dose. **AND** - Biomarker is derived from multiple parent chemicals.
Low	- Evidence exists for a relationship between biomarker in a specified matrix and external exposure, internal dose or target dose, but there has been no assessment of accuracy and precision or none was reported.

Data Quality Rating	Description
Critically Deficient	- Biomarker in a specified matrix is a poor surrogate (low accuracy, specificity, and precision) for exposure/dose.
Not Rated/Not Applicable	- Select "N/A" if no human biological samples were assessed or if the only biomarkers assessed were biomarkers of effect or biomarkers of susceptibility.
Reviewer's Comments	Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance.
Metric 17. Effect Biomarker (detection/measurement/information biases)	
High	- Effect biomarker measured is an indicator of a key event in an adverse outcome pathway (AOP).
Medium	- Biomarkers of effect shown to have a relationship to health outcomes using well validated methods, but the mechanism of action is not understood.
Low	- Biomarkers of effect shown to have a relationship to health outcomes, but the method is not well validated and mechanism of action is not understood.
Critically Deficient	- Biomarker has undetermined consequences (*e.g.*, biomarker is not specific to a health outcome).
Not Rated/Not Applicable	- Select "N/A" if no human biological samples were assessed or if the only biomarkers assessed were biomarkers of exposure or biomarkers of susceptibility.
Reviewer's Comments	Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance.
Metric 18. Method Sensitivity (detection/measurement/information biases)	
High	- Do not select for this metric.
Medium	- Limits of detection are low enough to detect chemicals in a sufficient percentage of the samples to address the research question. Analytical methods measuring biomarker are adequately reported. The limit of detection (LOD) and limit of quantification (LOQ) (value or %) are reported.
Low	- Frequency of detection too low to address the research hypothesis. **OR** - LOD/LOQ (value or %) are not stated.
Critically Deficient	- Do not select for this metric.
Not Rated/Not Applicable	- Do not select "N/A" for this metric if the study assessed biomarkers. If LOD/LOQ are not stated then select Low.
Reviewer's Comments	Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance.
Metric 19. Biomarker Stability (detection/measurement/information biases)	
High	- Samples with a known storage history and documented stability data or those using real-time measurements.
Medium	- Samples have known losses during storage, but the difference between low and high exposures can be qualitatively assessed.
Low	- Samples with either unknown storage history and/or no stability data for target analytes and high likelihood of instability for the biomarker under consideration.
Critically Deficient	- Do not select for this metric.
Not Rated/Not Applicable	- Do not select "N/A" for this metric if the study assessed biomarkers.
Reviewer's Comments	Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance.

Data Quality Rating	Description
Metric 20. Sample Contamination (detection/measurement/information biases)	
High	- Samples are contamination-free from the time of collection to the time of measurement (*e.g.*, by use of certified analyte free collection supplies and reference materials, and appropriate use of blanks both in the field and lab). **AND** - Documentation of the steps taken to provide the necessary assurance that the study data are reliable is included.
Medium	- Samples are stated to be contamination-free from the time of collection to the time of measurement. **AND** - There is incomplete documentation of the steps taken to provide the necessary assurance that the study data are reliable. **OR** - Samples are known to have contamination issues, but steps have been taken to address and correct contamination issues. **OR** - There is no information included about contamination (only allowed for biomarker samples not susceptible to contamination).
Low	- Samples are known to have contamination issues, but steps have been taken to address and correct contamination issues. **OR** - Samples are stated to be contamination-free from the time of collection to the time of measurement, but there is no use or documentation of the steps taken to provide the necessary assurance that the study data are reliable.
Critically Deficient	- There are known contamination issues (*e.g.*, phthalate study that used plastic sample collection vials) and no documentation that the issues were addressed.
Not Rated/Not Applicable	- Do not select "N/A" for this metric if the study assessed biomarkers.
Reviewer's Comments	Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance.
Metric 21. Method Requirements (detection/measurement/information biases)	
High	- Instrumentation that provides unambiguous identification and quantitation of the biomarker at the required sensitivity (*e.g.*, gas chromatography/high-resolution mass spectrometry [GC–HRMS]; gas chromatography with tandem mass spectrometry [GC–MS/MS]; liquid chromatography with tandem mass spectrometry [LC–MS/MS]).
Medium	- Instrumentation that allows for identification of the biomarker with a high degree of confidence and the required sensitivity (*e.g.*, gas chromatography mass spectrometry [GC–MS], gas chromatography with electron capture detector [GC–ECD]).
Low	- Instrumentation that only allows for possible quantification of the biomarker, but the method has known interferants (*e.g.*, gas chromatography with flame-ionization detection [GC–FID], spectroscopy).
Critically Deficient	- Do not select for this metric.
Not Rated/Not Applicable	- Do not select "N/A" for this metric if the study assessed biomarkers.
Reviewer's Comments	Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance.

Data Quality Rating	Description
Metric 22. Matrix Adjustment (detection/measurement/information biases)	
High	- If applicable for the biomarker under consideration, study provides results, either in the main publication or as a supplement, for both adjusted and unadjusted matrix concentrations (*e.g.,* creatinine-adjusted or specific gravity-adjusted and non-adjusted urine concentrations) and reasons are given for adjustment approach.
Medium	- If applicable for the biomarker under consideration, study only provides results using one method (matrix-adjusted or not).
Low	- If applicable for the biomarker under consideration, no established method for matrix adjustment was conducted.
Critically Deficient	- Do not select for this metric
Not Rated/Not Applicable	- If metrics 16 and 17 are both NA, then the remaining biomarker metrics are automatically not rated. Otherwise: Select "N/A" if matrix adjustment is not required for assessment of the biomarker.
Reviewer's Comments	Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance.
[a] Smoking fits in Metrics 9 and 10, not Metric 11; Metric 9 addresses whether there was appropriate adjustment or consideration of confounders (such as stratification) (other than co-exposures); Metric 10 addresses how the potential confounders (other than co-exposures) were measured; Metric 11 assesses co-exposure confounding.	

2164