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Office of Chemical Safety and
Pollution Prevention

Final Risk Evaluation for Asbestos Part 1: Chrysotile Asbestos

Systematic Review Supplemental File:

Data Quality Evaluation of Human Health Hazard Studies: Mesothelioma and Lung Cancer Studies

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1. Asbestos-specific evaluation criteria for epidemiologic studies

1.1. Rationale for asbestos-specific evaluation criteria

For the first 10 Toxic Substances Control Act (TSCA) chemicals, a general set of study evaluation criteria was developed. These evaluation criteria were not tailored to any specific exposure or outcome. In the Problem Formulation step of the asbestos assessment, it was accepted that asbestos was a known cause of lung cancer and mesothelioma, and that the purpose of the systematic review would be the identification of studies which could inform the estimation of an exposure-response function allowing for the derivation of an asbestos inhalation unit risk for these two cancer sites combined. While there is also evidence that asbestos exposure is associated with an increased risk of laryngeal and ovarian cancer, there is inadequate data for exposure-response analyses. For the reasons described below, the study domains of exposure, outcome, study participation, potential confounding, and analysis were further tailored to the specific needs of evaluating asbestos studies for their potential to provide information on the exposure-response relationship between asbestos exposure and mortality from lung cancer and from mesothelioma (see sections 1.2 and 1.3).

In terms of evaluating exposure information, asbestos is unique among these first 10 TSCA chemicals as it is a fiber and has a long history of different exposure assessment methodologies. For mesothelioma, this assessment is also unique with respect to the impact of the timing of exposure relative to the cancer outcome as the time since first exposure plays a dominant role in modeling risk. The most relevant exposures for understanding mesothelioma risk were those that occurred decades prior to the onset of cancer, and subsequent cancer mortality. Asbestos measurement methodologies have changed over those decades; from early measurement of total dust particles measured in units of million particles per cubic foot of air (mppcf) (by samplers called midget impingers), to fibers per milliliter (f/ml), or the equivalent fibers per cubic centimeter (f/cc) (where fiber samples were collected on membrane filters and the f/ml or f/cc was measured using phase contrast microscopy (PCM) analysis of the filters). In several studies encompassing several decades of asbestos exposure, matched samples from midget impingers and membrane filters were compared to derive job- (or location-) specific factors allowing for the conversion of earlier midget impinge measurements to estimate PCM measurement of asbestos air concentrations. While some studies were able to provide these factors for specific locations and jobs, other studies were only able to derive one factor for all jobs and locations. The use of such data has allowed asbestos researchers to investigate the risk of asbestos and successfully model lung cancer and mesothelioma mortality over several decades of evaluation

(U.S. EPA, 2014, 1988, 783514). Thus, the general exposure evaluation criteria were adjusted to be specific to exposure assessment methodologies such as midget impingers and PCM with attention to the use of job-exposure-matrices (JEMs) to reconstruct workers' exposure histories and the reporting of key metrics needed to derive exposure-response functions for lung cancer and mesothelioma.

In terms of evaluating the quality of outcome information, lung cancer is relatively straightforward to evaluate as an outcome. Specific International Classification of Disease (ICD) codes for lung cancer have existed for the entire time period of the studies making it possible to identify cases from mortality databases. On the other hand, there was no diagnostic code for mesothelioma in the ICD prior to the introduction of the 10th revision (ICD-10) which was not implemented in United States until 1999. Before ICD-10, individual researchers had to go beyond ICD codes and generally search original death certificates for mention of mesothelioma. Thus, the general outcome evaluation criteria were adjusted to be specific to mesothelioma and outcome ascertainment strategies.

Mesothelioma is a very rare cancer. As noted by U.S. EPA (2014, 3827272), the "Centers for Disease Control and Prevention estimated the death rate from mesothelioma, using 1999 to 2005 data, as approximately 23.2 per million per year in males and 5.1 per million per year in females (CDC, 2009, 783733)." While extremely rare, the overwhelmingly dominant cause of mesothelioma is asbestos exposure (Tossavainen, 1997, 3081272) making the observance of mesothelioma in a population a sentinel for asbestos exposure. It is critical to understand that the prevailing risk model for mesothelioma models is an absolute risk model of mesothelioma mortality which assumes there is no risk at zero exposure (U.S. EPA, 1988, 783514; Peto et al., 1982, 165; Peto, 1978, 2238688). This use of an absolute risk model is in stark contrast to the standard use of a relative risk model for lung and other cancers. For the relative risk model, the risk of lung cancer in an asbestos exposed population would multiply the background risk in an unexposed population, and consideration of study quality would be the evaluation of the comparison population. There is, however, no background risk in developing mesothelioma in an unexposed population. As a result, no comparison population was needed to estimate the absolute risk among people exposed to asbestos, and therefore, criteria including comparison population were adjusted for mesothelioma.

In terms of evaluating potential confounding variables, the potential confounding section recognized that there are both direct and indirect methods for controlling for some confounders – specifically that methodologies involving internal comparisons in a working population may

indirectly control for smoking and other factors assuming these factors do not vary with asbestos exposure concentrations in the workplace. In contrast to lung cancer, mesothelioma is much simpler to evaluate for potential confounding as chest radiation is the only other known risk factor that could lead to mesothelioma, and this rare exposure is unlikely to be a confounder.

In terms of analysis, the evaluation criteria needed to be adapted for both mesothelioma and lung cancer. For mesothelioma, the Peto model (Peto et al., 1982, 165; Peto, 1978, 2238688) was traditionally used for summary data published in the literature (U.S. EPA, 1988, 783514), so only modeling using the Peto model by the authors, or the presentation of sufficient information to fit the Peto model post hoc were considered acceptable. For lung cancer, a wider selection of statistical models was acceptable, with the preference generally given to modeling that used individual data in the analysis. Grouped data modeling would also reported but would be carried forward to the summary only if no individual data modeling were available.

Lastly for Asbestos, studies from the same cohort were evaluated collectively to assess the overall quality of the data collected from the cohort across all years of follow-up. This was done to consider all information from a cohort that was presented across multiple studies as a whole. For example, the most recent article for a cohort may not have presented the details necessary to fully evaluate the number one domain criterion (Study Participation), whereas the first or subsequent studies out of the cohort may have filled in data gaps.

1.2. Evaluation Criteria for Epidemiological Studies: Asbestos Exposure and Lung Cancer Health Outcome

Confidence Level (Score)	Description	Selected Score
Domain 1. Study Participation		
Metric 1. Participant selection (selection, performance biases)		
Instructions: To meet criteria for confidence ratings for metrics where 'AND' is included, studies must address both conditions where 'AND' is stipulated. To meet criteria for confidence ratings for metrics where 'OR' is included studies must address at least one of the conditions stipulated. In Metrics 3 and 4, criteria that must be met concurrently are enclosed in parentheses and linked with an indented 'AND.'		
High (score = 1)	• ***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 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 (score = 2)	***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 (score = 3)	• ***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, 4263036)].	
Unacceptable (score = 4)	***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/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 (score = 1)	• ***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** • Loss of subjects (e.g., incomplete outcome data) or missing exposure and outcome data was adequately* addressed (as described below) and reasons were documented when human subjects were removed from a study (NTP,	

Confidence Level (Score)	Description	Selected Score
	2015, 2823411). **AND** • 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, 2823411). • ***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, 2823411). ***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 (score = 2)	• ***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, 2823411).	
Low (score = 3)	• ***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, 4263036)]. • ***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-	

Confidence Level (Score)	Description	Selected Score
	participation at each stage [STROBE Checklist Item 13 (Von Elm et al., 2008, 4263036)].	
Unacceptable (score = 4)	• ***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/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 3. Comparison Group (selection, performance biases)		
High (score = 1)	• ***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 groups 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, 2823411). • ***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, 2823411). • ***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 (score = 2)	• ***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	

Confidence Level (Score)	Description	Selected Score
	evidence); choice of reference population (e.g., general population) is reported.	
Low (score = 3)	• ***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 (Source: (NTP, 2015, 2823411). **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.	
Unacceptable* (score = 4)	• ***For cohort studies:*** Subjects in all exposure groups were not similar **OR** • (Information was not reported to determine if participant groups were similar [STROBE Checklist 6 (Von Elm et al., 2008, 4263036) **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, 2823411). **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, 2823411). **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, 4263036)]. • ***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, 2823411). **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	

Confidence Level (Score)	Description	Selected Score
	were not reported [STROBE Checklist 6 (Von Elm et al., 2008, 4263036)]. • ***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/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 (score = 1)	• ***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).	
Medium* (score = 2)	• ***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 (score = 3)	• ***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.	
Unacceptable (score = 4)	• ***For all study types:*** There was no quantitative measure or estimate of exposure. **OR** • 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, 4263036)]. **OR** There is evidence of substantial exposure misclassification that would significantly bias the results.	
Not rated/applicable	• Do not select for this metric.	
Reviewer's	*[Document concerns, uncertainties, limitations, and deficiencies and any*	

Confidence Level (Score)	Description	Selected Score
comments	*additional comments that may highlight study strengths or important elements such as relevance]*	
Metric 5. Exposure levels (Detection/measurement/information biases)		
High (score = 1)	• Do not select for this metric.	
Medium (score = 2)	• ***For all study types:*** The range and distribution of exposure is sufficient or adequate to develop an exposure-response estimate (Cooper et al., 2016, 3121908). **AND** • Reports 3 or more levels of exposure (referent group + 2 or more) or an exposure-response model using a continuous measure of exposure.	
Low (score = 3)	***For all study types:*** The range of exposure in the population is limited. **OR** • Reports 2 levels of exposure (e.g., exposed/unexposed)) (Cooper) (Source: IRIS).	
Unacceptable (score = 4)	• ***For all study types:*** The range and distribution of exposure are not adequate to determine an exposure-response relationship (Cooper et al., 2016, 3121908). **OR** • No description is provided on the levels or range of exposure.	
Not rated/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 (score = 1)	• ***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, 2713602).	
Medium (score = 2)	• ***For all study types:*** 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, 2713602).	
Low (score = 3)	• ***For all study types:*** The temporality of exposure and outcome is uncertain (5-10 years). **OR** • There is inadequate follow-up of the cohort considering the latency period.	
Unacceptable (score = 4)	• ***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, 2713602). **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, 4263036)).	
Not rated/applicable	• Do not select for this metric.	

Confidence Level (Score)	Description	Selected Score
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 (score = 1)	• ***For all study types:*** The outcome was assessed using one or a combination of the following well-established methods: ○ Lung cancer cases confirmed by histological or cytological means (including subtypes of lung cancer) ○ ICD-10 C34 (lung and bronchus with or without C33 (trachea) ○ ICD-9 (5-digit code) 162.2-162.9 or ○ ICD-8 (4-digit code) 162.1 or ○ ICD-7 (4-digit code) 162.1 and 163 ○ ICD-9 (3-digit code) 162 ○ ICD-8 (3-digit code) 162 ○ ICD-7 (3-digit code) 162 and 163	
Medium (score = 2)	• ***For all study types:*** Although authors state they identified lung cancer cases they did not report the ICD codes.	
Low (score = 3)	• *Do not select for this metric.*	
Unacceptable (score = 4)	• ***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/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 (score = 1)	• ***For all study types:*** Lung cancer 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, 2823411).	
Medium (score = 2)	• ***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 (score = 3)	• ***For all study types:*** Lung cancer outcomes outlined in the methods, abstract, and/or introduction (that are relevant for the evaluation) have not been reported. (NTP, 2015, 2823411).	
Unacceptable (score = 4)	• Do not select for this metric.	
Not rated/applicable	• Do not select for this metric.	

Confidence Level (Score)	Description	Selected Score
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/Variable Control		
Metric 9. Covariate Adjustment (confounding)		
High (score = 1)	• ***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, 2823411). • ***For Studies reporting SMRs or SIRs:*** Adjustments are described and results are age-, race-, and sex-adjusted (or stratified) if applicable.	
Medium (score = 2)	• ***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:*** Indirect evidence that results are age, sex-, and race-adjusted (or stratified) if applicable.	
Low (score = 3)	• ***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, 2823411). **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, 2823411). • ***For Studies reporting SMRs or SIRs:*** Results are age-, race-, OR sex-adjusted (or stratified) if applicable (i.e., if 2 or all *should* have been adjusted).	
Unacceptable (score = 4)	• ***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, 2823411). • ***For Studies reporting SMRs or SIRs:*** No discussion of adjustments. Results are not adjusted for age, sex, and race (or stratified) if applicable.	
Not rated/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]*	

Confidence Level (Score)	Description	Selected Score
Metric 10. Covariate Characterization (measurement/information, confounding biases)		
High (score = 1)	• ***For all study types:*** Potential confounders (e.g. age, sex, SES, race, etc.) and were assessed using valid and reliable methodology where appropriate (e.g., validated questionnaires, biomarker).	
Medium (score = 2)	• ***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 (score = 3)	• ***For all study types:*** The confounder assessment method is an insensitive instrument or measure or a method of unknown validity.	
Unacceptable (score = 4)	• ***For all study types:*** Confounders were assessed using a method or instrument known to be invalid.	
Not rated/applicable	• 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 (score = 1)	• Do not select for this metric.	
Medium (score = 2)	• ***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.	
Low (score = 3)	• ***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.	
Unacceptable (score = 4)	• Do not select for this metric.	
Not rated/applicable	• Enter 'NA' and do not score 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 5. Analysis		
Metric 12. Study Design and Methods		
High (score = 1)	• Do not select for this metric.	
Medium (score = 2)	• ***For all study types:*** The study design chosen was appropriate for the research question. **AND** • 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.	

Confidence Level (Score)	Description	Selected Score
(score = 3)		
Unacceptable (score = 4)	• ***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/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 (score = 1)	• Do not select for this metric.	
Medium (score = 2)	• ***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 high is 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 was high enough (≥ 80%) to detect an effect in the exposure population and/or subgroups of the total population.	
Low (score = 3)	• Do not select for this metric.	
Unacceptable (score = 4)	• ***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/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 14. Reproducibility of analyses [adapted from Blettner et al. (2001, 4149692)]		
High (score = 1)	• Do not select for this metric.	
Medium (score = 2)	• ***For all study types:*** The description of the analysis is sufficient to understand precisely what has been done and to be conceptually reproducible with access to the analytic data.	
Low (score = 3)	• ***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	

Confidence Level (Score)	Description	Selected Score
	presented, exclusion of outliers was not elucidated and how missing values are dealt with was not mentioned).	
Unacceptable (score = 4)	• Do not select for this metric.	
Not rated/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 (score = 1)	• Do not select for this metric.	
Medium (score = 2)	• ***For all study types:*** The model or method for calculating the risk estimates (e.g., odds ratios, SMRs, SIRs) is transparent (it is stated how/why variables were included or excluded) **AND** • Model assumptions were met.	
Low (score = 3)	• ***For all study types:*** The statistical model building process is not fully appropriate **OR** • Model assumptions were not met **OR** • A description of analyses is not present [STROBE Checklist 12e (Von Elm et al., 2008, 4263036)].	
Unacceptable (score = 4)	• Do not select for this metric.	
Not rated/applicable	• Enter 'NA' 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]*	

1.3. Evaluation Criteria for Epidemiological Studies: Asbestos Exposure and Mesothelioma Health Outcome

Confidence Level (Score)	Description	Selected Score
Domain 1. Study Participation		
Metric 1. Participant selection (selection, performance biases)		
Instructions: To meet criteria for confidence ratings for metrics where 'AND' is included, studies must address both conditions where 'AND' is stipulated. To meet criteria for confidence ratings for metrics where 'OR' is included studies must address at least one of the conditions stipulated.		
High	• ***For all study types:*** All key elements of the study design are reported (e.g.,	

Confidence Level (Score)	Description	Selected Score
(score = 1)	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 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 (score = 2)	• ***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 (score = 3)	• ***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, 4263036)].	
Unacceptable (score = 4)	• ***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/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 (score = 1)	• ***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** • Loss of subjects (e.g., incomplete outcome data) or missing exposure and outcome data was adequately* addressed (as described below) and reasons were documented when human subjects were removed from a study (NTP, 2015, 2823411). **AND** • 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, 2823411). • ***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, 2823411). ***NOTE for all study types:*** Adequate handling of subject attrition can include: Use of imputation methods for missing outcome and exposure data; reasons	

Confidence Level (Score)	Description	Selected Score
	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 (score = 2)	• ***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, 2823411).	
Low (score = 3)	• ***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, 4263036)]. • ***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, 4263036)].	
Unacceptable (score = 4)	• ***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.	

Confidence Level (Score)	Description	Selected Score
Not rated/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 3. Comparison Group (selection, performance biases) [See special instructions for mesothelioma studies in "Not rated/applicable"]*		
High (score = 1)	• ***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 groups 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, 2823411). • ***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, 2823411). • ***For studies reporting Standardized Mortality Ratios (SMRs) or Standardized Incidence Ratios (SIRs):*** Age, sex (if applicable), race (if applicable), and calendar time adjustment or stratification is described and choice of reference population (e.g., general population) is reported.	
Medium (score = 2)	• ***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), race (if applicable), and calendar time adjustment or stratification is not specifically described (i.e., indirect evidence) in the text, but results tables are stratified by age, sex (if applicable), race (if applicable); choice of reference population (e.g., general population) is reported.	
Low (score = 3)	• ***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 (Source: (NTP, 2015, 2823411). **AND** • Differences in groups is not adequately controlled for in the statistical analysis.	

Confidence Level (Score)	Description	Selected Score
	• ***For studies reporting SMRs or SIRs***: Indirect evidence of a lack of adjustment or stratification for age, sex (if applicable), race (if applicable), and calendar time; or indirect evidence that choice of reference population (e.g., general population) is inappropriate.	
Unacceptable (score = 4)	• ***For cohort studies:*** Subjects in all exposure groups were not similar **OR** • (Information was not reported to determine if participant groups were similar [STROBE Checklist 6 (Von Elm et al., 2008, 4263036) **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, 2823411). **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, 2823411). **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, 4263036)]. • ***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, 2823411). **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 6 (Von Elm et al., 2008, 4263036)]. • ***For studies reporting SMRs or SIRs:*** Lack of adjustment or stratification for both age, sex (if applicable), race (if applicable), and calendar time; or choice of reference population (e.g., general population) is not reported.	
Not rated/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"	
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 (score = 1)	• ***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	

Confidence Level (Score)	Description	Selected Score
	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 (score = 2)	• ***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 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 (score = 3)	• ***For all study types:*** Exposure was estimated solely using professional judgement. **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.	
Unacceptable (score = 4)	• ***For all study types:*** There was no quantitative measure or estimate of exposure. **OR** • 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, 4263036)]. **OR** • There is evidence of substantial exposure misclassification that would significantly bias the results.	
Not rated/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 (score = 1)	Do not select for this metric.	
Medium (score = 2)	• ***For all study types:*** The range and distribution of exposure is sufficient or adequate to develop an exposure-response estimate (Cooper et al., 2016, 3121908).	
Low (score = 3)	• ***For all study types:*** The range of exposure in the population is limited.	
Unacceptable (score = 4)	• ***For all study types:*** The range and distribution of exposure are not sufficient or adequate to determine an exposure-response relationship (Cooper et al., 2016, 3121908). **OR**	

Confidence Level (Score)	Description	Selected Score
	• No description is provided on the levels or range of exposure.	
Not rated/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 (score = 1)	• ***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, 2713602).	
Medium (score = 2)	• ***For all study types:*** 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, 2713602).	
Low (score = 3)	• ***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.	
Unacceptable (score = 4)	• ***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, 2713602). **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/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 (score = 1)	• ***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)	
Medium (score = 2)	• ***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 (score = 3)	• *Do not select for this metric.*	

Confidence Level (Score)	Description	Selected Score
Unacceptable (score = 4)	• ***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	
Not rated/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 (score = 1)	• ***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, 2823411).	
Medium (score = 2)	• ***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 (score = 3)	• ***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, 2823411).	
Unacceptable (score = 4)	• Do not select for this metric.	
Not rated/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/Variable Control		
Metric 9. Covariate Adjustment (confounding) [See special instructions for mesothelioma studies in "Not rated/applicable"] *		
High (score = 1)	• ***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, 2823411). • ***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	

Confidence Level (Score)	Description	Selected Score
(score = 2)	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:*** Indirect evidence that results are age, sex-, and race-adjusted (or stratified) if applicable.	
Low (score = 3)	• ***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, 2823411). **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, 2823411). • ***For Studies reporting SMRs or SIRs:*** Results are age-, race-, **OR** sex-adjusted (or stratified) if applicable (i.e., if 2 or all *should* have been adjusted).	
Unacceptable (score = 4)	• ***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, 2823411). • ***For Studies reporting SMRs or SIRs:*** No discussion of adjustments. Results are not adjusted for age, sex, and race (or stratified) if applicable.	
Not rated/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".	
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) [See special instructions for mesothelioma studies in "Not rated/applicable"]*		
High (score = 1)	• ***For all study types:*** Potential confounders (e.g. age, sex, SES, race, etc.) were assessed using valid and reliable methodology where appropriate (e.g., validated questionnaires, biomarker).	
Medium (score = 2)	• ***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 (score = 3)	• ***For all study types:*** The confounder assessment method is an insensitive instrument or measure or a method of unknown validity.	

Confidence Level (Score)	Description	Selected Score
Unacceptable (score = 4)	• ***For all study types:*** Confounders were assessed using a method or instrument known to be invalid.	
Not rated/applicable	• 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) [See special instructions for mesothelioma studies in "Not rated/applicable"]*		
High (score = 1)	• Do not select for this metric.	
Medium (score = 2)	• ***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.	
Low (score = 3)	• ***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.	
Unacceptable (score = 4)	• Do not select for this metric.	
Not rated/applicable	• For mesothelioma, there are no established risk factors other than exposure to asbestos, therefore no known co-exposures are of concern. Enter 'NA' and do not score 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 5. Analysis		
Metric 12. Study Design and Methods		
High (score = 1)	• Do not select for this metric.	
Medium (score = 2)	• ***For all study types:*** The study design chosen was appropriate for the research question. **AND** • The study uses an appropriate statistical method to address the research question(s) (e.g., Cox and Poisson regression for cohort studies, logistic regression analysis for case-control studies.	
Low (score = 3)	• Do not select for this metric.	
Unacceptable (score = 4)	• ***For all study types:*** The study design chosen was not appropriate for the research question.	
Not rated/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) [See special instructions for mesothelioma studies in "Not rated/applicable"]*		

Confidence Level (Score)	Description	Selected Score
High (score = 1)	• Do not select for this metric.	
Medium (score = 2)	• ***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 high is 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 was high enough (≥ 80%) to detect an effect in the exposure population and/or subgroups of the total population.	
Low (score = 3)	• Do not select for this metric.	
Unacceptable (score = 4)	• ***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/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.	
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), 4149692] [See special instructions for mesothelioma studies in "Not rated/applicable"]*		
High (score = 1)	• Do not select for this metric.	
Medium (score = 2)	• ***For all study types:*** The description of the analysis is sufficient to understand precisely what has been done and to be conceptually reproducible with access to the analytic data.	
Low (score = 3)	• ***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).	
Unacceptable (score = 4)	• Do not select for this metric.	
Not rated/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.	

Confidence Level (Score)	Description	Selected Score
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) [See special instructions for mesothelioma studies in "Not rated/applicable"]*		
High (score = 1)	• Do not select for this metric.	
Medium (score = 2)	• ***For all study types:*** The model or method for calculating the risk estimates (e.g., odds ratios, SMRs, SIRs) is transparent (it is stated how/why variables were included or excluded).	
Low (score = 3)	• ***For all study types:*** The statistical model building process is not fully appropriate **OR** • Model assumptions were not met **OR** • A description of analyses is not present [STROBE Checklist 12e (Von Elm et al., 2008, 4263036)].	
Unacceptable (score = 4)	• Do not select for this metric.	
Not rated/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.	
Reviewer's comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*	

2. Data Evaluation of Lung Cancer Studies

2.1. Table of studies evaluated for asbestos exposure and lung cancer incidence

Study Cohort	Author, Year	HERO ID
South Carolina, US	(Berman and Crump, 2008)	626405
	(Brown et al., 1994)	3081832
	(Cole et al., 2013)	3078261
	(Dement et al., 1983b)	67
	(Dement and Brown, 1994a)	3094565
	(Dement et al., 1994)	3081766
	(Dement and Brown, 1994b)	3081783
	(Edwards et al., 2014)	3078061
	(Elliott et al., 2012)	1247861
	(Hein et al., 2007)	709498
	(Loomis et al., 2012)	1257856
	(SRC, 2019c)	5080236
	(Stayner et al., 1997)	3081241
	(Stayner et al., 2008)	2604140
Qinghai, China - miners	(Wang et al., 2012)	2572504
	(Wang et al., 2013)	2548289
	(Wang et al., 2014)	2538846
Balangero, Italy	(Piolatto et al., 1990)	3082492
	(Pira et al., 2009)	2592425
	(Pira et al., 2017)	5060134
	(Rubino et al., 1979)	178
North Carolina, US	(Berman and Crump, 2008)	626405
	(Dement et al., 2008)	626406
	(Elliott et al., 2012)	1247861
	(Loomis et al., 2009)	3079232
	(Loomis et al., 2010)	2225695
	(Loomis et al., 2012)	1257856
	(Loomis et al., 2019)	5160027
	(SRC, 2019a)	5080241
Salonit Anhovo, Slovenia	(Dodic Fikfak, 2003)	3080279
	(Dodic Fikfak et al., 2007)	3079664

Study Cohort	Author, Year	HERO ID
Quebec, Canada	(Berman and Crump, 2008)	626405
	(Gibbs and Lachance, 1972)	3580825
	(Liddell et al., 1997)	3081408
	(Liddell et al., 1998)	3081200
	(Liddell and Armstrong, 2002)	3080504
	(Mcdonald et al., 1993a)	3081910
	(Mcdonald et al., 1993b)	3081911
	(SRC, 2019b)	5080232
	(Vacek, 1998)	3081118
Chongqing, China – asbestos products factory including textiles	(Courtice et al., 2016)	3520560
	(Deng et al., 2012)	2573093
	(Wang et al., 2014)	2538846
	(Yano et al., 2001)	3080569

Shaded rows indicate studies used for derivation of Inhalation Unit Risk (IUR).

2.2. Data Evaluation Scoring Sheets: Lung Cancer Outcome

2.2.1. Epidemiology evaluation results of the South Carolina, US cohort studies on asbestos exposure and lung cancer incidence

Study reference:	**This cohort evaluation represents all identified publications pertaining to the South Carolina cohort of textile workers. A full list of related papers reviewed during this evaluation are listed in Table 2.1.**					
Domain	**Metric**	**Comments**	**Qualitative Determination**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
Study Participation	1. Participant selection	a. Setting and methods of case ascertainment were reported in (Dement et al., 1983b, 67) p. 422 and (Hein et al., 2007, 709498) p 617. Participant selection and inclusion/exclusion criteria varied by study and analysis. The initial cohort consisted of white men employed for at least one month in a production job at the South Carolina plant between 1/1/1940 and 12/31/1965 ((Dement et al., 1983b, 67) p 422). Subsequent analyses added non-white men and/or women ((Stayner et al., 1997, 3081241), (Dement et al., 1994, 3081766) (Brown et al., 1994, 3081832), (Elliott et al., 2012, 1247861) , (Edwards et al., 2014, 3078061), (Cole et al., 2013, 3078261), (Hein et al., 2007, 709498)). b. Selection in or out of the study was based on 1) employment in production job during designated time frame and b) availability of necessary data (birth and hire dates; work history; vital status). These criteria are unlikely to result in biased subject participation.	High	1	0.400	0.400

Study reference:	This cohort evaluation represents all identified publications pertaining to the South Carolina cohort of textile workers. A full list of related papers reviewed during this evaluation are listed in Table 2.1.					
Domain	**Metric**	**Comments**	**Qualitative Determination**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	2. Attrition	Attrition/missing data exclusions were reported in (Dement et al., 1983b, 67) (p. 423 and Table 1) and (Hein et al., 2007, 709498) (p 618 and Table 1). The number of eligible workers and number excluded due to incomplete work histories was not reported in the sources reviewed. (Dement et al., 1983b, 67) (p 422) reports that each worker was assigned a card at hire on which was tracked the date of birth, sex, race, and SSN, and job or department changes throughout the career were recorded on the card; these were used in the cohort establishment. The suggestion is that all cohort members had complete work histories; however, (Hein et al., 2007, 709498) (p 624) reported that the study was limited by incomplete lifetime work histories. Vital status was unknown for 2.1% of the original 1261 cohort members, and cause of death was unknown for 5.5% of the deaths in 1975. At the 2001 follow up (Hein et al., 2007, 709498), vital status was unknown for 8.6% of the larger cohort of 3072, and cause of death was unknown for 3.9%. The latter paper cited high rate of loss to follow-up as a limitation of the study. Thus, loss to follow up is judged to be moderate, and the lack of information on number eligible and number with incomplete work histories leads to low confidence.	Low	3	0.400	1.200
	3. Comparison Group	Any differences in baseline characteristics (e.g., age, sex, race) were controlled by statistical analysis ((Dement et al., 1983b, 67), p. 422; (Hein et al., 2007, 709498), p 617). In (Hein et al., 2007, 7069498) (p 617), it is reported that birth cohort was used in statistical analysis as a surrogate for smoking. Setting, inclusion and exclusion criteria, and methods of participant selection are reported ((Dement et al., 1983b, 67), p. 422 and (Hein et al., 2007, 709498) p 617), and these suggest that the groups were 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.	High	1	0.200	0.200

Study reference:	This cohort evaluation represents all identified publications pertaining to the South Carolina cohort of textile workers. A full list of related papers reviewed during this evaluation are listed in Table 2.1.					
Domain	**Metric**	**Comments**	**Qualitative Determination**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
Exposure Characterization	4. Measurement of Exposure	(Dement et al., 1983a, 66) describes the plant processes and the exposure estimation methods. More than 6000 air samples obtained at the plant from 1930 to 1975 were analyzed by PCM to yield chrysotile concentrations (fibers >5 um/mL; (Hein et al., 2007, 709498), p 617). Exposure concentrations were estimated by department, job, and time period; individual cumulative exposure assessed using the modeled concentrations and JEM (methods outlined in (Dement et al., 1983a, 66)). In 2008, an updated JEM was developed to estimate fiber size-specific exposure estimates (based on TEM analysis of archived samples) in (Dement et al., 2008, 626406).	High	1	0.400	0.400
	5. Exposure levels	Exposure-response relationships were developed (see Figure 2 and Table VIII of (Dement et al., 1983b, 67), Table 3 of (Hein et al., 2007, 709498), (Elliott et al., 2012, 1247861) see Table 2. A total of 6 cumulative exposure levels are analyzed in Table 3 of (Hein et al., 2007, 709498).	Medium	2	0.200	0.400
	6. Temporality	Temporality was established (exposure preceded death). Exposure response analysis in initial cohort (Dement et al., 1983b, 67) was restricted to individuals with at least 15 years follow up since first employment (p 426). The longest follow-up time for the cohort was at least 36 years (1965-2001; (Hein et al., 2007, 709498) p 617). A ten year lag time was used in the analyses in (Hein et al., 2007, 709498) (p 617). In (Elliott et al., 2012, 1247861), the assessment of the SC cohort also used a ten year lag time (Table 2).	High	1	0.400	0.400
Outcome Assessment	7. Outcome measurement or characterization	Lung cancer deaths (underlying and contributing cause) were determined from the National Death Index Plus (1979 and later; (Hein et al., 2007, 709498) p 617) or death certificates (before 1979; sources of certificates not specified; (Dement et al., 1983b, 67) p 422). ICD in effect at time of death was used ((Dement et al., 1983b, 67) p 422). Deaths before 1979 were coded manually by a nosologist. ICD codes 162 and 163 (trachea, bronchus, and lung) were considered lung cancers ((Dement et al., 1983b, 67) Tables II, III, IV, VIII, XI).	High	1	0.667	0.667

Study reference:	This cohort evaluation represents all identified publications pertaining to the South Carolina cohort of textile workers. A full list of related papers reviewed during this evaluation are listed in Table 2.1.					
Domain	**Metric**	**Comments**	**Qualitative Determination**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	8. Reporting Bias	Lung cancer deaths and person-years at risk by exposure category are reported in Table 3 of (Hein et al., 2007, 709498); lung cancer cases and person-years at risk are reported in Table 1 of (Elliott et al., 2012, 1247861). Rate ratio estimates are reported with CIs in (Hein et al., 2007, 709498) and (Elliott et al., 2012, 1247861) ; coefficients for Poisson regression are reported without SE in Table 2 of (Elliott et al., 2012, 1247861) , but rate ratios with CIs are also reported for the same models.	High	1	0.333	0.333
Potential Confounding/Variable Control	9. Covariate Adjustment	Analyses in (Hein et al., 2007, 709498) and (Elliott et al., 2012, 1247861) were adjusted for age, sex, race, decade of follow-up and birth cohort. No adjustment was made for smoking in (Dement et al., 1983b, 67), which could bias SMR analyses. However, the authors of (Dement et al., 1983b, 67) used available information on smoking rates among cohort members to compare with rates in U.S. white males; patterns (Table XII) were similar between the groups. (Hein et al., 2007, 709498) and (Elliott et al., 2012, 1247861) evaluated birth cohort as a surrogate for smoking; lack of direct consideration of smoking is not likely to bias internal analysis in an occupational cohort.	Medium	2	0.500	1.000
	10. Covariate Characterization	(Dement et al., 1983b, 67) (p 422) reports that each worker was assigned a card at hire on which was included the date of birth, sex, and race, presumably as reported by the employee; this appears to be a valid and reliable source of data. (Dement et al., 1983b, 67) (p 430) indicated that data on smoking rates collected on US Public Health Service questionnaires in 1964 and 1971 and from medical records were used to estimate patterns of smoking in the cohort and compared with US White males (comparison group for SMR analyses). Data were not available for all cohort members.	Medium	2	0.250	0.500

Study reference:	This cohort evaluation represents all identified publications pertaining to the South Carolina cohort of textile workers. A full list of related papers reviewed during this evaluation are listed in Table 2.1.					
Domain	**Metric**	**Comments**	**Qualitative Determination**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	11. Co-exposure Confounding	Small amounts of crocidolite yarn were used between 1950s and 1975, but the total quantity was reported to be small (2000 lbs total vs 6-8 million lbs/yr of chrysotile during that time period). In addition, workers did not card, spun, or twist the crocidolite; a single loom was used; and weaving was performed wet, which minimized exposure to crocidolite ((Hein et al., 2007, 709498) p 616). The distribution of this co-exposure relative to chrysotile exposure was not evaluated, and no effort was made to adjust for this co-exposure. However, available information suggests the coexposure would be negligible relative to chrysotile exposures.	Medium	2	0.250	0.500
Analysis	12. Study Design and Methods	Study design was retrospective cohort; Poisson regression used for internal analyses in ((Hein et al., 2007, 709498) p 617) and (Elliott et al., 2012, 1247861) p 386.	Medium	2	0.400	0.800
	13. Statistical power	None of the related studies report power calculations; however, statistically significant exposure-response relationships suggest there was adequate power to detect the effect.	Medium	2	0.200	0.400
	14. Reproducibility of analyses	Analysis description in (Hein et al., 2007, 709498) appears to be complete. Statistical tests and estimation procedures and variables considered are reported ((Hein et al., 2007, 709498) p 617). For internal analyses, cumulative exposure was treated as a continuous variable and/or partitioned into categories with approximately equal numbers of deaths ((Hein et al., 2007, 709498) p 617 and footnote to Table 3). There were no variable transformations, outlier exclusions, or imputation of missing values. Analysis description in (Elliott et al., 2012, 1247861) appears to be complete. Statistical tests and estimation procedures and variables considered are reported (Elliott et al., 2012, 1247861) p 386. Cumulative exposure was analyzed as a continuous variable (Elliott et al., 2012, 1247861), p 386. No variable transformations were reported.	Medium	2	0.200	0.400
	15. Statistical Models	Statistical models and methods are described in detail later publications (see (Hein et al., 2007, 709498) p 617-618 and (Elliott et al., 2012, 1247861) p 386, including how variables were included or excluded.	Medium	2	0.200	0.400
		Sum of scores:			**5**	**8**

Study reference:	**This cohort evaluation represents all identified publications pertaining to the South Carolina cohort of textile workers. A full list of related papers reviewed during this evaluation are listed in Table 2.1.**					
Domain	**Metric**	**Comments**	**Qualitative Determination**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
High: >=1 and <1.7 Medium: >=1.7 and <2.3 Low: >=2.3 and <=3		**Overall Score = Sum of Weighted Scores/Sum of Metric Weighting Factors:**		**1.6**	**Overall Score: Nearest tenth:**	**1.6**
		Overall Quality Level:		**High**		
Study Quality Comment:	**The reviewer agreed with this study's overall quality level.**					

2.2.2. Epidemiology evaluation results of the Chongqing, China mining cohort studies on asbestos exposure and lung cancer incidence

Study reference:	This cohort evaluation represents all identified publications pertaining to the cohort of miners in Chongqing, China. A full list of related papers reviewed during this evaluation are listed in Table 2.1.					
Domain	**Metric**	**Comments**	**Qualitative Determination**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
Study Participation	1. Participant selection	The key elements of the study design are reported ((Wang et al., 2013, 2548289) p. 2, and (Wang et al., 2012, 2572504) p. 20). All male workers employed for at least one year in the chrysotile mine were included in the study (participation is not likely to be biased).	High	1	0.400	0.400
	2. Attrition	There was no subject loss to follow up during the study; outcome and exposure data were complete ((Wang et al., 2013, 2548289) p. 2, and (Wang et al., 2012, 2572504) p. 20).	High	1	0.400	0.400
	3. Comparison Group	Inclusion criteria and the methods of participant selection were reported. All subjects were recruited from the same eligible population within the same time frame. In studies reporting SMRs ((Wang et al., 2012, 2572504) p. 407, and (Wang et al., 2013, 2548289) p. 3), the choice of a reference population is reported (based on age-specific national mortality data for males). However, data on cause-specific mortality data were limited (rates of 1990 and 2004 were used to correspond to periods of 1981-1995 and 1996-2006, respectively ((Wang et al., 2012, 2572504) p. 411).	High	1	0.200	0.200

Study reference:	This cohort evaluation represents all identified publications pertaining to the cohort of miners in Chongqing, China. A full list of related papers reviewed during this evaluation are listed in Table 2.1.					
Domain	**Metric**	**Comments**	**Qualitative Determination**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
Exposure Characterization	4. Measurement of Exposure	Periodic asbestos dust measurements were available from 1984 to 1995 ((Wang et al., 2013, 2548289) p.2). In 2006, additional measurements in various workshops were performed ((Wang et al., 2013, 2548289) p.2, (Wang et al., 2014, 2538846) p. 120, and (Wang et al., 2012, 2572504) p. 406); these samples were also analyzed by TEM. Paired samples from 1991 (using simultaneous gravimetric and membrane filter methods) from the main workshop only were used to define the relationship between dust and fiber concentrations ((Wang et al., 2013, 2548289) p. 2). From these data, (and using all periodically measured data at different workshops), average fiber concentrations by workshop/job were calculated. Cumulative individual exposures were estimated as the product of (fiber concentration at a specific workshop/job) x (duration of job) ((Wang et al., 2013, 2548289) p. 3 and (Wang et al., 2014, 2538846) p. 120). Side-by-side analyses were not conducted for all operations or at all time points (i.e. systematic dust/fiber data were not available; (Wang et al., 2012, 2572504) p. 409). There were no exposure data prior to 1984. The study authors acknowledge that there may have been exposure misclassification based on these estimations, but the misclassification was likely to be non-differential ((Wang et al., 2013, 2548289) p. 7 and (Wang et al., 2014, 2538846) p. 123).	Medium	2	0.400	0.800
	5. Exposure levels	The range and distribution of exposure is sufficient to develop and exposure-response estimate. The Wang et al. 2014 study ((Wang et al., 2014,2538846) p. 122) reports 4 levels of exposure (referent + 3); cumulative exposures were categorized quartiles for analyses of lung cancer deaths.	Medium	2	0.200	0.400
	6. Temporality	The study establishes appropriate temporality; the interval between exposure and outcome is long enough considering latency of the disease ((Wang et al., 2013, 2548289) p. 1, (Wang et al., 2014, 2538846) p. 119, and (Wang et al., 2012, 2572504) p. 406). The cohort was followed for 26 years.	High	1	0.400	0.400

Study reference:	This cohort evaluation represents all identified publications pertaining to the cohort of miners in Chongqing, China. A full list of related papers reviewed during this evaluation are listed in Table 2.1.					
Domain	**Metric**	**Comments**	**Qualitative Determination**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
Outcome Assessment	7. Outcome measurement or characterization	The Wang et al. 2013 study ((Wang et al., 2013, 2548289) p. 2) indicates that causes of death were obtained from hospitals and verified with the death registry; the study indicated that "there are consistent diagnostic criteria for cancers in China, largely based on clinical manifestations and pathological confirmation or biopsy." The study cites that SMRs for "lung cancer" included cancers of the lung, trachea, bronchus, and other thoracic neoplasm, encompassing ICD-10 C37 and ICD-10 C38 in addition to ICD-10 C34 (lung and bronchus) and C33 (trachea). In the Wang et al. 2014 publication ((Wang et al., 2014, 2538846) p. 120), ICD codes corresponding to lung cancer were not provided.	Medium	2	0.667	1.333
	8. Reporting Bias	Lung cancer findings are reported in the results. In studies reporting SMRs ((Wang et al., 2013, 2548289) p. 4-5, and (Wang et al., 2012, 2572504) p. 409), numbers of observed and expected cases and SMRs with 95% confidence intervals were provided. In the later study ((Wang et al., 2014, 2538846) p. 122), risk estimate data (hazard ratio and 95% confidence interval) were complete.	High	1	0.333	0.333
Potential Confounding/Variable Control	9. Covariate Adjustment	In studies reporting SMRs ((Wang et al., 2013, 2548289) p.3 and (Wang et al., 2012, 2572504) p. 407), final analyses were adjusted for smoking, age at entry, and/or employment years. In the later study ((Wang et al., 2014, 2538846) p. 121), the final risk estimate model was adjusted for age and smoking. There were no adjustments for sex, because the cohort consisted of only males. Demographic data from Wang et al. 2012 ((Wang et al., 2012, 2572504) p. 408) and Wang et al. 2014 ((Wang et al., 2014, 2538846) p. 121) suggest that the distribution of confounders was similar among miners and controls (although there was some indication that miners may have a relatively low SES compared to the general population; (Wang et al., 2012, 2572504) p. 411). Smoking was slightly more prevalent in miners than controls ((Wang et al., 2012, 2572504) p. 410), but analyses were adjusted for smoking.	Medium	2	0.500	1.000

Study reference:	This cohort evaluation represents all identified publications pertaining to the cohort of miners in Chongqing, China. A full list of related papers reviewed during this evaluation are listed in Table 2.1.					
Domain	**Metric**	**Comments**	**Qualitative Determination**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	10. Covariate Characterization	Covariates were assessed using reliable methodology. Vital status information was obtained from personnel records. Information on smoking habits and verification of occupational history was obtained from workers or their immediate relatives (if deceased) through personal contact ((Wang et al., 2013, 2548289) p. 2 and (Wang et al., 2012, 2572504) p. 407). The Wang et al. 2014 study ((Wang et al., 2014, 2538846) p. 120) indicated that vital status was obtained through follow-up and links to death certificates and using structured questionnaires. Although individual smoking status information was available, information on the duration and/or intensity of smoking was not available.	High	1	0.250	0.250
	11. Co-exposure Confounding	The members of the cohort were workers at an asbestos mine in China. There was no evidence that there was an unbalanced provision of co-exposures among exposure groups ((Wang et al., 2013, 2548289) p. 7, (Wang et al., 2014, 2538846) p. 123). At least one of the studies ((Wang et al., 2013, 2548289) p. 7) indicated that workers generally stayed with the mine for a lifetime, with little opportunity to change jobs (making exposure to other occupational carcinogens unlikely). Two of the studies ((Wang et al., 2012, 2572504) p. 406 and (Wang et al., 2013, 2548289) p. 2) indicated no detection of tremolite (amphibole contamination < 0.1%, the limit of detection).	Medium	2	0.250	0.500
Analysis	12. Study Design and Methods	The study design was appropriate to address the research question. Cox and/or Poisson regression analyses were used ((Wang et al., 2013, 2548289) p. 3, (Wang et al., 2014, 2538846) p. 121, and (Wang et al., 2012, 2572504) p. 407). The Wang et al. 2012 study ((Wang et al., 2012, 2572504) p. 407) and Wang et al. 2014 study ((Wang et al., 2014, 2538846) p. 121) used Cox proportional hazard models to obtain hazard ratios for lung cancer mortality in relation to asbestos exposure (cumulative exposure for the latter study). The Wang et al. 2013 study ((Wang et al., 2013, 2548289) p. 3) used Poisson regression to estimate relative risks for lung cancer.	Medium	2	0.400	0.800

Study reference:	This cohort evaluation represents all identified publications pertaining to the cohort of miners in Chongqing, China. A full list of related papers reviewed during this evaluation are listed in Table 2.1.					
Domain	**Metric**	**Comments**	**Qualitative Determination**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	13. Statistical power	The number of participants (cohort size = 1539 workers) was large enough to detect an effect in the exposed population. However, it was noted that there was a relatively small number of nonsmokers in the cohort ((Wang et al., 2013, 2548289) p. 6 and (Wang et al., 2012, 2572504) p. 410).	Medium	2	0.200	0.400
	14. Reproducibility of analyses	The methods used to estimate exposures were not described in a way that would facilitate reproducibility (string references were cited in (Wang et al., 2013, 2548289) p. 2 and (Wang et al., 2014, 2538846) p. 120 as supporting evidence for dust to fiber concentration conversions). In general, the statistical analyses used were described, including variables used in the analyses.	Medium	2	0.200	0.400
	15. Statistical Models	The methods used to calculate risk estimates (SMRs and HRs) were adequately described ((Wang et al., 2013, 2548289) p. 3 and (Wang et al., 2014, 2538846) p. 121).	Medium	2	0.200	0.400
High: >=1 and <1.7 Medium: >=1.7 and <2.3 Low: >=2.3 and <=3		**Sum of scores:**			**5**	**8.0166**
		Overall Score = Sum of Weighted Scores/Sum of Metric Weighting Factors:		**1.6033**	**Overall Score: Nearest tenth:**	**1.6**
		Overall Quality Level:		**High**		
Study Quality Comment:	**The reviewer agreed with this study's overall quality level.**					

2.2.3. Epidemiology evaluation results of the Balangero, Italy cohort of studies on asbestos exposure and lung cancer incidence

Study reference:	This evaluation represents all identified publications pertaining to the Balangero, Italy cohort of miners. A full list of related papers reviewed during this evaluation are listed in Table 2.1.					
Domain	**Metric**	**Comments**	**Qualitative Determination**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
Study Participation	1. Participant selection	Subjects included men from the Balangero mine worker cohort that were employed in an Italian asbestos mine. The initial cohort ((Rubino et al., 1979, 178), pg 188) consisted of 952 men employed between 1/1/1930 and 12/31/1965, with at least 30 calendar days' employment during that period. Mortality data were collected from 1/1/1946 to 12/31/1975. Workers for which vital status could not be acertained and a small number of contract workers employed intermittently were excluded. In the first follow-up, 1058 workers were included that had worked at least one year between 1946 and 1987 and mortality follow-up was extended through 12/31/1987 ((Piolatto et al., 1990, 3082492), pg 810). In subsequent follow-ups ((Pira et al., 2009, 2592425) pg 805, and (Pira et al., 2017, 5060134)), subjects included 1056 men from the Balangero mine worker cohort employed between 1930 and 1990, and mortality records were evaluated though 2003 and 2014, respectively. Records were not available between 1987 and 1990, when the mine closed, so workers employed in 1987 were assumed to be employed through 1990 unless they died during that period. Additional details in the most recent following indicated that the initial cohort included 1182 men; the 126 excluded subjects were contract workers, those employed <1 yr, those with inconsistencies in data, and those known to have died prior to 1946 (Pira et al., 2017, 5060134) pg 558.	High	1	0.400	0.400
	2. Attrition	In the most recent follow-up, study authors report that one of the strengths of the study is low proportion of subjects lost to follow-up (Pira et al., 2017, 5060134) pg 562. Loss to follow-up was 2% in the initial cohort (Rubino et al., 1979, 178), 3% in the first follow-up ((Piolatto et al., 1990, 3082492), pg 810), and 4% in the most recent follow-ups (Pira et al., 2009, 2592425) pg 805; (Pira et al., 2017, 5060134) pg 559.	High	1	0.400	0.400

Study reference:	This evaluation represents all identified publications pertaining to the Balangero, Italy cohort of miners. A full list of related papers reviewed during this evaluation are listed in Table 2.1.					
Domain	**Metric**	**Comments**	**Qualitative Determination**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	3. Comparison Group	The most complete data on comparison groups is available from the most recent follow-up (Pira et al., 2017, 5060134). General population mortality rates using the whole country from 1955 until 1980 and specifically the Piedmont Region (where the mine is located) from 1981 onwards (no regional rates available prior to 1981). The 1955-1959 rates were applied to 1946-1954 period (no available data); this may have led to an underestimate of expected deaths which may have showed and increased rate during this period. Expected numbers of deaths (overall and selected cancers) were computed using age-specific and calendar-year-specific (5-year categories) male death rates (Pira et al., 2017, 5060134) pg 559. The only deviation from this was in the first follow-up, which used national mortality rates were for the entire follow-up period (through 1987) (Piolatto et al., 1990, 3082492) pg. 811). In the initial study on this cohort ((Rubino et al., 1979, 178), pg. 189), an additional case-control study was performed in which 5 age-matched controls were selected at random; they were confirmed alive at the time of death for the matched case. No details on what population provided controls. The evaluation is based on the cohort mortality study only, as this was the analysis carried through the 3 follow-up studies (Pira et al., 2017, 5060134; Pira et al., 2009, 2592425; Piolatto et al., 1990, 3082492).	High	1	0.200	0.200
Exposure Characterization	4. Measurement of Exposure	Most complete report of exposure assessment is in initial cohort study ((Rubino et al., 1979, 178) pg 189). Chrysotile fiber counts were first measured in 1969 using membrane filter collection and phase contrast microscopy (frequency not reported). To estimate exposure from 1946-1969, factory records on daily production, equipment used, characteristics of the job and number of hours/day were used (this method has considerable limitations due to basis on mean values for large job categories and no allowance for changes in weather). Simulated and measured data were made comparable by using weighting factors (e.g., more dusty operation for 1-2 hr/d compared with longer working hours in the past). Less detailed information was included in follow-up reports ((Piolatto et al., 1990, 3082492) pg. 810; (Pira et al., 2017, 5060134), pg 558-559)	Medium	2	0.400	0.800

Study reference:	This evaluation represents all identified publications pertaining to the Balangero, Italy cohort of miners. A full list of related papers reviewed during this evaluation are listed in Table 2.1.					
Domain	**Metric**	**Comments**	**Qualitative Determination**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	5. Exposure levels	In the initial cohort ((Rubino et al., 1979, 178), Table 8), exposure was reported as up to 100 fiber/yr or >100 fiber/year. In the follow-ups, exposure was reported as <100 fiber/mL-yr, 100-<400 fiber/mL-yr, and >=400 fiber/ml-yr ((Piolatto et al., 1990, 3082492), Table 3; (Pira et al., 2009, 2592425), Table 2; (Pira et al., 2017, 5060134), Tables 3-4)	Medium	2	0.200	0.400
	6. Temporality	Evaluation is based on the most recent publication, which is has the longest follow-up period for this cohort (follow up of the 1946-1990 cohort through 2014) ((Pira et al., 2017, 5060134), pg 559). The first two studies on this cohort ((Rubino et al., 1979, 178) pg.188, (Piolatto et al., 1990, 3082492) pg 811) have inadequate follow-up duration for lung cancer (<15 years).	High	1	0.400	0.400
Outcome Assessment	7. Outcome measurement or characterizati	Lung cancer mortality was assessed based on death certificate cause of death according to ICD rubrics 162/163 ((Pira et al., 2017, 5060134), Table 1; (Rubino et al., 1979, 178) pg 189; (Piolatto et al., 1990, 3082492) pg 189).	High	1	0.667	0.667
	8. Reporting Bias	Overall SMRs plus 95% CIs for lung cancer are reported for the initial study and all 3 follow-ups with 95% CI values in Table 2 of the most recent follow-up (Pira et al., 2017, 5060134). Lung and pleural cancers are grouped together for the SMR from the original study. The most recent follow-up also reports RRs with confidence intervals for lung cancer mortality (Table 4; (Pira et al., 2017, 5060134)). The case-control report in the initial study [(Rubino et al., 1979, 178), Table 5] did not include confidence intervals. The evaluation is based on the SMR analyses carried forward in the follow-ups and the RR analyses conducted in the most recent follow-up.	High	1	0.333	0.333
Potential Confounding/Variable Control	9. Covariate Adjustment	SMR was stratified by age and calendar year (5-yr categories). Only males were included. ((Rubino et al., 1979, 178) pg 189; (Piolatto et al., 1990, 3082492) pg 811; (Pira et al., 2009, 2592425), pg 806; (Pira et al., 2017, 5060134), pg 559. In the most recent follow-up, data on smoking was limited to 14.5% of the cohort, but the prevelance of smoking in this subset of the cohort was comparable to that of the general male population ((Pira et al., 2017, 5060134) pg 562).	High	1	0.500	0.500

Study reference:	This evaluation represents all identified publications pertaining to the Balangero, Italy cohort of miners. A full list of related papers reviewed during this evaluation are listed in Table 2.1.					
Domain	**Metric**	**Comments**	**Qualitative Determination**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	10. Covariate Characterization	Empirical data obtained from employment records. Smoking information was obtained from medical records (when available).	High	1	0.250	0.250
	11. Co-exposure Confounding	No adjustments for potential coexposures were described. Dust identified as primarily chrysotile, no amphibole fibers dectected, but a fibrous silicate (balangeroite) was detected (0.2-0.5% of total sample) ((Pira et al., 2017, 5060134) pg 560).	Low	3	0.250	0.750
Analysis	12. Study Design and Methods	For this retrospective cohort there is an initial study ((Rubino et al., 1979, 178)) and 3 follow-up studies ((Piolatto et al., 1990, 3082492), (Pira et al., 2009, 2592425), (Pira et al., 2017, 5060134)). Evaluation is based on the most recent follow-up ((Pira et al., 2017, 5060134), pg 559), in which SMRs were calculated for entire cohort as well as based on indicators of asbestos exposure (duration of exposure, age at first exposure, years since first exposure, years since last exposure, period at first exposure, and cumulative dust exposure). RRs were also calculated using Poisson regression. In this recent follow-up, cohort members contributed to person-time of observation starting 1 year after first employment (or 1946), and ended at death, date of last contact for those lost to follow-up, 85th birthday, or December 31, 2014.	Medium	2	0.400	0.800
	13. Statistical power	The evaluation is based on the most recent follow-up ((Pira et al., 2017, 5060134), pg 516), which has a 90% statistical power to detect a SMR of 2.0 for lung cancer among workers with <100 fiber/mL-years cumulative exposure (determined SMR [95% CI] was 0.82 [0.44-1.40]; 13 deaths). The power of the analysis for <25 fibers/mL-years cumulative exposure was reported as "low" (determined SMR [95% CI] was 2.40 [0.49-7.01]; 3 deaths). The power for analyses at higher exposure levels (>=100 fiber/mL-years) was not reported.	Medium	2	0.200	0.400
	14. Reproducibility of analyses	The evaluation is based on the most recent follow-up ((Pira et al., 2017, 5060134)). For SMR calculations, expected deaths were not reported for SMRs from selected causes according to indicators of asbestos exposure. All other relevant data are reported in Tables 1-4.	Medium	2	0.200	0.400

Study reference:	This evaluation represents all identified publications pertaining to the Balangero, Italy cohort of miners. A full list of related papers reviewed during this evaluation are listed in Table 2.1.					
Domain	**Metric**	**Comments**	**Qualitative Determination**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	15. Statistical Models	The evaluation is based on the most recent follow-up ((Pira et al., 2017, 5060134), pg 559). SMRs were calculated for entire cohort as well as based on indicators of asbestos exposure (duration of exposure, age at first exposure, years since first exposure, years since last exposure, period at first exposure, and cumulative dust exposure). RRs were calculated using Poisson regression.	Medium	2	0.200	0.400
High: >=1 and <1.7 Medium: >=1.7 and <2.3 Low: >=2.3 and <=3		**Sum of scores:**			**5**	**7.1**
		Overall Score = Sum of Weighted Scores/Sum of Metric Weighting Factors:		**1.42**	**Overall Score: Nearest tenth:**	**1.4**
		Overall Quality Level:		**High**		
Study Quality Comment:	**The reviewer agreed with this study's overall quality level.**					

2.2.4. Epidemiology evaluation results of the North Carolina, US cohort studies on asbestos exposure and lung cancer incidence

Study reference:	This evaluation represents all identified publications pertaining to the North Carolina cohort of textile workers. A full list of related papers reviewed during this evaluation are listed in Table 2.1.					
Domain	**Metric**	**Comments**	**Qualitative Determination**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
Study Participation	1. Participant selection	a. Setting and methods of case ascertainment were reported in (Loomis et al., 2009, 3079232), p. 535-536. Participant selection and inclusion/exclusion criteria varied by study and analysis. Although there were 4 plants in the cohort, exposure data were available only for three of the four, so exposure-response analyses were limited to these three plants. Original selection criteria reported in (Loomis et al., 2009, 3079232) p 536 (participants had to work at least 1 day between 1950 and 1973) and p 539 (participants excluded due to missing data). (Elliott et al., 2012, 1247861) evaluated a subset of the cohort that worked >30 days during the same time frame. b. Selection in or out of the study was based on 1) employment in production job during designated time frame and b) availability of necessary data (birth and hire dates; work history; vital status). These criteria are unlikely to result in biased subject participation.	High	1	0.400	0.400
	2. Attrition	Attrition/missing data exclusions were reported in both (Loomis et al., 2009, 3079232) (p. 539) and (Elliott et al., 2012, 1247861) see pg 386. The original cohort was 5770 persons; 373 workers at plant 2 were excluded due to lack of exposure data at this plant, 1596 were excluded due to incomplete work histories (at department level) or non-production jobs ((Loomis et al., 2009, 3079232) p. 539). Final cohort for exposure-response analyses was 3803. Vital status was unknown for 241 of the 3803 (6%) cohort members (suggesting moderate loss to follow up). The subgroup evaluated in (Elliott et al., 2012, 1247861) consisted of 3082 subjects (excluded persons who worked <30 days); the proportion for whom vital status was missing was not reported for the subgroup.	Medium	2	0.400	0.800

Study reference:	This evaluation represents all identified publications pertaining to the North Carolina cohort of textile workers. A full list of related papers reviewed during this evaluation are listed in Table 2.1.					
Domain	**Metric**	**Comments**	**Qualitative Determination**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	3. Comparison Group	There is potential for selection bias. All plants were subject to surveillance program that removed workers from exposure if they developed x-ray changes attributable to dust exposure (typical change was pneumoconiosis). Study authors reported that some x-ray changes are associated with higher lung cancer risk. Thus, the surveillance program could have selected workers at greater risk of lung cancer for lower cumulative exposure ((Loomis et al., 2009, 3079232) p. 542, and (Elliott et al., 2012, 1247861) pg. 388.	Medium	2	0.200	0.400
Exposure Characterization	4. Measurement of Exposure	Air samples were available for 3 plants covering period from 1935 to 1986 (459 <1950; 1674 from 1950-1969, and 1287 from 1970 forward; (Loomis et al., 2009, 3079232), p. 536). Measurements used impinger before 1964 and PCM thereafter; paired and concurrent samples between 1964 and 1971 were used to relate impinger to PCM-equivalent concentrations. Air samples were not collected yearly, so mean PCM-equivalent concentrations were estimated by plant, department, job, and time period using multivariate mixed models ((Loomis et al., 2009, 3079232), p. 536). Individual cumulative exposure assessed using the modeled concentrations and JEM ((Loomis et al., 2009, 3079232), p 536); details of JEM reported in (Dement et al., 2008, 626406).	High	1	0.400	0.400
	5. Exposure levels	Exposure-response relationships were developed (see Table 5 of (Loomis et al., 2009, 3079232) and (Elliott et al., 2012, 1247861) see Table 2). A total of 5 cumulative exposure levels are analyzed in Table 5 of (Loomis et al., 2009, 3079232).	Medium	2	0.200	0.400
	6. Temporality	Temporality was established (exposure preceded death). The follow-up time was at least 30 years (1973-2003); lag times of 0, 10, 20, and 30 years were analyzed ((Loomis et al., 2009, 3079232) Table 5 and (Elliott et al., 2012, 1247861) see Table 2).	High	1	0.400	0.400
Outcome Assessment	7. Outcome measurement or characterization	Lung cancer deaths (underlying or immediate cause or other significant condition at time of death) were determined from the National Death Index Plus (1979 and later) or state records (before 1979). Specific ICD codes were not reported, but ICD in effect at time of death was used ((Loomis et al., 2009, 3079232), p 536). Deaths before 1979 were coded manually by a nosologist.	Medium	2	0.667	1.333

Study reference:	This evaluation represents all identified publications pertaining to the North Carolina cohort of textile workers. A full list of related papers reviewed during this evaluation are listed in Table 2.1.					
Domain	**Metric**	**Comments**	**Qualitative Determination**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	8. Reporting Bias	Lung cancer findings are reported in abstract, results, and discussion of key publications ((Loomis et al., 2009, 3079232) and (Elliott et al., 2012, 1247861)). Lung cancer deaths and person-years at risk by exposure category are reported in Table 5 of (Loomis et al., 2009, 3079232); lung cancer cases and person-years at risk are reported by plant in Table 1 of (Elliott et al., 2012, 1247861). Rate ratio estimates are reported with CIs in (Loomis et al., 2009, 3079232) and (Elliott et al., 2012, 1247861); coefficients for Poisson regression are reported without SE in Table 2 of (Elliott et al., 2012, 1247861), but rate ratios with CIs are also reported for the same models.	High	1	0.333	0.333
Potential Confounding/Variable Control	9. Covariate Adjustment	Analyses in (Loomis et al., 2009, 3079232) and (Elliott et al., 2012, 1247861) were adjusted for age, sex, race, decade of follow-up and birth cohort. No adjustment was made for smoking, which could bias SMR analyses (reported in (Loomis et al., 2009, 3079232)) but is not likely to bias internal analysis in an occupational cohort (e.g., exposure-response analyses in (Loomis et al., 2009, 3079232) and (Elliott et al., 2012, 1247861).	Medium	2	0.500	1.000
	10. Covariate Characterization	While not specified, information on covariates included in the analyses were likely obtained from same sources as vital status/cause of death. Subjects with missing hire or birth date were excluded ((Loomis et al., 2009, 3079232), p 539). Smoking information was available for <15% of the cohort.	Medium	2	0.250	0.500
	11. Co-exposure Confounding	One plant used a limited amount of amosite between 1963 and 1976 ((Loomis et al., 2009, 3079232), p. 536). Adjustment for this coexposure was not possible because none of the lung cancer deaths were among workers involved in activities using amosite ((Loomis et al., 2009, 3079232), p. 539)	Medium	2	0.250	0.500
Analysis	12. Study Design and Methods	Study design was retrospective cohort; Poisson regression used for internal analyses in (Loomis et al., 2009, 3079232) (p. 537) and (Elliott et al., 2012, 1247861) (p. 386).	Medium	2	0.400	0.800

Study reference:	This evaluation represents all identified publications pertaining to the North Carolina cohort of textile workers. A full list of related papers reviewed during this evaluation are listed in Table 2.1.					
Domain	**Metric**	**Comments**	**Qualitative Determination**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	13. Statistical power	None of the related studies report power calculations. Authors ((Loomis et al., 2009, 3079232), p. 541) cite large size of cohort (3803 who worked for at least 1 day in plants with exposure data [(Loomis et al., 2009, 3079232)]; 3082 who worked at least 30 days in plants with exposure data (Elliott et al., 2012, 1247861), high proportion of subjects with vital status ascertained, and long follow-up (30+ yrs; total 124,029 person-years working at least 1 day [(Loomis et al., 2009, 3079232)]; 100742 person-years working at least 30 days (Elliott et al., 2012, 1247861) as strengths.	Medium	2	0.200	0.400
	14. Reproducibility of analyses	Analysis description in (Loomis et al., 2009, 3079232) appears to be complete. Statistical tests and estimation procedures and variables considered are reported ((Loomis et al., 2009, 3079232) p 537-538 and supplemental file); cumulative exposure categories for internal analysis define quantiles of exposure among cases (footnote to Table 5 in (Loomis et al., 2009, 3079232)). There were no variable transformations, outlier exclusions, or imputation of missing values. Analysis description in (Elliott et al., 2012, 1247861) appears to be complete. Statistical tests and estimation procedures and variables considered are reported (Elliott et al., 2012) pg 386. Cumulative exposure was analyzed as a continuous variable (Elliott et al., 2012, 1247861) pg 386. No variable transformations were reported.	Medium	2	0.200	0.400
	15. Statistical Models	Statistical models and methods are described in each publication (see (Loomis et al., 2009, 3079232) p 537-538 and (Elliott et al., 2012, 1247861) p 386), including how variables were included or excluded; supplemental file to Loomis et al. (2009, 3079232) provides details of SMR computation when race was unknown and further explanation of the Poisson exposure-response models. For (Elliott et al., 2012, 1247861), covariates were assessed as confounders using a 10% change in estimate method and as effect measure modifiers using likelihood ratio test.	Medium	2	0.200	0.400
High: >=1 and <1.7 Medium: >=1.7 and <2.3 Low: >=2.3 and <=3		**Sum of scores:**			**5**	**8.4666**
		Overall Score = Sum of Weighted Scores/Sum of Metric Weighting Factors:		**1.6933**	**Overall Score: Nearest tenth:**	**1.7**

Study reference:	This evaluation represents all identified publications pertaining to the North Carolina cohort of textile workers. A full list of related papers reviewed during this evaluation are listed in Table 2.1.					
Domain	**Metric**	**Comments**	**Qualitative Determination**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
		Overall Quality Level:		**Medium**		
Study Quality Comment:	**The reviewer agreed with this study's overall quality level.**					

2.2.5. Epidemiology evaluation results of the Salonit Anhovo, Slovenia cohort studies on asbestos exposure and lung cancer incidence

Study reference:	This cohort evaluation represents all publications pertaining to the Slovenian cohort of asbestos-cement workers. A full list of related papers reviewed during this evaluation are listed in Table 2.1.					
Domain	**Metric**	**Comments**	**Qualitative Determination**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
Study Participation	1. Participant selection	This study included 58 histologically confirmed incident lung cancer cases from the national cancer registrar and 290 matched controls from a cohort of 6714 workers employed at Salonit Anhovo factory after Dec 31 1946 who worked there for at least one day between 1964 and 1994 (pg. 263-264). DOB, gender, and year of hire (pre-1959 or post-1959, based on better quality of exposure data after 1959) were used as matching factors. Five controls closest to the birth date were selected and had to be alive at time of diagnosis (using national mortality registrar) (pg. 263). The follow-up begins at 1964 because the cancer registrar data were only available in a computerized form from 1964 onward (registry established in 1957) (pg. 263).	High	1	0.400	0.400
	2. Attrition	Initial study pop was 67 cases of lung cancer, 335 controls (5 controls/case) were selected based on original. Nine cases were excluded because they were hired prior to 1947 (a priori date cut-off; factory was owned by Italians from 1921-1947 and the Slovenian republic from 1947 onward), so those 45 matched controls were also excluded. This left 58 cases and 290 matched controls. (pg. 264) Retention of 87% (58/67 cases) was characterized as moderate subject exclusion.	Medium	2	0.400	0.800
	3. Comparison Group	Cases and controls were selected from the same occupational cohort. Matched based on DOB, gender, and year of hire (pre- or post-1959). (pg. 263) Controls were confirmed alive at age of diagnosis for case. (pg. 263) Other demographics were also similar (see Table 1, pg 264).	High	1	0.200	0.200

Study reference:	This cohort evaluation represents all publications pertaining to the Slovenian cohort of asbestos-cement workers. A full list of related papers reviewed during this evaluation are listed in Table 2.1.					
Domain	**Metric**	**Comments**	**Qualitative Determination**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
Exposure Characterization	4. Measurement of Exposure	A total of 1030 air measurements from factory were available from 1961-1995 using several different monitoring methods, including a set of 78 paired measurements using side-by-side gravimetric and membrane filter methods. An early publication on this cohort by Dodic Fikfak (2003,3080279) (pg 171) indicates that gravimetric is a mass based method (units of mg/m3) and the membrane filter method is a fiber counting method (units of f/cm3). Microscopy analysis was not described; therefore TEM and PCM methods were likely not used. The non-parametric classification and regression tree (CART) method was used to calculate conversion factors for different combinations of fiber type, product, and production method. Exposure levels were measured at fixed locations close to worker's breathing zones. Exposures were estimated for missing years using previous or next values (or average of both). Exposures for most workers were based on measured exposure values in work area. A few jobs did not have applicable air sample measurements, and exposures were estimated with JEM. The percentage of individuals in the JEM group were not reported; however, study authors state that subjects from this group were not selected for the study. (pg. 263)	Low	3	0.400	1.200
	5. Exposure levels	Evaluated as dichotomous exposure definitions: exposed/unexposed, above/below median, and above/below 90th percentile. (pg. 263-264)	Low	3	0.200	0.600
	6. Temporality	Average latency between start of employment and diagnosis in cases was 24.9 years (pg. 264). Study authors conducted evaluations with different latency periods (0-15 yrs, 16-35 yrs, and >35 yrs) (pg. 263). The primary analysis is exposure >15 years prior to diagnosis (Table 4, pg. 266).	High	1	0.400	0.400
Outcome Assessme	7. Outcome meas	All cases were histologically confirmed incident cases of primary lung cancer (pg. 263).	High	1	0.667	0.667

Study reference:	This cohort evaluation represents all publications pertaining to the Slovenian cohort of asbestos-cement workers. A full list of related papers reviewed during this evaluation are listed in Table 2.1.					
Domain	**Metric**	**Comments**	**Qualitative Determination**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	8. Reporting Bias	The primary analysis is limited to cases (and matched controls) with exposure >15 years prior to diagnosis of case (Table 4, pg. 266). The study does not report the number of cases and controls exposed for >15 years only. Additionally, exposure estimates are for all years, 0-15 yr, 16-35 yr, and >35 yrs (data are very limited for >35), separated by case and control (Table 3, pg. 266). Based on data reporting, it is not clear exactly which exposure-cutoff values were used for median and 90th percentile analyses.	Medium	2	0.333	0.667
Potential Confounding/Variable Control	9. Covariate Adjustment	Matching variables of birth and gender were included in models as covariates. The matching factor of pre vs. post 1959 hire was also evaluated as a potential covariate. However, a comparison of analyses did not show evidence that pre/post 1959 hire introduced confounding, so this covariate was not maintained in the primary analysis. (pg. 263). Separate analyses were calculated for smokers and non-smokers, but non-smoking population was very small (pg. 263, 265). Logistic regression models were adjusted for smoking (yes/no) (pg. 264). No further covariate assessment/adjustments made (except co-exposure, addressed in Metric 11).	Medium	2	0.500	1.000
	10. Covariate Char	Covariates were empirical data obtained from employment records (age, sex) (pg. 263).	High	1	0.250	0.250
	11. Co-exposure Confounding	Amphibole asbestos: Amphibole exposure made up for 10% of the total asbestos exposure (pg. 261). Detailed records allowed the estimation of separate individual exposure histories for different forms (pg. 261). Methods indicate that models were adjusted for confounders (pg. 263), but did not specifically indicate whether or not final model was adjusted for amphibole asbestos exposure. Non-asbestos: Duration of exposure to silica dust (containing silicon dioxide) and cement dust (containing Cr6+) were included in model with 15 yr latency with and without simultaneous fitting of smoking and asbestos variables (no concentration data, assigned presence/absence based on job) (pg. 263, 264). No evidence of confounding was observed in analyses of cement and silica dust. Methods indicate that models were adjusted for confounders (pg. 263), but did not specifically indicate whether or not final model was adjusted for co-exposures.	Low	3	0.250	0.750

Study reference:	This cohort evaluation represents all publications pertaining to the Slovenian cohort of asbestos-cement workers. A full list of related papers reviewed during this evaluation are listed in Table 2.1.					
Domain	**Metric**	**Comments**	**Qualitative Determination**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
Analysis	12. Study Design and Methods	Study was a case-control design. Models of exposure and risk were adjusted for confounding using unconditional or conditional multivariate logistic regression (pg. 263). Matching variables were included as covariates in unconditional models (pg. 263). Primary evaluation used OR calculations to determine risk from cumulative exposure estimates using 15-year latency for main analysis (Table 4, pg 266).	Medium	2	0.400	0.800
	13. Statistical power	Low would be selected if it was an option. No statistically significant findings were observed (Table 4, pg 266); study authors attribute this to low statistical power-confidence intervals. Low statistical power was reported as a limitation of the study by study authors (pg 266-267).	Medium	2	0.200	0.400
	14. Reproducibility of analyses	Median and 90th percentile cutoffs were not explicitly reported for chrysotile asbestos for >15 yr latency analysis. Number of cases and controls included in >15 yr latency analysis not reported.	Low	3	0.200	0.600
	15. Statistical Models	Logistic regression models were constructed for each of the following dichotomous exposure definitions: ever/never, above/below median, and above/below 90th percentile (pg. 263-264).	Medium	2	0.200	0.400
High: >=1 and <1.7 Medium: >=1.7 and <2.3 Low: >=2.3 and <=3		**Sum of scores:**			**5**	**9.1334**
		Overall Score = Sum of Weighted Scores/Sum of Metric Weighting Factors:		**1.8267**	**Overall Score: Nearest tenth:**	**1.8**
		Overall Quality Level:		**Medium**		
Study Quality Comment:	**The reviewer agreed with this study's overall quality level.**					

2.2.6. Epidemiology evaluation results of the Quebec, Canada cohort studies on asbestos exposure and lung cancer incidence

Study reference:	**This evaluation represents all identified publications pertaining to the Quebec, Canada cohort of miners. A full list of related papers reviewed during this evaluation are listed in Table 2.1.**					
Domain	**Metric**	**Comments**	**Qualitative Determination**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
Study Participation	1. Participant selection	Some details of the setting (e.g., the mine locations and production quantities, but no description of the facilities and exposure conditions) are provided in (Liddell et al., 1997, 3081408) (p 14); additional information may be available in Gibbs and Lachance (1972, 3580825) (cited as the source of the exposure assessment), but no pdf was available in HERO at the time of evaluation. Participant selection, inclusion/exclusion criteria, case ascertainment, and participation at each level are described in detail ((Liddell et al., 1997, 3081408), p 14-16). Selection into the cohort was based on a) male sex; b) birth year between 1890 and 1920; b) employment at the Thetford Mines or Asbestos mine/mill or factory for at least one month. Participant selection and participation were not likely to be biased based on these criteria.	High	1	0.400	0.400
	2. Attrition	Numbers of subjects lost to follow up are reported in (Liddell et al., 1997, 3081408), Table 4; there it is reported that a total of 1138/10918 (~10%) were lost to follow-up. No information comparing the demographics or exposure of those lost to follow up to the study subjects was located in the six selected HERO IDs. Missing data were not imputed; however, censoring of survival data is unlikely to introduce bias. This level of attrition is considered to be moderate.	Medium	2	0.400	0.800
	3. Comparison Group	Internal analysis was reported only in the nested case-control study in Liddell et al. (1998, 3081200) (ORs in Table 4). Most of the publications (see (Liddell et al., 1997, , 3081408) p 18; Liddell and Armstrong (2002, 3080504) p 9) reported SMR analyses using age- sex- and calendar year (5 year intervals) -adjusted general population (Quebec when available, or Canada for earlier time periods) mortality rates as the comparison group. No adjustment for race was made.	Medium	2	0.200	0.400
Exposure Characterization	4. Measurement of Exposure	Exposure levels measured exclusively using midget impinger ((Liddell et al., 1997, 3081408), p 17) and conversion factors were not determined (based on review of the six selected HERO IDs).	Low	3	0.400	1.200

Study reference:	This evaluation represents all identified publications pertaining to the Quebec, Canada cohort of miners. A full list of related papers reviewed during this evaluation are listed in Table 2.1.					
Domain	**Metric**	**Comments**	**Qualitative Determination**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	5. Exposure levels	Cumulative exposure-response relationships were developed (see for example Table 8 of (Liddell et al., 1997, 3081408)). A total of 7 cumulative exposure levels (exposure through age 55) are reported in Table 8 of (Liddell et al., 1997, 3081408); in Liddell and Armstrong (2002, 3080504), 10 exposure levels are reported in Table 5.	Medium	2	0.200	0.400
	6. Temporality	Temporality was established (exposure preceded death), and there was adequate follow-up for consideration of latency. Of the total cohort of 10918 men, 6415 were still employed when the cohort was first established in 1966, and follow up extended to 1992 ((Liddell et al., 1997, 3081408) p 15). Entry into the cohort was restricted to men born between 1891 and 1920 ((Liddell et al., 1997, 3081408) p 15), so the youngest subjects at the end of follow up were 72 years old. There was no indication in the studies reviewed that the operations at Thetford or Asbestos had ceased at any point during the follow up time.	High	1	0.400	0.400
Outcome Assessment	7. Outcome measurement or characterization	ICD code 162 (ICD-9) used. Cause of death was obtained from death certificate (or other "reliable" information, primarily from hospitals); these were available for over 98% of the cohort followed through 1992 ((Liddell et al., 1997, 3081408), p 16). Cause-specific death rates (referent group for SMRs) were available only for deaths from 1950 forward.	High	1	0.667	0.667
	8. Reporting Bias	In most analyses SMRs are reported without CI estimates (e.g., Table 8 in (Liddell et al., 1997, 3081408); Tables 3-5 of Liddell and Armstrong (2002, 3080504)).	Medium	2	0.333	0.667
Potential Confounding/Variable Control	9. Covariate Adjustment	SMRs were calculated using gender-specific rates across 16 age categories ((Liddell et al., 1997, 3081408) p 18). In Liddell et al. (1998, 3081200), a detailed analysis of the effect of smoking on risk estimates was presented. Vacek (1998, 3081118) also included an analysis of the impact of smoking. No adjustment for race was made.	Medium	2	0.500	1.000

Study reference:	This evaluation represents all identified publications pertaining to the Quebec, Canada cohort of miners. A full list of related papers reviewed during this evaluation are listed in Table 2.1.					
Domain	**Metric**	**Comments**	**Qualitative Determination**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	10. Covariate Characterization	Information on sex and birth date or age at first employment were recorded from personnel records in 1966 and reviewed and/or corrected during subsequent analyses ((Liddell et al., 1997, 13081408) p 14-15). No information on race of cohort members was located in any of the 8 selected HERO IDs. A questionnaire was administered in 1970 to obtain smoking histories; subjects still living completed the questionnaires (99.6% of 6583 men alive completed their own questionnaires), and proxies provided the information for deceased subjects (for 90% of those who died after 1950; (Liddell et al., 1997, 13081408) p 18). Each subject was assigned to the smoking category in which his response placed him at the time of the questionnaire ((Liddell et al., 1997, 13081408) p 18). A total of 891 questionnaires, mostly completed by proxies, were judged unreliable and the subjects omitted from analyses that considered smoking ((Liddell and Armstrong, 2002, 3080504) p 7). While the methods to assess potential confounders were not validated, there is little indication that the methods had poor validity.	Medium	2	0.250	0.500
	11. Co-exposure Confounding	Liddell et al. (1997, 13081408) (p 33) reports that analysis of fibers in the lungs of workers in the Quebec industry showed higher levels of tremolite fibers than chrysotile fibers, especially at the Thetford mines. On p 34, Liddell et al. (1997, 13081408) states that the chrysotile produced in Quebec may be contaminated not only with tremolite but with other amphibole fibers. Liddell and Armstrong (2002, 3080504) (p 8) reports that the Thetford mines complex had "more substantial" tremolite contamination than the mine and mill at Asbestos, and suggests that it is therefore desirable to analyze the sites separately. None of the 8 selected HERO IDs provided quantitative estimation of the degree of contamination. Thus, there is no information to indicate how the co-exposure may have been distributed across cohort members and/or its relationship to chrysotile exposure. It is possible that additional information is available in Gibbs and Lachance (1972, 3580825), which is cited as the source of the JEM and exposure assessment, but no pdf was available in HERO at the time of evaluation.	Low	3	0.250	0.750

Study reference:	This evaluation represents all identified publications pertaining to the Quebec, Canada cohort of miners. A full list of related papers reviewed during this evaluation are listed in Table 2.1.					
Domain	**Metric**	**Comments**	**Qualitative Determination**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
Analysis	12. Study Design and Methods	Study design was retrospective cohort. Poisson regression used in some analyses (Liddell and Armstrong (2002, 3080504) p. 8) but not others. Liddell et al. (1998, 3081200) reported a nested case-control study within the cohort and used conditional logistic regression	Medium	2	0.400	0.800
	13. Statistical power	Power calculations were not reported. The number of participants was sufficient to detect an effect (statistically significant association reported in Vacek (1998, 3081118)). However, many of the studies did not report statistical significance or confidence intervals for calculated SMRs (see for example Tables 8 and 10 of Liddell et al. (1997, 3081408)).	Medium	2	0.200	0.400
	14. Reproducibility of analyses	The analysis description varied by study. This metric is rated based exclusively on the description in Liddell et al. (1997, 3081408), which is based on the combined longest follow up and largest population. The effect estimation methods in this paper were reported (p. 18-19), but the rules for cumulative exposure categorization (as shown in Tables 7 and 8) were not reported. There were no variable transformations or outlier exclusions, and no true statistical analyses (CIs were not reported for the SMRs).	Low	3	0.200	0.600
	15. Statistical Models	Liddell et al. (1997, 3081408) did not include any statistical models per se (effect estimates calculated as SMRs = O/E without CIs). Liddell et al. (1998, 3081200) reported a nested case-control study within the cohort and used conditional logistic regression. 90% Confidence intervals were estimated from the regression on the assumption that the regression coefficients are normally distributed; no information on whether assumptions were met was provided. Liddell and Armstrong (2002, 3080504) provided detailed description of statistical models (p 8-9) but did not describe model assumptions or whether they were met.	Low	3	0.200	0.600
High: >=1 and <1.7 Medium: >=1.7 and <2.3 Low: >=2.3 and <=3		**Sum of scores:**			**5**	**9.5834**
		Overall Score = Sum of Weighted Scores/Sum of Metric Weighting Factors:		**NA**	**Overall Score: Nearest tenth:**	**NA**
		Overall Quality Level:		**Low**		

Study reference:	**This evaluation represents all identified publications pertaining to the Quebec, Canada cohort of miners. A full list of related papers reviewed during this evaluation are listed in Table 2.1.**					
Domain	**Metric**	**Comments**	**Qualitative Determination**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
Study Quality Comment:	**This study's overall quality rating was downgraded during conflict resolution between primary review and QA/QC review. Downgrading was due to lack of PCM or TEM-equivalent exposure estimates and potentially significant co-exposure to tremolite or other amphiboles. Note: The original calculated score for this study was 1.9. This value is not presented above because the final rating was changed based on professional judgement.**					

2.2.7. Epidemiology evaluation results of the Chongqing, China textile worker cohort studies on asbestos exposure and lung cancer incidence

Study reference:	This evaluation represents all identified publications pertaining to the Chongqing, China cohort of textile workers. A full list of related papers reviewed during this evaluation are listed in Table 2.1.					
Domain	**Metric**	**Comments**	**Qualitative Determination**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
Study Participation	1. Participant selection	The key elements of the study design are reported. The fixed cohort is well-established. The inclusion criteria were clearly specified (male workers registered with the plant by January 1 1972, employed for at least one year; Deng et al. (2012, 2573093) p. 82 and Courtice et al. (2016, 3520560) p. 370). Workers with cardiopulmonary disease, or those employed after January 1 1972 were excluded. The reported information indicates that selection into/out of the study was not likely biased.	High	1	0.400	0.400
	2. Attrition	There was minimal loss of subjects at follow-up. The 2016 study (conducted 37 years after establishment of the cohort) reported that 577 of 586 workers (99%) were successfully followed through 2008 (Courtice et al. (2016, 3520560) p. 370). Therefore, exposure and outcome data were largely complete.	High	1	0.400	0.400
	3. Comparison Group	Inclusion criteria and the methods of participant selection were reported. All subjects were recruited from the same eligible population within the same time frame. In the Wang et al. 2012 study reporting SMRs (and RRs; (Wang et al., 2014, 2538846) p. 121), the choice of a reference population is reported (based on age-specific national mortality data for males). However, data on cause-specific mortality data were limited (rates of 1990 and 2004 were used to correspond to periods of 1981-1995 and 1996-2006, respectively. The Courtice et al. (2016, 3520560) (p. 375) used the lowest continuous cumulative exposure category (i.e., members of the same cohort in the lowest exposure quartile) as the reference group.	High	1	0.200	0.200

Study reference:	This evaluation represents all identified publications pertaining to the Chongqing, China cohort of textile workers. A full list of related papers reviewed during this evaluation are listed in Table 2.1.					
Domain	**Metric**	**Comments**	**Qualitative Determination**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
Exposure Characterization	4. Measurement of Exposure	Asbestos dust measurements were available starting in 1955 (Courtice et al. (2016, 3520560) p.371, Deng et al. (2012, 2573093) p. 82). Starting in 1999, samples were also analyzed by phase contrast and/or electron scanning microscopy (Courtice et al. (2016, 3520560) p. 371, Deng et al. (2012, 2573093) p. 82). Paired gravimetric and membrane filter samples from 1999 and 2002 (Courtice et al. (2016, 3520560) p. 371, (Wang et al., 2014, 2538846) p. 120) or from 1999, 2002, and 2006 (Deng et al. (2012, 2573093) p. 82) were used to define the relationship between dust and fiber concentrations. From these data, (and using periodically measured data), average fiber concentrations by job type/exposure area were calculated. Studies for this cohort ((Wang et al., 2014, 2538846) p. 120 and Deng et al. (2012, 2573093) p. 82) indicate that conversion from dust to fiber concentrations required log transformation of the paired samples (the distribution of paired samples was positively skewed). Individual cumulative exposures were estimated as the product of (fiber concentration at a specific workshop/job) x (duration of job) (Courtice et al. (2016, 3520560) p.371, Deng et al. (2012, 2573093) p. 82). There were no exposure data prior to 1955; exposure was assumed to be the same as the earliest time measurement in 1955 (Courtice et al. (2016, 3520560) p. 371). There was also no samples for administration or rear service workers; these groups were assumed to belong in the lowest cumulative exposure group (Courtice et al. (2016, 3520560) p. 371). The lack of detailed exposure information and the use of recent (since 1999) samples to convert to historical measurements since 1955 are limitations of the study (Courtice et al. (2016, 3520560) p. 375-376). In addition, workers may have been additionally exposed to chrysotile at home (from spinning; Courtice et al. (2016, 3520560) p. 376). The study authors acknowledge that there may have been exposure misclassification based on these estimations, but the misclassification was likely to be non-differential.	Medium	2	0.400	0.800

Study reference:	This evaluation represents all identified publications pertaining to the Chongqing, China cohort of textile workers. A full list of related papers reviewed during this evaluation are listed in Table 2.1.					
Domain	**Metric**	**Comments**	**Qualitative Determination**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	5. Exposure levels	The range and distribution of exposure is sufficient to develop and exposure-response estimate. The Courtice et al. 2016 study (Courtice et al. (2016, 3520560) p. 375) reports 4 levels of exposure (referent + 3); cumulative exposures were categorized into quartiles for analyses of lung cancer deaths.	Medium	2	0.200	0.400
	6. Temporality	The study establishes appropriate temporality; the interval between exposure and outcome is long enough considering latency of the disease. The cohort was followed for 35 years (Deng et al. (2012, 2573093) p. 81), 26 years ((Wang et al., 2014, 2538846) p. 119) and 37 years (Courtice et al. (2016, 3520560) p. 370). The study by Deng et al. 2012 (Deng et al. (2012, 2573093) p. 83) incorporated lag periods of 5 or 10 years into the models. The Courtice et al. 2016 study (Courtice et al. (2016, 3520560) p. 371) also used exposure lagged by 10 years to account for effects of disease latency. The cohort experienced an average of 41 years since initial exposure (Courtice et al. (2016, 3520560) p. 376).	High	1	0.400	0.400
Outcome Assessment	7. Outcome measurement or characterization	The Wang et al. 2014 publication ((Wang et al., 2014, 2538846) p. 120), does not report ICD codes corresponding to lung cancer. However, the studies by Deng et al. 2012 (Deng et al. (2012, 2573093) p. 82) and Courtice et al. 2016 (Courtice et al. (2016, 3520560) p. 370) clearly identify lung cancers included for analyses by ICD code (ICD-10 C33/C34). About half of the cancer cases were verified pathologically (biopsy or autopsy); others were diagnosed by CT scan and clinical manifestations (Courtice et al. (2016, 3520560) p. 370).	High	1	0.667	0.667
	8. Reporting Bias	Lung cancer findings are reported in the results. In the Wang et al. 2012 study ((Wang et al., 2012, 2572504) p. 122), SMRs and hazard ratio data (with 95% confidence intervals) were complete. The Courtice et al. 2016 study (Courtice et al. (2016, 3520560) p. 375) provides hazard ratios and 95% confidence intervals for lung cancer mortality using cumulative exposure categorized into 4 groups (as a continuous variable).	High	1	0.333	0.333

Study reference:	This evaluation represents all identified publications pertaining to the Chongqing, China cohort of textile workers. A full list of related papers reviewed during this evaluation are listed in Table 2.1.					
Domain	**Metric**	**Comments**	**Qualitative Determination**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
Potential Confounding/Variable Control	9. Covariate Adjustment	In the Wang et al. 2014 study ((Wang et al., 2014, 2538846) p. 121), the final risk estimate model was adjusted for age and smoking. In the Coutice et al. 2016 study (Courtice et al. (2016, 3520560) p. 371), age served as the time dimension for Cox proportional hazard models; smoking status was included as a covariate. There were no adjustments for sex, because the cohort consisted of only males. The Courtice et al. 2016 study (Courtice et al. (2016, 3520560) p. 371) used the lowest exposure category as the reference group rather than an external control group; therefore, the differences among groups are expected to be minimal (for example, with respect to SES).	High	1	0.500	0.500
	10. Covariate Characterization	Covariates were assessed using reliable methodology. Vital status information was obtained from personnel records and interviews (Courtice et al. (2016, 3520560) p. 370). The Wang et al. 2014 and Coutice e et al. 2016 studies ((Wang et al., 2014, 2538846) p. 120 and Courtice et al. (2016, 3520560) p. 370) indicated that vital status was obtained through follow-up and links to records at hospitals, death registry, and using structured questionnaires. Information on smoking habits and verification of occupational history was obtained from workers or their immediate relatives (if deceased) through personal contact (Deng et al. (2012, 2573093)). Although individual smoking status information was available, information on the duration and/or intensity of smoking was not available.	High	1	0.250	0.250
	11. Co-exposure Confounding	The members of the cohort were workers at chrysotile products plant in China. There was no evidence that there was an unbalanced provision of co-exposures (other than asbestos) among exposure groups. The Courtice et al. (2016, 3520560) study indicated that workers rarely changed jobs or between job types (making exposure to other occupational carcinogens unlikely). However, there is uncertainty with respect to the purity of the chrysolite to which the workers were exposed. Samples collected in 2006 showed evidence of tremolite contamination (Courtice et al. (2016, 3520560) p. 376). The study authors suggested that low incidences of mesothelioma in this cohort suggest that amphibole contamination was limited (Courtice et al. (2016, 3520560) p. 376).	Medium	2	0.250	0.500

Study reference:	This evaluation represents all identified publications pertaining to the Chongqing, China cohort of textile workers. A full list of related papers reviewed during this evaluation are listed in Table 2.1.					
Domain	**Metric**	**Comments**	**Qualitative Determination**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
Analysis	12. Study Design and Methods	The study design (cohort) was appropriate to address the research question. In the Deng et al. 2012 study (Deng et al. (2012, 2573093) p. 81), Poisson regression analyses was used to fit models (log-linear, log-quadratic, power, additive relative risk and categorical) to estimate relationships between cumulative exposure and mortality from lung cancer. The Wang et al. 2012 study ((Wang et al., 2012, 2572504) p. 407) used Cox proportional hazard models to obtain hazard ratios for lung cancer mortality in relation to cumulative asbestos exposure. The study by (Courtice et al. (2016, 3520560) p. 371) estimated exposure-response relationships using Cox proportional hazard models.	Medium	2	0.400	0.800
	13. Statistical power	The number of participants (cohort size = 577 workers) was sufficiently large to detect an effect in the exposed population. However, it was noted that there was a relatively small number of nonsmokers in the cohort (Deng et al. (2012, 2573093) p. 86).	Medium	2	0.200	0.400
	14. Reproducibility of analyses	The methods used to estimate exposures were not described in a way that would facilitate reproducibility; a process "similar" to those in other studies was cited (Courtice et al. (2016, 3520560) p. 371) or a string of references was provided ((Wang et al., 2014, 2538846) p. 120) for dust to fiber concentration conversions. In general, the statistical analyses used were described, including variables used in the analyses.	Medium	2	0.200	0.400
	15. Statistical Models	The data analysis section of the Deng et al. paper (Deng et al. (2012, 2573093) p. 83) describes the analyses used in detail (including calculations, model considerations, variables). The methods used to calculate risk estimates (HRs) in Wang et al. 2014 were adequately described ((Wang et al., 2014, 2538846) p. 121). In the Courtice et al. 2016 study (Courtice et al. (2016, 3520560) p. 371), the methods used to generate HRs were briefly described (i.e. age included as a time dimension for Cox proportional hazard modeling).	Medium	2	0.200	0.400
High: >=1 and <1.7 Medium: >=1.7 and <2.3 Low: >=2.3 and <=3		**Sum of scores:**			**5**	**6.85**
		Overall Score = Sum of Weighted Scores/Sum of Metric Weighting Factors:		**1.37**	**Overall Score: Nearest tenth:**	**1.4**

Study reference:	This evaluation represents all identified publications pertaining to the Chongqing, China cohort of textile workers. A full list of related papers reviewed during this evaluation are listed in Table 2.1.					
Domain	**Metric**	**Comments**	**Qualitative Determination**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
		Overall Quality Level:		**High**		
Study Quality Comment:	**The reviewer agreed with this study's overall quality level.**					

3. Data Quality Evaluation of Mesothelioma Data Sources

3.1. Data Evaluation Scoring Sheets: Mesothelioma Outcome

3.1.1. Epidemiology evaluation results of the Quebec, Canada cohort studies on asbestos exposure and mesothelioma incidence

Study reference:	This evaluation represents all identified publications pertaining to the Quebec, Canada cohort of miners. A full list of related papers reviewed during this evaluation are listed in Table 2.1.					
Domain	**Metric**	**Comments**	**Qualitative Determination**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
Study Participation	1. Participant selection	Some details of the setting (e.g., the mine locations and production quantities, but no description of the facilities and exposure conditions) are provided in Liddell et al. (1997, 3081408) (p 14); additional information may be available in Gibbs and Lachance (1972, 3580825) (cited as the source of the exposure assessment), but no pdf was available in HERO at the time of evaluation. Participant selection, inclusion/exclusion criteria, case ascertainment, and participation at each level are described in detail ((Liddell et al., 1997, 3081408), p 14-16). Selection into the cohort was based on a) male sex; b) birth year between 1890 and 1920; b) employment at the Thetford Mines or Asbestos mine/mill or factory for at least one month. Participant selection and participation were not likely to be biased based on these criteria.	High	1	0.500	0.500

Study reference:	This evaluation represents all identified publications pertaining to the Quebec, Canada cohort of miners. A full list of related papers reviewed during this evaluation are listed in Table 2.1.					
Domain	**Metric**	**Comments**	**Qualitative Determination**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	2. Attrition	Numbers of subjects lost to follow up are reported in Liddell et al. (1997, 3081408), Table 4; there it is reported that a total of 1138/10918 (~10%) were lost to follow-up. No information comparing the demographics or exposure of those lost to follow up to the study subjects was located in the eight selected HERO IDs. Missing data were not imputed; however, censoring of survival data is unlikely to introduce bias. This level of attrition is considered to be moderate.	Medium	2	0.500	1.000
	3. Comparison Group	Not applicable for mesothelioma studies	Not Rated	NA	NA	NA
Exposure Characterization	4. Measurement of Exposure	Exposure levels measured exclusively using midget impinger (Liddell et al. (1997, 3081408), p 17) and conversion factors were not determined (based on review of the eight selected HERO IDs). In (Berman and Crump, 2008, 626405), a single conversion factor is applied to all operation for estimation of equivalent exposure concentrations.	Medium	2	0.400	0.800
	5. Exposure levels	Cumulative exposure-response relationships were developed (see for example Table 9 of Liddell et al. (1997, 3081408)). A total of 6 cumulative exposure levels (exposure through age 55) are reported in Table 9 of Liddell et al. (1997, 3081408). (Berman and Crump, 2008, 626405) reports Km estimate for mesothelioma exposure-response.	Medium	2	0.200	0.400
	6. Temporality	Temporality was established (exposure preceded death), and there was adequate follow-up for consideration of latency. Of the total cohort of 10918 men, 6415 were still employed when the cohort was first established in 1966, and follow up extended to 1992 (Liddell et al. (1997, 3081408) p 15). Entry into the cohort was restricted to men born between 1891 and 1920 (Liddell et al. (1997, 3081408) p 15), so the youngest subjects at the end of follow up were 72 years old. There was no indication in the studies reviewed that the operations at Thetford or Asbestos had ceased at any point during the follow up time.	High	1	0.400	0.400

Study reference:	This evaluation represents all identified publications pertaining to the Quebec, Canada cohort of miners. A full list of related papers reviewed during this evaluation are listed in Table 2.1.					
Domain	**Metric**	**Comments**	**Qualitative Determination**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
Outcome Assessment	7. Outcome measurement or characterization	Mesothelioma cases post-1966 were identified via examination of "all related clinical, biopsy, and necropsy records" (Liddell et al. (1997, 3081408) p 16).	High	1	0.667	0.667
	8. Reporting Bias	Rate estimates by exposure level are reported without CI estimates (e.g., Table 9 in Liddell et al. (1997, 3081408)). (Berman and Crump, 2008, 626405) reports Km estimate for mesothelioma exposure-response data.	Medium	2	0.333	0.667
Potential Confounding/Variable Control	9. Covariate Adjustment	Not applicable for mesothelioma studies	Not Rated	NA	NA	NA
	10. Covariate Characterization	Not applicable for mesothelioma studies	Not Rated	NA	NA	NA
	11. Co-exposure Confounding	Not applicable for mesothelioma studies	Not Rated	NA	NA	NA
Analysis	12. Study Design and Methods	Study design was retrospective cohort. Poisson regression used in some analyses (Liddell and Armstrong (2002, 3080504) p. 8) but not others. Appropriate statistical method was used in (Berman and Crump, 2008, 626405)	Medium	2	1.000	2.000
	13. Statistical power	Not applicable for mesothelioma studies	Not Rated	NA	NA	NA

Study reference:	This evaluation represents all identified publications pertaining to the Quebec, Canada cohort of miners. A full list of related papers reviewed during this evaluation are listed in Table 2.1.					
Domain	**Metric**	**Comments**	**Qualitative Determination**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	14. Reproducibility of analyses	(Berman and Crump, 2008, 626405) reports Km estimate for mesothelioma exposure-response.	Not Rated	NA	NA	NA
	15. Statistical Models	(Berman and Crump, 2008, 626405) reports Km estimate for mesothelioma exposure-response.	Not Rated	NA	NA	NA
High: >=1 and <1.7 Medium: >=1.7 and <2.3 Low: >=2.3 and <=3		**Sum of scores:**			**4**	**6.4334**
		Overall Score = Sum of Weighted Scores/Sum of Metric Weighting Factors:		**NA**	**Overall Score: Nearest tenth:**	**NA**
		Overall Quality Level:		**Medium**		
Study Quality Comment:	**This study's overall quality was downgraded during conflict resolution between primary review and QA/QC review. Downgrading due to lack of PCM or TEM-equivalent exposure estimates and potentially significant co-exposure to tremolite or other amphiboles. Note: The original calculated score for this study was 1.9. This value is not presented above because the final rating was changed based on professional judgement**					

3.1.2. Epidemiology evaluation results of the South Carolina, US cohort studies on asbestos exposure and mesothelioma incidence

Study reference:	This cohort evaluation represents all identified publications pertaining to the South Carolina cohort of textile workers. A full list of related papers reviewed during this evaluation are listed in Table 2.1.					
Domain	**Metric**	**Comments**	**Qualitative Determination**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
Study Participation	1. Participant selection	a. Setting and methods of case ascertainment were reported in (Dement et al., 1983b, 67), p. 422 and (Hein et al., 2007, 709498), pg 617. Participant selection and inclusion/exclusion criteria varied by study and analysis. The initial cohort consisted of white men employed for at least one month in a production job at the South Carolina plant between 1/1/1940 and 12/31/1965 ((Dement et al., 1983b, 67) p 422). Subsequent analyses added non-white men and/or women ((Stayner et al., 1997, 3081241), (Dement et al., 1994, 3081766), (Brown et al., 1994, 3081832), (Elliott et al., 2012, 1247861), (Edwards et al., 2014, 3078061), (Cole et al., 2013, 3078261), (Hein et al., 2007, 709498)). b. Selection in or out of the study was based on 1) employment in production job during designated time frame and 2) availability of necessary data (birth and hire dates; work history; vital status). These criteria are unlikely to result in biased subject participation.	High	1	0.500	0.500

Study reference:	This cohort evaluation represents all identified publications pertaining to the South Carolina cohort of textile workers. A full list of related papers reviewed during this evaluation are listed in Table 2.1.					
Domain	**Metric**	**Comments**	**Qualitative Determination**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	2. Attrition	Attrition/missing data exclusions were reported in (SRC, 2019c, 5080236), (Dement et al., 1983b, 67) (p. 423 and Table 1) and (Hein et al., 2007,709498), see pg 618 and Table 1. The number of eligible workers and number excluded due to incomplete work histories was not reported in the sources reviewed. ((Dement et al., 1983b, 67) p 422) reports that each worker was assigned a card at hire on which was tracked the date of birth, sex, race, and SSN, and job or department changes throughout the career were recorded on the card; these were used in the cohort establishment. The suggestion is that all cohort members had complete work histories; however, ((Hein et al., 2007, 709498) pg 624) reported that the study was limited by incomplete lifetime work histories. Vital status was unknown for 2.1% of the original 1261 cohort members, and cause of death was unknown for 5.5% of the deaths in 1975. At the 2001 follow up (Hein et al., 2007, 709498), vital status was unknown for 8.6% of the larger cohort of 3072, and cause of death was unknown for 3.9%. The latter paper cited high rate of loss to follow-up as a limitation of the study. Thus, loss to follow up is judged to be moderate, and the lack of information on number eligible and number with incomplete work histories leads to low confidence.	Low	3	0.500	1.500
	3. Comparison Group	Not applicable for mesothelioma studies	Not Rated	NA	NA	NA
Exposure Characterization	4. Measurement of Exposure	(Dement et al., 1983a, 66) describes the plant processes and the exposure estimation methods. More than 6000 air samples obtained at the plant from 1930 to 1975 were analyzed by PCM to yield chrysotile concentrations (fibers >5 um/mL) (Hein et al., 2007, 709498), pg 617. Exposure concentrations were estimated by department, job, and time period; individual cumulative exposure assessed using the modeled concentrations and JEM (methods outlined in (Dement et al., 1983a, 66). In 2008, an updated JEM was developed to estimate fiber size-specific exposure estimates (based on TEM analysis of archived samples) in (Dement et al., 2008, 626406).	High	1	0.400	0.400

Study reference:	This cohort evaluation represents all identified publications pertaining to the South Carolina cohort of textile workers. A full list of related papers reviewed during this evaluation are listed in Table 2.1.					
Domain	**Metric**	**Comments**	**Qualitative Determination**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	5. Exposure levels	(Berman and Crump, 2008, 626405) reports Km estimate for mesothelioma exposure-response data obtained from the primary investigators for this cohort.	Medium	2	0.200	0.400
	6. Temporality	Temporality was established (exposure preceded death). (Hein et al., 2007, 709498) p 618 reports number of years between first employment and death for one of the 3 mesothelioma cases (~50 years). The other two cases had been identified in an earlier analysis (Dement et al., 1994, 3081766); that paper reported latency periods of 37 and 34 years for those cases.	High	1	0.400	0.400
Outcome Assessment	7. Outcome measurement or characterization	ICD-10 code C45 used to identify mesothelioma cases after 1998; to identify earlier cases, death certificates were reviewed for any mention of mesothelioma ((Hein et al., 2007, 709498) p 617).	High	1	0.667	0.667
	8. Reporting Bias	None of the publications reports exposure-response information for mesothelioma; however (Berman and Crump, 2008, 626405) reports Km estimate for mesothelioma exposure-response data obtained from the primary investigators for this cohort.	Low	3	0.333	1.000
Potential Confounding/Variable Control	9. Covariate Adjustment	Not applicable for mesothelioma studies	Not Rated	NA	NA	NA
	10. Covariate Characterization	Not applicable for mesothelioma studies	Not Rated	NA	NA	NA
	11. Co-exposure Confounding	Not applicable for mesothelioma studies	Not Rated	NA	NA	NA

Study reference:	This cohort evaluation represents all identified publications pertaining to the South Carolina cohort of textile workers. A full list of related papers reviewed during this evaluation are listed in Table 2.1.					
Domain	**Metric**	**Comments**	**Qualitative Determination**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
Analysis	12. Study Design and Methods	Study design was retrospective cohort (Hein et al., 2007, 709498) and the appropriate statistical method was used in (Berman and Crump, 2008, 626405).	Medium	2	1.000	2.000
	13. Statistical power	Not applicable for mesothelioma studies	Not Rated	NA	NA	NA
	14. Reproducibility of analyses	(Berman and Crump, 2008, 626405) reports Km estimate for mesothelioma exposure-response data obtained from the primary investigators for this cohort.	Not Rated	NA	NA	NA
	15. Statistical Models	(Berman and Crump, 2008, 626405) reports Km estimate for mesothelioma exposure-response data obtained from the primary investigators for this cohort.	Not Rated	NA	NA	NA
High: >=1 and <1.7 Medium: >=1.7 and <2.3 Low: >=2.3 and <=3		**Sum of scores:**			**4**	**6.8667**
		Overall Score = Sum of Weighted Scores/Sum of Metric Weighting Factors:		**1.7167**	**Overall Score: Nearest tenth:**	**1.7**
		Overall Quality Level:		**Medium**		
Study Quality Comment:	**The reviewer agreed with this study's overall quality level.**					

3.1.3. Epidemiology evaluation results of the North Carolina, US cohort studies on asbestos exposure and mesothelioma incidence

Study reference:	This evaluation represents all identified publications pertaining to the North Carolina cohort of textile workers. A full list of related papers reviewed during this evaluation are listed in Table 2.1.					
Domain	**Metric**	**Comments**	**Qualitative Determination**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
Study Participation	1. Participant selection	a. Setting and methods of case ascertainment were reported in (Loomis et al., 2009, 3079232), p. 535-536. Participant selection and inclusion/exclusion criteria varied by study and analysis. Although there were 4 plants in the cohort, exposure data were available only for three of the four, so exposure-response analyses were limited to these three plants. Original selection criteria reported in (Loomis et al., 2009, 3079232) p 536 (participants had to work at least 1 day between 1950 and 1973) and p 539 (participants excluded due to missing data). (Elliott et al., 2012, 1247861) evaluated a subset of the cohort that worked >30 days during the same time frame. b. Selection in or out of the study was based on 1) employment in production job during designated time frame and b) availability of necessary data (birth and hire dates; work history; vital status). These criteria are unlikely to result in biased subject participation.	High	1	0.500	0.500
	2. Attrition	Attrition/missing data exclusions were reported in ((SRC, 2019a, 5080241) p. 1), ((Loomis et al., 2009, 3079232) p. 539) and (Elliott et al., 2012, 1247861) pg 386. The original cohort was 5770 persons; 373 workers at plant 2 were excluded due to lack of exposure data at this plant, 1596 were excluded due to incomplete work histories (at department level) or non-production jobs ((Loomis et al., 2009, 3079232) p. 539). Final cohort for exposure-response analyses was 3803. Vital status was unknown for 241 of the 3803 (6%) cohort members (suggesting moderate loss to follow up). The subgroup evaluated in (Elliott et al., 2012, 1247861) consisted of 3082 subjects (excluded persons who worked <30 days); the proportion for whom vital status was missing was not reported for the subgroup.	Medium	2	0.500	1.000
	3. Comparison Group	Not applicable for mesothelioma studies	Not Rated	NA	NA	NA

Study reference:	This evaluation represents all identified publications pertaining to the North Carolina cohort of textile workers. A full list of related papers reviewed during this evaluation are listed in Table 2.1.					
Domain	**Metric**	**Comments**	**Qualitative Determination**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
Exposure Characterization	4. Measurement of Exposure	(SRC, 2019a, 5080241) reports air concentrations and exposure duration by interval of TSFE. Air samples were available for 3 plants covering period from 1935 to 1986 (459 <1950; 1674 from 1950-1969, and 1287 from 1970 forward; (Loomis et al., 2009, 3079232), p. 536). Measurements used impinger before 1964 and PCM thereafter; paired and concurrent samples between 1964 and 1971 were used to relate impinger to PCM-equivalent concentrations. Air samples were not collected yearly, so mean PCM-equivalent concentrations were estimated by plant, department, job, and time period using multivariate mixed models ((Loomis et al., 2009, 3079232), p. 536). Individual cumulative exposure assessed using the modeled concentrations and JEM ((Loomis et al., 2009, 3079232) p 536); details of JEM reported in (Dement et al., 2008, 626406).	Medium	2	0.400	0.800
	5. Exposure levels	(SRC, 2019a, 5080241) reports air concentrations and exposure durations by interval of TSFE.	Medium	2	0.200	0.400
	6. Temporality	Temporality was established (exposure preceded death). (SRC, 2019a, 5080241) reports cases by interval of TSFE ranging up to 72 years since first exposure.	High	1	0.400	0.400
Outcome Assessment	7. Outcome measurement or characterization	High rating applies to cases assessed with ICD10. For some analyses, the authors pooled these cases with cases coded to cancer of the pleura in ICDs 6-9, which is not considered a reliable measure of mesothelioma outcome. (SRC, 2019a, 5080241) reports cases assessed with ICD10 by interval of TSFE	High	1	0.667	0.667

Study reference:	This evaluation represents all identified publications pertaining to the North Carolina cohort of textile workers. A full list of related papers reviewed during this evaluation are listed in Table 2.1.					
Domain	**Metric**	**Comments**	**Qualitative Determination**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	8. Reporting Bias	(SRC, 2019a, 5080241) provides mesothelioma cases and person-years at risk by interval of TSFE, including separate reporting of those assessed by ICD10. Mesothelioma cases (with detail of those assessed by ICD10) reported by employment duration in Table 4 of (Loomis et al., 2009, 3079232) (2 coded cases with 5-10 years employment and 1 coded case each with 10-20 and 20-30 years employment). SMR with CI reported in Table 3 (Loomis et al., 2009, 3079232). and in (SRC, 2019a, 5080241) . (Loomis et al., 2009, 3079232) reports number in cohort, total PY of follow-up, and median duration employment. In (Elliott et al., 2012, 1247861), Table 1 reports cohort characteristics including age at entry, age at first employment, person years at risk, cumulative exposures, for the subset of workers who were employed at least 30 days (by NC plant and for the whole NC cohort).	High	1	0.333	0.333
Potential Confounding/Variable Control	9. Covariate Adjustment	Not applicable for mesothelioma studies	Not Rated	NA	NA	NA
	10. Covariate Characterization	Not applicable for mesothelioma studies	Not Rated	NA	NA	NA
	11. Co-exposure Confounding	Not applicable for mesothelioma studies	Not Rated	NA	NA	NA
Analysis	12. Study Design and Methods	Study design was retrospective cohort and SMR analysis was performed. (Loomis et al., 2009, 3079232)	Medium	2	1.000	2.000

Study reference:	This evaluation represents all identified publications pertaining to the North Carolina cohort of textile workers. A full list of related papers reviewed during this evaluation are listed in Table 2.1.					
Domain	**Metric**	**Comments**	**Qualitative Determination**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	13. Statistical power	Not applicable for mesothelioma studies	Not Rated	NA	NA	NA
	14. Reproducibility of analyses	(SRC, 2019a, 5080241) provides individual data elements allowing independent analysis	Not Rated	NA	NA	NA
	15. Statistical Models	(SRC, 2019a, 5080241) provides individual data elements allowing independent analysis	Not Rated	NA	NA	NA
High: >=1 and <1.7 Medium: >=1.7 and <2.3 Low: >=2.3 and <=3		**Sum of scores:**			**4**	**6.1**
		Overall Score = Sum of Weighted Scores/Sum of Metric Weighting Factors:		**1.525**	**Overall Score: Nearest tenth:**	**1.5**
		Overall Quality Level:		**High**		
Study Quality Comment:	**The reviewer agreed with this study's overall quality level.**					

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