APPENDIX A. EPA RESPONSE TO MAJOR EXTERNAL PEER REVIEW AND PUBLIC COMMENTS

The 2011 External Review Draft (ERD) of the U.S. Environmental Protection Agency's (EPA's) *Toxicological Review of Libby Amphibole Asbestos* underwent a formal external peer review in accordance with EPA guidance on peer review (U.S. EPA, 2006c). In August 2011, EPA released the assessment for public review and comment, and held a public listening session on October 6, 2011 in Arlington, VA. In December 2011, EPA's Science Advisory Board announced a public peer review meeting on the draft assessment that was held on Feb 6-8, 2012 in Alexandria, VA. In March 2012, the SAB announced two public teleconferences of the SAB Libby Amphibole Asbestos Panel to discuss the Panel's draft review report on May 1 and May 8, 2012. In January 2013, EPA's SAB released the final report from the "Review of EPA's Draft Assessment Entitled Toxicological Review of Libby Amphibole Asbestos (August 2011)."

The SAB was tasked with evaluating the following: the accuracy, objectivity, and transparency of the EPA assessment and the data and methods used to synthesize the scientific evidence for health hazards. In this Appendix, the specific peer review recommendations from the Letter to the Administrator are followed by recommendations from SAB's Response to EPA's Charge Questions. Individual recommendations from SAB (2013) are quoted verbatim wherever possible. Page numbers for each quotation are also noted. In some instances, sets of comments were paraphrased by EPA and so noted.

There were public comments provided directly to EPA on the ERD, as well as public comments provided to the SAB Libby Amphibole Asbestos panel and the Chartered SAB. This appendix summarizes the main comments made by the public and responds to those comments. A letter characterized by its authors as a "Request for Correction" on the draft IRIS assessment was received by EPA on February 26, 2014 (http://www.epa.gov/QUALITY/informationguidelines/iqg-list.html), with supplemental information provided on June 25, 2014; many of the previous public comments to the SAB were included as attachments to this Request for Correction. The response to public comments addresses the main issues raised in this letter and its supplemental materials.

Section A.1 responds to the major SAB peer review recommendations to EPA summarized in the SAB Letter to the Administrator.

Sections A.2 through A.7 respond to more detailed SAB recommendations, with each section addressing a different general topic. Section A.8 responds to public comments on specific topics, with each subsection addressing a different general topic. Section A.9 responds to general public comments on the ERD.

A.1. MAJOR SAB RECOMMENDATIONS IN SAB LETTER TO THE ADMINISTRATOR WITH EPA RESPONSES

Major SAB Recommendation *Letter #1*: [Letter to the Administrator, p. 1] "Localized pleural thickening is an appropriate health endpoint for the derivation of the inhalation reference concentration (RfC). It is an irreversible structural, pathological alteration of the pleura and is generally associated with reduced lung function. The SAB has identified additional references and recommends that the agency include a more detailed review of the literature to further support this conclusion."

EPA Response: In response to the SAB's identification of additional references and recommendation that the Agency include a more detailed review of the literature, EPA conducted a more detailed review of the literature examining the relationship between lung function measures and localized pleural thickening (LPT) or pleural plaques ("pleural plaques" as defined in some, particularly older, studies is a subset of LPT). The additional systematic review not only included the additional references noted by the Science Advisory Board, but comprises a systematic and well-documented literature search and review of the published literature. This work is presented in Appendix I and discussed in Section 5.2.2.3.

This additional literature review and analysis demonstrates that pleural plaques (a subset of LPT) are associated with a decrease in two key measures of lung function, and that these decreases are unlikely to be due to other factors such as excess body fat or undetected changes in lung tissue (other than the pleural plaques) that might have also been caused by exposure to asbestos. Thus, these additional references and analysis support the EPA's conclusions in its External Review Draft, and the SAB advice to EPA that LPT is an appropriate health endpoint for the derivation of the inhalation reference concentration.

EPA's literature search identified epidemiology studies examining lung function in asbestos-exposed populations with and without pleural plaques. Twenty studies relating changes in forced vital capacity (FVC) to the presence of pleural plaques and 15 studies relating changes in forced expiratory volume in 1 second (FEV_1) to the presence of pleural plaques were included in a meta-analysis.

A meta-analysis of the identified studies conducted by EPA estimated a statistically significant decrement of 4.09 (95% CI: −5.86, −2.31) and 1.99 (95% CI: −3.77, −0.22) percentage points respectively in predicted forced FVC and FEV_1 attributable to the presence of pleural plaques.

Additional analyses indicated that these decrements are not likely to be due to limitations in the study designs or conduct, undetected subclinical fibrosis, or misidentification of pleural plaques due to subpleural fat pads. Further, the extent of plaques was found to correlate with the degree of lung function decrement, and longitudinal studies indicate that decrements increase with longer follow-up.

These findings support the conclusion that pleural plaques, and thus LPT, are an appropriate health endpoint for the derivation of the RfC.

Major SAB Recommendation *Letter #2*: [Letter to the Administrator, p. 1] "The SAB supports the derivation of an RfC for LAA based on radiographic evidence of localized pleural thickening in an occupationally exposed Marysville, Ohio, cohort. However, the SAB recommends that the EPA conduct additional analyses to substantiate the RfC (to the extent data permit) of pleural abnormalities using the recently published studies on two other cohorts."

EPA Response: EPA notes that alternative phrasings of this recommendation were included in the executive summary (p. 1) as well as in the SAB's response to EPA's first charge question on the Selection of Critical Studies and Effects (see Section 3.2.3.1 of the SAB Report—p. 14). For clarity, EPA quotes the detailed SAB response on page 14 here:

> "Another suggestion for providing support and perspective to the Marysville findings is to conduct analogous analyses (to the extent the data permit) of pleural abnormalities among the Libby workers cohort (Larson et al., 2012)and among the Minneapolis exfoliation community cohort (Alexander et al., 2012; Adgate et al., 2011). The Libby workers have higher, well characterized occupational exposures compared to the Marysville cohort. The Minneapolis cohort of nonworkers generally had estimated exposures at the lower end of the Marysville cohort but included women and children, thus providing a cohort more representative of the general population. However, because the Minneapolis cohort had estimated, not measured exposures, it would not be suitable for the primary RfC analysis. Similarly, because the Libby workers have both environmental and occupational exposures, this cohort should not be used for primary RfC analysis."

As recommended by the SAB, EPA examined two recently published studies of pleural changes in persons exposed to Libby amphibole asbestos at their homes in Minneapolis, MN, and of pleural changes in persons with occupational exposure in Libby, MT (Alexander et al., 2012) and (Larson et al., 2012). These studies were evaluated along with the critical study of pleural changes in persons with occupational exposure in Marysville, OH (Rohs et al., 2008).

The evaluation of these studies is summarized in the final assessment in Section 5.2.1 and a review of the three studies was published in a peer-reviewed journal article in the *Journal of Occupational and Environmental Medicine* (Christensen et al., 2013). The evaluation of these studies (in both the publication and in the assessment) included examination of various aspects including study population, study design, outcome evaluation, and exposure characteristics.

All three studies demonstrated that inhalation exposure to LAA is associated with increased risk of LPT even at the lowest levels of exposure in each study (Christensen et al., 2013). The results of these three studies provide additional support to EPA's conclusion that low levels of exposure to Libby amphibole asbestos is associated with increased prevalence of LPT.

EPA evaluated whether the study of residential exposure in Minneapolis could provide useful information as to whether children or women had a different response to exposure than did adult men even if the Minneapolis study was not the strongest database for estimating a benchmark response. However, the overall quality of the exposure

assessment in this investigation and the lack of detail on the various routes of exposure for men compared to women complicates the evaluation of any effect modification by gender at this time. Likewise, the data on risks in children were also limited.

The EPA analysis of the Marysville cohort remains EPA's preferred basis for deriving an RfC; the Marysville cohort had exposure concentrations closer to residential concentrations in Libby, relatively high-quality exposure estimates, and the ability to identify the time of first exposure to Libby Amphibole asbestos. In contrast, the Minneapolis study had more uncertain estimates of exposure than did the study of the Marysville workers. While the Libby workers had reasonably good estimates of occupational exposures for workers whose work history information was available, the occupational exposure levels were higher in Libby than in Marysville. In addition, Libby workers overall exposure levels included additional residential exposures and data were not available as to when that residential exposure started. This is a drawback for modeling the noncancer effects because time since first exposure (TSFE) was determined to be a very important variable for modeling the pleural changes (see response for Letter #3 comment, below) and that time of first exposure was unavailable for many of the Libby workers who were also residents in Libby.

Major SAB Recommendation *Letter #3*: [Letter to the Administrator, p. 2] "The SAB recommends that more justification be provided for the selection of the 'best' model for noncancer exposure-response analysis. The SAB also recommends examining other exposure metrics besides the simple cumulative exposure, such as time-weighting of exposures. In addition, more justification is needed for the selection of 10% extra risk as the benchmark response since it is not consistent with the guideline for epidemiological data in EPA's *Benchmark Dose Technical Guidance*."

EPA Response: In accordance with the SAB recommendation, EPA provides a more thorough explanation of its selection of the best model for noncancer exposure-response analysis. EPA examined exposure metrics other than cumulative exposure, such as mean exposure concentration, and time-weighting of exposures. EPA also provides more explanation of its selection of 10% extra risk as the benchmark response rate, explaining how in this case the selection is consistent with EPA's *Benchmark Dose Technical Guidance*.

EPA provides a more thorough explanation of model selection and exposure metrics in Section 5.2.2.6 and in Appendix E. Following the guidance in the final updated *Benchmark Dose Technical Guidance* (U.S. EPA, 2012), EPA explained that there are several stages of exposure-response modeling. Once the appropriate data set(s), endpoint(s) and BMR are determined, an appropriate set of statistical model forms is selected and evaluated for model fit to determine which models adequately represent the data. Among those models with adequate fit, one or more models are selected to derive a point of departure for the RfC. Regarding the selection of models to evaluate, the *Benchmark Dose Technical Guidance* notes that additional criteria may be used, "governed by the nature of the measurement that represents the endpoint of interest and the experimental design used to generate the data" (page 26). When modeling the Marysville data, certain biological and epidemiological features must be considered, including the nature of the data set, ability to estimate the effects of exposure and of

important covariate(s), the existence of a plateau or theoretical maximum response rate in a population, and the ability to estimate a background rate of the outcome in a population.

For the primary modeling in Section 5.2.2.6., EPA selected the Dichotomous Hill model, (a minor variation on the model proposed in its External Review Draft, the Michaelis-Menten model) because it allowed fuller consideration of the biological and epidemiological features described above.

Evaluation of the three exposure metrics considered for the primary analytic data set (Marysville workers with health evaluations performed in 2002−2005 and hired in 1972 or later) showed that mean exposure consistently led to improved model fit across the range of model forms evaluated, in comparison with either cumulative or residence time-weighted exposure (see Section 5.2.2.6).

Time since first exposure (TSFE), which is known from the epidemiological literature to be an important determinant of LPT risk, was not a significant predictor in this data set. In order to incorporate TSFE, a "hybrid" modeling approach was taken, as recommended by the SAB. Here, the effect of TSFE was estimated using a broader subset of the Marysville workers, with a wider range of TSFE values. This estimated effect of TSFE was carried over to the modeling performed in the primary analytic data set as a fixed effect. In this "hybrid" modeling, mean exposure provided adequate goodness of fit, while cumulative exposure did not. Thus, while the External Review Draft used cumulative exposure, the primary analysis in the final draft uses mean (occupational) exposure concentration to derive an RfC.

In an alternative analysis (see Appendix E) that combines data across two health evaluations (1980 and 2002−2005), EPA selected both the Dichotomous Hill model using mean occupational exposure concentration and a variant of the Dichotomous Hill model where TSFE is incorporated into the plateau term (the "cumulative normal" Dichotomous Hill model). For the cumulative normal Dichotomous Hill model, EPA utilized the cumulative exposure metric (which was proposed in its External Review Draft) because of some expectation that it might better reflect the accumulated impact of inhaled asbestos and because it provided adequate goodness of fit for this particular model form and data set. As explained in Section 5.2.5, this alternative analysis yielded potential reference concentrations that ranged from threefold lower than the selected reference concentration to twofold higher than the selected reference concentration.

EPA considered its choice of a benchmark response and includes a more thorough explanation of this is Section 5.2.2.5. EPA concluded that a benchmark of 10% extra risk remains appropriate because LPT represents a persistent, structural change to the pleura, but is not severe enough to justify a lower BMR. While EPA has sometimes utilized much lower BMRs when using epidemiology data, that usage is usually in connection with very large epidemiology studies of cancer endpoints that often have power to detect small changes in extra risk.

Note that with regards to exposure metrics, the cumulative exposure measure (done on an annual basis) is the sum, in units of fibers/cc-years, of the work season-specific time-weighted concentrations. The mean exposure measure is the cumulative occupational exposure divided by the duration of occupational exposure. EPA additionally considered a time-weighted measure, the "residence time-weighted" exposure metric. Here, the

average exposure in each time interval is multiplied by the number of time intervals elapsed between that exposure and the x-ray evaluation of pleural abnormalities; these multiplied exposures are then summed across the individual's work history. The calculation of these exposure metrics is described in Section 5.2.2.6.2 and in Appendix E.

The result of the above changes in model and exposure metric and some other similar changes is that the RfC in the final assessment is about 4.5-fold higher than the RfC in the External Review Draft.

Major SAB Recommendation *Letter #4*: [Letter to the Administrator, p. 2] "A composite uncertainty factor of 100 was applied to the point of departure to obtain the RfC. EPA applied an uncertainty factor of 10 to account for human variability and sensitive subpopulations, and a database uncertainty factor of 10 to account for database deficiencies in the available literature for the health effects of LAA. The SAB recommends that the EPA reevaluate the use of a default database uncertainty factor of 10 as part of the consideration of additional studies; additional data (e.g., Minnesota cohort and data on other amphiboles) might support a lower value, such as 3, for the database uncertainty factor. In addition, the SAB recommends EPA revisit its judgement of a subchronic-to-chronic uncertainty factor and a LOAEL-to-NOAEL uncertainty factor of onefold."

EPA Response: EPA has reconsidered the choice of uncertainty factors (see Section 5.2.3). In the External Review Draft, EPA did not apply an uncertainty factor (or, equivalently, divided by an uncertainty factor of 1) to account for adjustment from a LOAEL to a NOAEL, or to adjust for using subchronic exposure data to estimate a chronic RfC. An uncertainty factor of 10 was applied to reflect database uncertainty (due to a limited amount of information on pleural effects after exposure to LAA, and the potential for autoimmune effects) and an uncertainty factor of 10 was applied to account for human variability in response.

With respect to adjustment for LOAEL to NOAEL, EPA guidance does not call for such an uncertainty factor when benchmark dose modeling is used (as it was here) to derive a confidence interval around an estimate of the concentration associated with an appropriate benchmark response rate. As explained in response to Recommendation #3, EPA determined and more thoroughly explained why it concluded a benchmark response rate of 10% was appropriate, and through exposure-response modeling, determined a confidence interval on the concentration for that response rate. Hence, EPA did not change the conclusion from its External Review Draft that an uncertainty factor other than one is needed for a LOAEL to NOAEL adjustment.

With respect to adjustment from subchronic data to chronic data, EPA reconsidered and did increase this uncertainty factor value from 1 to 10. This was despite the fact that the average duration of worker exposure in the key study was more than 7 years, which is often considered to represent a chronic exposure for humans. The reason EPA concluded an uncertainty factor of 10 is appropriate is that the exposure-response modeling demonstrated that the range of time elapsed since first exposure (TSFE) in the Marysville workers may not be sufficiently long to appropriately describe the effects of a lifetime (i.e., 70 years) of exposure to LAA. EPA performed an analysis on the impact of TSFE, and found that longer TSFE led to a substantial increase in the risk of LPT (see Section 5.2.2.6.2), with an approximately 10-fold increase in risk when comparing a

TSFE of 70 years (i.e., a lifetime of exposure) to a TSFE of 28 years (the median in the primary analytic data set). Based on this analysis, EPA concluded an uncertainty factor of 10 is appropriate to reflect that with lifetime exposure, TSFE would increase as would its effect on lifetime prevalence or pleural abnormalities.

With respect to human variability, neither the SAB nor EPA concluded there was a basis for a change to the uncertainty factor of 10 in EPA's External Review Draft. The Marysville data (and the Libby data) comprise occupational workers (primarily men) sufficiently healthy for full-time employment, and thus are not likely to capture the full range of human responses and potential sensitive subpopulations.

Finally, with respect to database uncertainty, EPA concluded that while uncertainties remain, there is a basis to reduce the database uncertainty from 10 to 3. Since the release of the External Review Draft, two newly published studies provide further information on the pleural and parenchymal health effects of exposure to Libby Amphibole asbestos (Alexander et al., 2012; Larson et al., 2012). Both of these studies support the derivation of the RfC based on pleural effects among Marysville workers. However, some uncertainty remains regarding autoimmune effects, and consequently, the database UF has been reduced to 3.

Major SAB Recommendation *Letter #5*: [Letter to the Administrator, p. 2] "The SAB agrees that the weight of evidence for LAA supports the descriptor 'Carcinogenic to Humans by the Inhalation Route' in accordance with EPA's *Guidelines for Carcinogen Risk Assessment*. The SAB views the mode of carcinogenic action of LAA as complex, and recommends that the agency conduct a formal mode of action analysis in accordance with EPA's *Guidelines for Carcinogen Risk Assessment*. Based on this formal analysis, the agency may still conclude that the default linear extrapolation at low doses is appropriate."

EPA Response: EPA acknowledges that the mode of carcinogenic action of LAA is complex and multifactorial, and EPA has conducted a formal mode-of-action (MOA) analysis in accordance with EPA's *Guidelines for Carcinogen Risk Assessment* in Section 4.6 of the Toxicological Review. As recommended by the SAB, the focus of this analysis is LAA, with some discussion of other amphiboles for context when appropriate literature was available. Further discussion of the mechanistic data in support of the MOA for asbestos in general has been included in Section 4.4, with the formal carcinogenic MOA focused on mutagenicity, chronic inflammation, and cytotoxicity for LAA in Section 4.6. The formal mode of carcinogenic action framework analysis demonstrated that although evidence is generally supportive of an MOA involving chronic inflammation or cellular toxicity and repair, there is insufficient evidence to determine an MOA for LAA. Thus, a linear approach is used to calculate the inhalation cancer unit risk in accordance with EPA's *Guidelines for Carcinogen Risk Assessment*. Section 4.6.2.2 has also been revised to reflect that there are insufficient data to determine whether a mutagenic mode of action for LAA is supported.

Major SAB Recommendation *Letter #6*: [Letter to the Administrator, p. 2] "The SAB supports the selection of the Libby worker cohort for the derivation of the inhalation unit risk (IUR) and agrees that the use of the subcohort post-1959 for quantification may be reasonable due to the lack of exposure information for many of the workers in earlier years. The SAB has suggested sensitivity analyses that would explore the implications of the selection of the

subcohort. The SAB finds it appropriate to use lung cancer and mesothelioma as endpoints for the derivation of the IUR. The SAB recommends a more detailed discussion and justification of how the use of mortality data rather than incidence data may have resulted in an undercount of cases of lung cancer and mesothelioma and what implications, if any, it may have for the derivation of the IUR."

On Page 19 of the SAB Report (a related more detailed comment): "Use of the subcohort post-1959 seems reasonable due to the lack of exposure information for many of the workers in earlier years. Out of 991 workers hired before 1960, 811 had at least one job with an unknown job assignment and of these 706 had all department and job assignments listed as unknown. It would seem highly problematic to include workers with limited or no job information in the model. However, at least some information existed for the remaining 285 workers. The EPA should strengthen the analysis to calculate an overall Standardized Mortality Ratio (SMR) for the Libby worker full- and subcohorts for lung cancer, using both Montana and U.S. data for comparison. The later cohort also had lower levels of exposure to asbestos, which would be closer to the lower levels found in the environment."

EPA Response: Per the SAB recommendation, EPA has added analyses of the Libby worker full- and subcohorts for lung cancer, using both Montana and U.S. data for comparison as well as parallel analyses of mesothelioma rates in the Libby worker full- and subcohorts. Sections 5.4.3.2 and 5.4.3.5 include new tables on the rates of mesothelioma and related text. New tables on the rates of lung cancer as well as SMRs and related text are included in Section 5.4.3.3 and 5.4.3.6. Because the rate of lung cancer mortality in Montana is lower than in the United States as a whole the SMRs based on Montana rates are somewhat higher. While such computations could not control for exposure because job history information was largely missing for the early hires, the rates and risks by categories of duration, age, and TSFE generally appeared to show similar patterns with highest duration and TSFE having noticeably higher rates. Absent similar quality exposure data on the early hires, it is difficult to assess the potential sensitivity of selecting the subcohort. In addition, EPA's revised Section 5.4.5.3.1 which compares EPA analyses with other published analyses of the Libby full cohort and concluded that the risk was not underestimated from the analysis of the subcohort.

In response to the SAB recommendation, EPA has also provided more detailed discussion of the use of mortality data rather than incidence data. Because mortality rates approximate incidence rates when the survival time between cancer incidence and cancer mortality is short, and median survival for both mesothelioma and lung cancer were less than 1 year, it is considered to be unlikely that such discrepancies would be significant. The revised text is shown in Section 5.4.2.2.

Major SAB Recommendation *Letter #7*: [Letter to the Administrator, p. 2] "The draft assessment clearly described the methods selected to conduct the exposure-response modeling for lung cancer and mesothelioma. However, the SAB recommends that the agency provide more support for its choice of statistical models for the exposure-response analysis. The SAB also recommends consideration of several models in addition to the Poisson and Cox models used in the draft assessment."

EPA Response: In response to the SAB recommendation, EPA has provided more support for its choice of models. EPA has strengthened the presentation of the relative merits of alternative models, including standard epidemiologic models such as Poisson, logistic, and Cox, as well as the Weibull model for mesothelioma and two-stage clonal expansion model for lung cancer. EPA has also enhanced its justification of the selected models with revised text on models for mesothelioma in Section 5.4.3.1 and for lung cancer in Section 5.4.3.3. Poisson and Cox models are traditional models that are widely used in occupational epidemiology cohort analyses. They are well suited to the Libby subcohort data and have been used by many investigators of the Libby worker cohort in particular. EPA carefully considered the relative merits of the various alternative models, noting, for example, that the Weibull model is generally not used for data with rare outcomes such as mesothelioma, and that EPA did not have available reliable data from the Libby cohort on which to make assumptions required for use of the two-stage clonal expansion model. Thus, EPA retained the Poisson and Cox models in the revised analyses for mesothelioma and lung cancer, respectively.

Major SAB Recommendation *Letter #8*: [Letter to the Administrator, p. 2] "The agency has been overly constrained by reliance on model fit statistics as the primary criterion for model selection. The SAB recommends graphical display of the fit to the data for both the main models and for a broader range of models in the draft document to provide a more complete and transparent view of model fit. The SAB also recommends that the EPA consider literature on epidemiological studies of other amphiboles for model selection for dose-response assessment, since the size of the Libby subcohort used in the exposure-response modeling is small."

EPA Response: To supplement the evaluation criteria for exposure-response model selection for the Libby cancer subcohort beyond the use of model-fit statistics alone, EPA has added graphical displays for a range of models for both mesothelioma (see Section 5.4.3.5) and for lung cancer (see Section 5.4.3.6) to provide a more complete and transparent view of model fit. These graphics further support the reasonable nature of the selected model for mesothelioma and lung cancer. EPA has also added graphical displays of model fit for the noncancer analyses.

EPA has considered the epidemiologic literature on other amphiboles and has now included additional analytic models on amphibole-related mesothelioma (model proposed by Peto et al. (1982) and its modifications proposed by Berry et al. (2012)). The results of these models support the selected model in the ERD.

Major SAB Recommendation *Letter #9*: [Letter to the Administrator, p. 3] "The EPA has summarized many sources of uncertainty, sometimes quantitatively, as well as the direction and magnitude of the likely impact of each source of uncertainty. The SAB recommends that model uncertainty be evaluated by estimating risks using a more complete set of plausible models for the exposure-response relationship. This sensitivity analysis, while not a full uncertainty analysis, would make explicit the implications of these key model choices."

EPA Response: With respect to model uncertainty in the cancer exposure-response analyses, EPA did identify additional uncertainty based on SAB's recommendation to more fully investigate models suggested by the epidemiologic literature, and this is discussed in Section 5.4.5.3. EPA estimated risks using literature-based models for

mesothelioma and presented LAA unit risks in Table 5-52 demonstrating twofold uncertainty around the final IUR value.

Major SAB Recommendation *Letter #10*: [Letter to the Administrator, p. 3] "Finally, the SAB has identified critical research needs for epidemiological studies, mode of action, and measurement methods for LAA to strengthen future LAA assessment."

EPA Response: EPA has conducted the *Toxicological Review of Libby Amphibole Asbestos* based on the best available data and literature available at the time of the assessment. EPA does recognize that ongoing scientific research in the fields of epidemiology, MOA, and exposure measurement methods will further inform future assessments of the toxicity and dose response of LAA.

SECTIONS A.2 THROUGH A.7 SUMMARIZE OTHER MAJOR SAB RECOMMENDATIONS BY TOPIC AND PROVIDE EPA'S RESPONSE

A.2. MINERALOGY – OTHER MAJOR SAB COMMENTS AND RECOMMENDATIONS WITH EPA RESPONSES:

SAB Mineralogy #1: **[Section 3.2.1 of the SAB Report, p. 10]:** "In general, the SAB finds that this section provides an important foundation for understanding the nature of Libby Amphibole asbestos (LAA) as related to evaluation of potential exposures. There are places where the clarity and accuracy of the section can be improved, and these are detailed below."

EPA Response: Section 2 of the LAA has been revised for accuracy and clarity. Additional details concerning the amphibole mineral species have been added to the text and table along with a discussion of the mining operations and temporal evaluation of the amphibole content of the ore over the period of mine operation.

SAB Mineralogy #2: **[Section 3.2.1 of the SAB Report, p. 10]:** "There is a mismatch between the mineralogical detail embodied in the definition of mineral species and the detail available relative to specific exposures in Libby. Specifically, mineral species define a very specific structure (e.g., amphibole) and a specific composition or range of compositions (e.g., winchite or tremolite). Given that these factors affect a mineral's physical and chemical behavior, they may in principle be factors to consider for potential hazard. The SAB recognizes that this level of detail is not typically available for toxicity studies to allow its application to the evaluation of LAA per se. In general, however, the observed unique aspects of amphibole asbestos support the evaluation of LAA through comparison with other amphiboles based on particle morphology and amphibole designation. Nevertheless, the SAB encourages a rigorous and accurate description of LAA in Section 2, perhaps while noting the potential ambiguities in the use of mineral-species names in other studies."

EPA Response: EPA agrees that there is a mismatch between the mineral species identified in the LAA mixture and the availability of mineral-specific physical and chemical behavior. EPA has revised Section 2 to reflect the available information on particle morphology and mineralogy of amphibole asbestos. Unfortunately, of the mineral constituents identified in LAA and aside from studies of LAA as a mixture, only

tremolite has been investigated in laboratory in vitro and in vivo studies, and it is the only regulated asbestiform in the LAA mixture. With the exception of magnesio-riebeckite, which rarely exhibits an asbestiform habit, all of the other constituents (winchite, richterite, tremolite, magnesio-arfvedsonite, and edenite) can occur in an asbestiform habit and exhibit similar particle morphologies (diameter, length, and aspect ratios; see Sections 2.2.3). As further explained in Section 2.4.1, the differences among the calcic, soda-calcic, and the sodic amphiboles relates to cation ratios (based on the number of cation atoms per formula unit) for sodium, sodium plus potassium, and aluminum plus calcium on the [Na_B] and [$Ca + Na_B$] site as shown in Figure 2-6. Table 2-1 illustrates further the similarities between the optical and crystallographic properties of the mineral species contained in the LAA mixture (see Section.2.4.1). It is not possible with the LAA mixture to assign a mineral-specific biologic activity to any one of the species or to assign biologic significance among rather small differences in cation ratios for the specific minerals. All of the mineral forms in LAA are respirable and all exhibit similar particle morphologies and there is no published evidence to indicate that there is or is not a difference in the biologic activity among the LAA mineral species.

SAB Mineralogy #3: **[Section 3.2.1 of the SAB Report, p. 11]:** "Discussions of mineralogy and morphology in Sections 2.2.1.1 and 2.2.1.2 are good, with appropriate discrimination between methods/definitions that are applied to mineral field samples collected from the site versus terms/definitions that are applied to environmental samples collected via air monitoring (line 16 of page 2-9 and lines 4 and 5 of page 2-10)."

EPA Response: Section 2.2 has been edited to clarify and correct some of the chemical formulas and add information concerning particle morphology (see Section 2.2.3). Additional references have been added and definitions corrected (see Text Box 2-1).

SAB Mineralogy #4: **[Section 3.2.1 of the SAB Report, p. 11]:** "Section 2.1 is generally sufficient for providing a background on historical aspects of the mining operations in Libby, Montana."

EPA Response: Section 2.5 (what was formerly Section 2.1) has been slightly expanded to include a more complete description of the mining operations at Libby and a discussion of historical content of amphiboles in the ore mined from Libby.

SAB Mineralogy #5: **[Section 3.2.1 of the SAB Report, p. 11]:** "Section 2.2 needs modification. This section should lay a foundation for understanding the nature of Libby Amphibole (e.g., mineralogical characteristics such as composition and morphology), information on how the material may vary spatially and temporally (with respect to mining operations), and other factors that may impact exposures. The section does contain much relevant information. There are parts of the section that are incorrect and misleading; recommendations to address these issues include:"

SAB comment p. 11: "Consistent use of terminology associated with particle morphology. The section mixes a number of terms that address particle morphology, and these are critically important in assessing potential exposures and subsequent impacts. As an example, 'fibers (e.g., acicular…)' implies fibrous and acicular are the same, when in conventional usage they are different (e.g., see Veblen and Wylie, 1993). A tight use of terms that are defined up front should be followed in the EPA document even when a lax use of terms may exist in the literature cited. A partial attempt is provided in Section 2.2.1.2, but it could be

expanded and carefully vetted with respect to accepted terminology. The four most important terms to lay out clearly are fibrous, acicular, prismatic, and asbestiform. If the report's intent is to note differences in these terms, they should be discussed; if the conclusion is that there are poorly defined distinctions, that topic also should be discussed. One specific example of inaccurate usage is the term 'prismatic,' which by definition is 'prism'-shaped (meaning parallel sides; it is incorrectly used in multiple places)."

EPA Response: Sections 2.2.3 and Text Box 2-1 have been edited to provide a more consistent terminology and definitions of particle morphologies. Unfortunately, there are several definitions for asbestiform, acicular, prismatic, or fibrous morphologies that are often used in an incorrect context in the published literature. For the purposes of this text, the mineralogical definition is used in the text (Lowers and Meeker, 2002). According to their report and survey of the literature, there are definitions based on industrial, interdisciplinary, medical, mineralogical, and regulatory usages and they all differ. For consistency, throughout the revised document EPA has chosen to use the mineralogical definitions for clarity and simplicity. A more complete listing of key definitions can be found in Appendix H of this document (Lowers and Meeker, 2002).

SAB comment p. 11: "Double-check all mineral formulae. There are numerous incorrect compositions in the report; although some of these may be typographic errors (which, of course, should be fixed), some may be incorrectly reported. An example of one incorrect formula is that attributed to vermiculite, which is listed incorrectly as: $[(Mg,Fe,A)_3(Al,Si)_2O_{10}(OH)_2 \bullet 4H_2O]$."

EPA Response: EPA has reviewed and edited Section 2.2.2 to provide correct mineral formulations in Figure 2-4.

SAB comment p. 11 "Double check that all mineral-species definitions used are accepted mineralogical standards. Mineral species are fundamental terms that describe a material with a specific structure and a specific composition or range of compositions; both factors are primary determinants of a material's properties. Indeed, at the heart of this report is the definition of likely exposures to (and risks from) inhaled particles and other fibers based on the use of mineral-species names. The problems in this category are probably most widespread in Section 2.2.1.1, which details amphibole mineralogy (which is central to the report). For example, anthophyllite is not a Libby amphibole."

EPA Response: EPA has edited Section 2.2 to correct and use a single mineralogical definition for particle morphologies in the text. Additions/edits to Sections 2.2.3 through 2.4.1 and 2.4.2 have added information on atomic differences among the various mineral species identified in LAA. Additional information on optical and crystallographic properties of the amphiboles has been added to the text and Table 2-1.

The use of anthophyllite in Section 2.2.1 of the External Review Draft was intended to illustrate that other amphiboles are referred to as asbestos; it was not intended to imply that anthophyllite was a constituent in the LAA mineral mixture. It has been replaced with actinolite in the revised document.

SAB Mineralogy #6: **[Section 3.2.1 of the SAB Report, p. 11−12]:** "The SAB appreciates the discussions that highlighted the complexity and variability of LAA in the context of compositional solid solutions, emphasizing that even the use of mineral-species names for LAA

may mislead readers to believe that LAA is represented by a few discrete materials as opposed to a mixture of materials with varying compositions. Overall, the mineralogy section could benefit from some technical editing. It presents some irrelevant material (e.g., Section 2.2.1, which is a general description of silicate mineral hierarchy), omits some critical information (e.g., Section 2.2.1.1 does not provide the mineralogical definitions of key minerals like winchite or richterite), and presents some erroneous and irrelevant characterizations (e.g., some of the vermiculite-mineralogy descriptions in Section 2.2.2)."

EPA Response: Section 2.2 has been revised and edited considering the review comments from the SAB. While the general description of silicate mineral hierarchy may not be key to understanding LAA mineralogy, it provides a generalized scheme for structurally related compounds that may occur concomitantly with amphibole asbestos.

The subsection and table describing vermiculite have been removed because the primary concern of this section is LAA.

Table 2-1 was added to the text in Section 2.4.1 to provide structural formulas and provide optical and crystallographic properties of the mineral species identified in LAA.

SAB Mineralogy #7: **[Section 3.2.1 of the SAB Report, p. 12]:** "The report provides a good summary of available information on the LAA. One specific observation that could be added is one reported by Sanchez et al. (2008), namely that they observed no correlation between morphology (fibrous vs. prismatic) and major-/minor-element chemistry. Webber et al. (2008) similarly concluded that there was no correlation between mineral species and fiber width for respirable fibers. In other words, this is consistent with the implication that the large set of compositional data from Meeker et al. (2003) shown in the report reflects the range of compositions associated with inhaled-fiber exposures."

EPA Response: Section 2.4.2 has been edited to include the observations of Sanchez et al. (2008) and Webber et al. (2008).

SAB Mineralogy #8: **[Section 3.2.1 of the SAB Report, p. 12]:** "Discussion on page 2-10 glosses over a serious shortcoming of phase contrast microscopy (PCM); namely, its inability to detect fibers narrower than ~0.25 μm. These thin fibers are among the most biologically potent according to the Stanton-Pott hypothesis. The fact that only a third of the Transmission Electron Microscopy (TEM)-visible Libby fibers were PCM-visible is buried in (McDonald et al., 1986). Furthermore, Text Box 2-2 does not adequately contrast the capability of EM versus PCM. EM's capability to yield elemental composition via Energy Dispersive Spectroscopy (EDS) and Wavelength Dispersive x-ray Spectroscopy (WDS) provides information to identify different asbestos types. PCM, in contrast, cannot even determine if the fiber is mineral. Furthermore, the Selected Area Electron Diffraction (SAED) capability of TEM allows determination of crystalline structure, e.g., amphibole versus serpentine. Finally, Box 2-2 incorrectly states that scanning electron microscopy (SEM) 'produces three-dimensional (3-D) images'. Rather, SEM produces 2-D images that reveal surface structure of particles."

EPA Response: The description of the analysis of asbestos fibers has been edited and moved to its own section, Section 2.3. The revised section addresses analysis of bulk materials (vermiculite and soil) and air filters. The bulk material analysis presents general methods of polarized light microscopy (PLM) and x-ray diffraction as current methods for analysis.

The description of the analysis of air samples by PCM and TEM has been edited to clarify the limitations of current counting methods. PCM analysis of fibers is limited by the resolution of the light microscope (cannot distinguish fibers <0.25 µm in diameter) and not all fibers observed on the filter are actual asbestos fibers. The lack of fiber size resolution may tend to underestimate actual fiber counts because fibers <0.25 µm are not resolved. The counting rules used for reporting PCM fibers are not regulations—they merely describe the size and shape of the fibers counted in an optical field. The Text Box 2-1 has been revised appropriately.

The description of the analysis of air samples using TEM has been edited and expanded. The discussion of EDS and SAED has been corrected and a discussion of how these analytical tools are used to identify the mineralogy of specific fibers observed in a grid field. TEM analysis of mineral fibers is used to confirm fiber analysis by PCM, and one generally records the total fibers counted on a sample grid and the number of phase contrast microscope equivalent (PCMe) fibers for assessing human exposure. Both values are recorded along with fiber size dimensions to gauge fiber size dimension and distribution. TEM analysis allows the microscopist to determine the mineralogy of a fiber of interest and to compare the ionic spectrum of the fiber to a known standard, thereby providing identification of the fiber. Asbestos fibers from the Rainy Creek complex are unique in having elevated sodium and potassium content in their atomic structure, which makes their analysis unlike similar amphiboles from other regions nationally or internationally.

SAB Mineralogy #9: **[Section 3.2.1 of the SAB Report, p. 12]:** "The electron microscopy section on page 2-11 could be clarified. SEM and TEM provide higher resolution to allow better particle morphological analysis. Electron diffraction allows mineralogical assessment. Energy dispersive x-ray analysis allows elemental composition determination, which can corroborate the mineralogical determination. X-ray diffraction (XRD) mentioned in this section is useful for bulk sample mineralogy measurements."

EPA Response: The electron microscopy section in Section 2.3.1 has been corrected and revised.

A.3. FIBER TOXICOKINETICS – OTHER MAJOR SAB COMMENTS AND RECOMMENDATIONS WITH EPA RESPONSES:

SAB Fiber Toxicokinetics #1: **Set of Related SAB Comments from p. 16, 20 and 21:**

[Section 3.2.3.2 of the SAB Report, p. 16]: "In general, the listing of the laboratory animal studies in Tables 4-15 and 4-16 and the underlying data summary in Appendix D are appropriate and complete. However, Tables 4-15 and 4-16 and the summary data in Appendix D do not include the distribution of fiber lengths, and Section 4.2.5 is therefore deficient as a summary of animal studies for LAA and tremolite, in terms of not discussing how the content of long fibers in the administered materials had an influence on the effects observed."

[Section 3.2.3.2 of the SAB Report, p. 16]: "The report text in Section 4.2.5 also is deficient in not discussing how the contents of long fibers in the administered materials had an influence on the effects observed. Therefore, the issue of the influence of fiber dimensions, and especially fiber length, needs to be strengthened. The LAA fiber dimensions, listed in

Table D-5 (page D-6) should be moved to the main text in Section 4.4, Mechanistic Data and Other Studies in Support of the Mode of Action. A recent paper by Berman (2011), which was not cited in the draft report, suggests that cancer risk coefficients for various amphiboles are more consistent when fiber length was taken into consideration. Berman (2011) also suggests that the health risks presented by amphibole are greater than those of chrysotile."

[Section 3.2.4.4 of the SAB Report, p. 20]: "It is generally accepted that the toxicity and carcinogenicity of mineral and synthetic vitreous fibers are governed by fiber dimensions, in vivo durability, and dose, and that all long amphibole fibers are very durable in vivo. Thus, the differences in biological potency among the various amphibole fiber types are due primarily to their differences in dimensions, especially in their fiber length distributions Berman (2011). The SAB noted that the text in Sections 4.2 and 4.3, and the tables cited therein, are deficient in not citing all that is known about the dimensions of the administered fibers."

[Section 3.2.4.4 of the SAB Report, Recommendations, p. 21]: "Areas of needed improvement in the report include: (1) a discussion on known determinants of fiber toxicity; and (2) the differences in fiber size distributions between LAA and other known amphiboles."

EPA Response: EPA revised the assessment to clarify the role of fiber determinants in toxicity in general (see Section 3) and how the fiber determinants of LAA inform the toxicity of LAA versus other amphiboles (see Section 4.2−4.4). EPA has moved the requested text on fiber dimensions from the Appendix D to the main document and included fiber characteristics for all studies in Tables 4-19 and 4-20 when available. Further, the EPA has drafted a new section (see Section 3.3) on the "Determinants of Toxicity" as part of the general description of the toxicokinetics of fibers, which includes SAB recommended references, including Berman (2011). This section addresses, in general, the role of fiber toxicity determinants, including length, in the biological response to fiber exposure. For example, in early studies, fiber length has been correlated with disease status, with shorter fibers (<2 μm) being associated with asbestosis while longer fibers (>5 μm) associated with mesothelioma (Lippmann, 1990). However, more recent studies have also suggested a role for surface area or surface chemistry, particularly surface iron, in disease status (reviewed in Aust et al., 2011). Specific information on fiber characteristics was not available for all studies on LAA and tremolite, but this information was included in Appendix D and Sections 4.2 and 4.3 in tables for each study when available. A more detailed discussion of the impact of these determinants of LAA and tremolite in the biological response to these fibers is included in Sections 4.4 through 4.6.

SAB Fiber Toxicokinetics #2: **Set of Related SAB Comments from p. 8 and pp. 12−14:**

[Section 3.1.1 of the SAB Report, p. 8]: "SAB has identified sections where extraneous and repetitive materials could be deleted. For Section 3, since the focus of the draft document is on Libby amphibole fibers, it would be better to limit the literature reviews and discussions to those dealing with the family of amphibole fibers. Chrysotile asbestos fibers are very different from amphibole fibers in terms of their airborne concentration measurement errors and uncertainties, much lower biopersistence, faster clearance, and different translocation pathways."

[Section 3.2.2 of the SAB Report, p. 12−13]: "The discussion of general fiber toxicokinetics is not clear, nor concise, especially since it fails to distinguish between chrysotile and amphibole fibers. Furthermore, it is inaccurate in many places, as noted below."

> "In view of the fact that the focus of the document is on Libby Amphibole fibers, it would be better to limit most of the literature reviews and discussions to those dealing with the various kinds of amphibole asbestos fibers. Chrysotile asbestos fibers, which are not a significant complication in exposures to Libby vermiculite, are very different from amphibole fibers in terms of their: (a) airborne concentration measurement errors and uncertainties (HEI, 1991); (b) much lower biopersistence (Bernstein et al., 2005b; Bernstein et al., 2005a; Bernstein et al., 2004); and (c) clearance and translocation pathways and rates (Bernstein et al., 2005b; Bernstein et al., 2005a; Bernstein et al., 2004)."

[Section 3.2.2 of the SAB Report, p. 13]: "There are some misstatements on fiber deposition and dosimetry in the document."

> "The authors should draw on more authoritative and comprehensive reviews in the literature (e.g., Mossman et al., 2011; Lippmann, 2009). One misstatement in the draft is that impaction is affected by fiber length. Another is that interception is affected by aspect ratio. The document should cite the work by Sussman et al. (1991a) and Sussman et al. (1991b) that demonstrates that interception of amphibole (crocidolite) fibers is only demonstrably in excess when fiber lengths are >10 µm. Also, the report should cite the work of Brody and colleagues (Warheit and Hartsky, 1990; Brody and Roe, 1983; Brody et al., 1981) on chrysotile fiber deposition in the alveolar region in rodents. In terms of deposition sites, there should be no significant difference between chrysotile and amphibole fibers."

[Section 3.2.2 of the SAB Report, p. 13]: "Another misstatement is that mucociliary clearance is complete within minutes or hours rather than the true time frame of hours to a few days (Albert et al., 1969). The authors also need to acknowledge that particles depositing in the alveolar region can reach the tracheobronchial tree in two ways: (a) on surface fluids drawn onto the mucociliary escalator by surface tension, and (b) by passing through lymphatic channels that empty onto the mucociliary escalator at bronchial bifurcations. The report also should acknowledge that macrophage-related clearance of fibers is only applicable to short fibers that can be fully phagocytosed. Nearly all of the references to chrysotile in the discussion of translocation should be deleted. The Libby asbestos fibers are essentially all amphibole fibers, and there is very little commonality among serpentine and amphibole fibers in terms of translocation or long-term retention."

[Section 3.2.2 of the SAB Report, p. 13]: "There are also toxicokinetic misstatements in Section 4.2 describing cancer bioassays in animals. The section should cite the inhalation study of Davis et al. (1985) with fibrous tremolite, which is very similar to Libby amphibole. Also, this section should discuss the tremolite inhalation study of Bernstein et al. (2003) and (Bernstein et al., 2005b) that is cited in Table 4-16, as well as the more recent study by Bernstein et al. (2011) that demonstrated pleural translocation in rats using noninvasive means following airborne amosite asbestos exposure. The study examined animals for up to 1 year following a short 1-week exposure to amphibole and characterized the size of fibers

that were present in parietal pleura. Noncancer inflammatory pleural changes were demonstrated associated with fiber translocation. This paper shows rapid translocation of fibers to the pleura (at least of rodents) and it should be referenced for completeness on toxicokinetic issues. Furthermore, the results of the various studies cited in Section 4.2 are almost all very difficult to interpret with respect to the toxic effects that were, or were not, reported, since no information was provided in Tables 4.15 and 4.16 on the key dosimetric factor of fiber dimensions. There were comprehensive summaries of available information on fiber dimensions of materials administered in the bioassays in Appendix D, including numbers of long fibers, but Section 4.2.5 is deficient as a summary of animal studies for LAA and tremolite because it does not discuss how the content of long fibers in the administered materials had an influence on the effects observed."

EPA Response: EPA agrees with this set of SAB comments and has made revisions to address them. EPA has edited the Toxicokinetics section of the Toxicological Review to reflect the SAB recommendation to limit discussions to amphibole asbestos in order to more appropriately focus the discussion on fibers more relevant to LAA. Further, EPA has corrected any misstatements and included the references requested, as appropriate.

A.4. NONCANCER HEALTH EFFECTS – OTHER MAJOR SAB COMMENTS AND RECOMMENDATIONS WITH EPA RESPONSES:

SAB Noncancer Health Effects #1: **[Section 3.2.3.2 of the SAB Report, p. 16]:** "The EPA draft document discusses the different types of minerals present in LAA and it is uncertain how the various components relate to adverse health effects. LAA contains ~6% tremolite and there is clear evidence from human and animal studies that tremolite causes adverse health effects in humans and experimental animals. However, since LAA also contains winchite (84%) and richterite (~11%), it would be prudent to determine whether these mineral forms contribute to the adverse health effects of LAA or whether there are interactive effects of winchite or richterite that modify the toxicity of tremolite. The SAB recommends that this issue be highlighted since it is well-known that tremolite is highly fibrogenic and causes malignant mesothelioma (MM). However, the contribution of winchite or richterite to adverse health effects is apparently unknown."

EPA Response: The contribution of the individual mineral types present in LAA on adverse health effects following exposure to LAA is currently unknown. There is limited information on these components individually, with peer-reviewed publications examining the role of these individual components on adverse health effects available only for tremolite. EPA included these studies of tremolite to inform conclusions related to the mechanisms of action for LAA. EPA has further clarified the purpose of including tremolite studies in the *Toxicological Review of Libby Amphibole Asbestos* at the beginning of Section 4.2. Further discussion of the mineralogy of LAA can also be found in Section 2. As described by Meeker et al. (2003), LAA is made up of winchite, richterite, and tremolite. Tremolite makes up less than 10% of the complex mixture that is LAA. EPA included analysis of in vitro and in vivo studies on tremolite in Section 4.2 and Appendix D. SAB requested clarification as to the purpose of including these studies, but not any studies of winchite or richterite. It is not known at this time whether the biological effects of LAA are induced by individual fiber types in the LAA mixture (i.e., tremolite, winchite, or richterite) or by the complex mixture itself. There is currently limited peer-reviewed published literature on LAA and on the individual fiber types in the LAA mixture, particularly in vivo inhalation studies. Because tremolite

makes up a small percentage of the LAA material of interest, information about the toxicity and carcinogenicity of tremolite may support conclusions related to the biological response to LAA. At this time, there are no comparable peer-reviewed published literature on winchite and richterite.

SAB Noncancer Health Effects #2: **[Executive Summary of the SAB Report, p. 3]:** "The SAB agrees that the database of laboratory animal and mechanistic studies pertaining to LAA is appropriately presented in the report and its Appendices for support of its analysis of the human effects observed. However, the SAB finds the body of the document deficient in not utilizing what is known about the dimensions of the administered fibers from Appendix D. It is generally accepted that differences in biological potency among the various amphibole fiber types are due primarily to differences in dimensions, especially in fiber length distributions. The SAB also recommends that Section 4.6.2.2 be modified to reflect that there are insufficient data to determine the mode of action for LAA."

EPA Response: Multiple fiber characteristics, including length, width, and durability, play a role in the toxicokinetics and toxicity of fibers. While there is extensive literature on the role of fiber determinants of toxicity relative to adverse health effects for fibers in general, the studies are often contradictory, making it difficult to draw conclusions for specific fiber characteristics. However, in response to the SAB recommendations, an increased discussion of the role of fiber characteristics, including fiber dimensions, in the biological effects of asbestos has been included in Section 3.3 (Determinants of Toxicity). In Section 4, discussion of fiber dimensions was included for each study when available. In general, when information for each study was available, the role of fiber dimensions individually or cumulatively in the biological response was discussed. This is discussed in Section 3 for asbestos in general, with further discussion specific to LAA available in Section 4.5 and 4.6. Although this information helps to inform MOA hypotheses for LAA, EPA has concluded, as the SAB notes, there is insufficient information at this time to reasonably establish a most likely MOA for LAA.

SAB Noncancer Health Effects #3: **[Section 3.2.4.4 of the SAB Report, p. 21]:** "Section 4.2 should start with a discussion of the relevance of routes of exposure, and then should proceed to discuss inhalation data, followed by a discussion of data from other, less relevant routes of exposure."

EPA Response: The EPA has revised Section 4.2 to include statements on the relevance of the inhalation route of exposure for studying health effects of fibers, and to discuss the inhalation data prior to the review of the data from studies that were performed with an alternate route of exposure. As noted in Section 3, the primary route of human exposure to asbestos is inhalation. Therefore, studies that expose animals through a pulmonary route are the most relevant for hazard identification.

SAB Noncancer Health Effects #4: **[Section 3.2.4.4 of the SAB Report, p. 20]:** "It is generally accepted that the toxicity and carcinogenicity of mineral and synthetic vitreous fibers are governed by fiber dimensions, in vivo durability, and dose, and that all long amphibole fibers are very durable in vivo. Thus, the differences in biological potency among the various amphibole fiber types are due primarily to their differences in dimensions, especially their fiber length distributions Berman (2011). The SAB noted that the text in Sections 4.2 and 4.3, and the tables

cited therein, are deficient in not citing all that is known about the dimensions of the administered fibers."

EPA Response: Information on fiber dimensions has been included when available for all laboratory animal studies of LAA and tremolite in Tables 4-19 and 4-20. Discussion of the role of these dimensions in the biological response to fibers is further discussed in Section 3. For example, in early studies, fiber length has been correlated with disease status, with shorter fibers (<2 μm) being associated with asbestosis while longer fibers (>5 μm) associated with mesothelioma (Lippmann, 1990). However, more recent studies have also suggested a role for surface area or surface chemistry, particularly surface iron, in disease status (reviewed in Aust et al., 2011). Multiple fiber characteristics, including length, width, and durability, play a role in the toxicokinetics and toxicity of fibers. As discussed in Section 3.3, while there is extensive literature on the role of fiber determinants of toxicity relative to adverse health effects for fibers in general, the studies are often contradictory, making it difficult to draw conclusions for specific fiber characteristics.

A.5. CARCINOGENICITY – OTHER MAJOR SAB COMMENTS AND RECOMMENDATIONS WITH EPA RESPONSES:

SAB Carcinogenicity #1: **Set of Three Related SAB Comments From:**

1) **Section 3.2.4.2 of the SAB Report, p. 18:** "A formal mode of action analysis in accordance with EPA's *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a) has not been conducted in the draft assessment. The mechanisms by which amphibole fibers produce malignancy and fibrosis are complex and likely to be multifactorial in nature. The induction of reactive radical species through persistent interaction of fibers with target cells, the involvement of chronic inflammatory response, the activation of certain oncogenes and inactivation of yet-to-be-identified suppressor gene(s), have been proposed as possible mechanisms. In addition, various in vitro and in vivo studies have shown that fiber dimensions, surface properties, shape and crystallinity, chemical composition, physical durability, and exposure route, duration, and dose are important determinants of the biological potency of fibers."

   "With the LAA, neither the fairly limited amount of research conducted using in vivo as well as in vitro assays that are described in the review, nor the more extensive body of published work on other asbestiform minerals, which is also summarized, lead to clear conclusions as to a single mode of carcinogenic action. The SAB agrees with the EPA conclusion that the laboratory-based weight of evidence for the mode of action of LAA is weak. Given the limited database available in the literature and some limited support from data on carcinogenesis by other amphiboles, the EPA's conclusion that there is insufficient information to identify the mode of carcinogenic action of LAA may be justified. However, there are extensive data suggesting multiple mechanisms of carcinogenic action of other amphibole asbestos fibers (IARC, 2012). The SAB finds that, given the available information, the default linear extrapolation at low doses may be appropriate."

2) **Section 3.2.4.2 of the SAB Report, Recommendation, p. 18:** "A formal mode of action analysis for LAA should be conducted in accordance with EPA's *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a)."

3) **Section 3.2.4.4 of the SAB Report, Recommendation, p. 21:** "Section 4.6.2.2 should be modified to reflect that there are insufficient data to determine if a mutagenic mode of action for LAA is supported."

EPA Response: Please see response above to **Major SAB Recommendation *Letter #5***.

SAB Carcinogenicity #2: **[Section 3.1.1 of the SAB Report, p. 8]** "There is inconsistency in the tone of the conclusions in Section 4.7.1.1 (Lifestage Susceptibility) and in Section 6.3.3 (Applications to Early Lifetime and Partial Lifetime Environmental Exposure Scenarios for IUR) to either support or refute early life stage susceptibility. The SAB recognizes that no firm conclusion can be drawn about differential risk of adverse health effects after early life stage exposure to LAA compared to exposure during adulthood, due to the limited and inconclusive studies on other forms of asbestos. However, the available limited evidence pointing to excess risk for exposures during childhood needs to be considered when considering a margin of safety."

EPA Response: The susceptibility section (see Section 4.7) has been revised to reflect the current state of the science on susceptibility to fibers, with a focus on the consistency of the tone and conclusions on the early-life susceptibility to fibers. The weight of evidence (WOE) does not support a mutagenic MOA for LAA carcinogenicity. Therefore, according to EPA's *Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens* (U.S. EPA, 2005b), the application of the age-dependent adjustment factors are not recommended.

A.6. INHALATION REFERENCE CONCENTRATION (RFC) - OTHER MAJOR SAB COMMENTS AND RECOMMENDATIONS WITH EPA RESPONSES:

SAB Inhalation Reference Concentration (RfC) #1**: [p. 1 Executive Summary]** "SAB recommends additional analyses/cohorts to strengthen and support the RfC since the size of the Marysville subcohort is small."

EPA Response: As noted above (see response to **Major SAB Recommendation *Letter #2***), EPA evaluated the two newly available studies of Libby workers and Minneapolis community residents and have added these results to Section 5.2.1. These studies, although not suitable for quantitative analyses for the derivation of the RfC, qualitatively inform the development of the RfC because they indicate that LAA is also associated with pleural effects at low levels of exposure. In addition, EPA included numerous sensitivity analyses to support the RfC (see Section 5.3 and Appendix E).

SAB Inhalation Reference Concentration (RfC) #2**: [p. 1 Executive Summary]** "In addition to localized pleural thickening (LPT), the SAB suggests that the EPA consider any x-ray abnormalities as the outcome: LPT, diffuse pleural thickening (DPT), or asbestosis."

EPA Response: EPA has derived values for chronic RfCs based on "any pleural thickening" and "all radiographic changes" as a sensitivity analysis of alternative endpoint definitions in Section 5.2.3. Section 5.2.3 and Appendix E also show PODs for alternative endpoint definition. The results in Section 5.2.3 for the three endpoint definitions show equivalent toxicity values. Additionally, EPA included as a sensitivity analysis a multinomial modeling approach, which simultaneously models all of the

different outcomes (i.e., LPT, DPT, and interstitial changes) in the larger subset of workers with more recent health evaluations (regardless of hire date; see Section 5.3.5).

***SAB Inhalation Reference Concentration (RfC) #3*: [p. 1 Executive Summary]** "The SAB also suggests that the EPA conduct analogous analyses (to the extent the data permit) of pleural abnormalities among the Libby workers cohort and the Minneapolis Exfoliation Community cohort."

EPA Response: Please see response above to **Major SAB Recommendation *Letter #2*: [Letter to the Administrator, p. 1].**

***SAB Inhalation Reference Concentration (RfC) #4*: [p. 3 Executive Summary]** "With regard to the exposure metric, the SAB recommends that the EPA reevaluate the raw exposure data and review pertinent sampling documentation to bolster its use of the geometric mean to represent the job group exposures, rather than an estimate of the arithmetic mean. The agency should consider whether a sensitivity analysis using the minimum variance unbiased estimator (MVUE) of the mean is warranted in the development of the cumulative exposure metric."

EPA Response: In response to this comment, EPA conducted an extensive re-evaluation of the data and the approach to estimation of job group exposures, as described in Appendix F. Evaluation of an updated job exposure matrix resulted in a decision to use a cumulative exposure metric based on the arithmetic mean since this is the method used for sampling in the field, rather than using the MVUE or some other statistical procedure to develop the cumulative exposure (CE) metric. The updated industrial hygiene data were used in these calculations (15 duplicate data points were excluded); use of the arithmetic rather than the geometric mean resulted in exposure estimates that were approximately threefold higher. These updated exposure measurements are used to support derivation of the RfC, and analogous results using the original geometric-mean based estimates are presented in the uncertainty discussion (see Section 5.3.1).

***SAB Inhalation Reference Concentration (RfC) #5*: [p. 3 Executive Summary]** "EPA's approach to the primary exposure-response modeling was generally appropriate, but the SAB recommends that the procedure be refined and the document should provide a clearer description of how the 'best' model was chosen, in accordance with EPA's 2012 *Benchmark Dose Technical Guidance* (U.S. EPA, 2012). Since the Marysville cohort does not support precise estimation of the plateau, the EPA should consider fixing the plateau level based on a study of highly exposed asbestos insulation workers."

EPA Response: Please see response to **Major SAB Recommendation *Letter #3*** for more detail on how EPA addressed the comment regarding modeling approach and model selection. With regards to the plateau, EPA reviewed the literature (e.g., see Winters et al., 2012; Järvholm, 1992; Lilis et al., 1991), and in the primary modeling, fixed the plateau at 85% consistent with a study of highly exposed workers. EPA explored the impact of this assumption in sensitivity analyses and found that the results were similar to the primary analysis (see Section 5.3.4 and Appendix E).

***SAB Inhalation Reference Concentration (RfC) #6*: [p. 4 Executive Summary]** "The SAB suggests examining other exposure metrics besides the simple cumulative exposure, such as time-weighting of exposures. In addition, the document uses a 10% Extra Risk (ER) as the benchmark response level (BMR) which is not typically used for human quantal response data.

The SAB recommends that EPA explain what features of the data set or outcome variable led the agency to choose a BMR that is considerably greater than the norm for epidemiological data."

> **EPA Response:** Regarding exposure metrics, EPA evaluated mean and residence time-weighted (RTW) exposure metrics, in addition to the CE metric included in the ERD analyses. The mean exposure metric was found to provide adequate goodness of fit and the best relative model fit, and was thus carried forward for RfC derivation. Regarding the BMR selection, please see response to **Major SAB Recommendation *Letter #3*** and Section 5.2.2.5; we followed the EPA's *Benchmark Dose Technical Guidance* when selecting a BMR. Briefly, EPA characterized LPT as having the lowest severity among the available pleural outcomes and thus selects a BMR of 10% extra risk for this endpoint.

***SAB Inhalation Reference Concentration (RfC) #7*: [p. 4 Executive Summary]** "The SAB recommends a revised strategy for evaluation of confounders and covariates. Since the quantity of interest in the analyses of the Marysville cohort is the point of departure (POD), the evaluation of the various covariates should be made with respect to this quantity. The SAB suggests that the covariates fall into two classes: exposure-related covariates (various exposure metrics and TSFE [time since first exposure]) and nonexposure-related covariates (age, body mass index [BMI], gender, and smoking status). For nonexposure-related covariates, no additional primary analyses are needed. For exposure-related covariates, the SAB recommends that additional work be done to refine the models to consider alternative exposure metrics, as well as the inclusion of TSFE or other time-related variables in the analyses of the full cohort."

> **EPA Response:** The primary modeling to support derivation of the RfC is performed in the subset of workers with more recent health evaluations and hired in 1972 or later (i.e., highest quality exposure information). In this primary data set, we evaluated confounding using both a theory-based method (whether the potential confounder is associated with both the exposure and with the outcome; see Section 5.2.2.6.1) as well as a data-based method (including each potential confounder in the final model to assess its statistical significance; see Section 5.3.3). No evidence of confounding was found in either case. With regards to TSFE specifically, we utilized a larger subset of workers to estimate the effect of TSFE and included this information in the primary exposure-response modeling. Comparable modeling of the full cohort is described in Appendix E.

***SAB Inhalation Reference Concentration (RfC) #8*: [p. 4 Executive Summary]** "The modeled POD is based on cumulative exposure estimates for the worker cohort examined. The SAB recommends using the full 70-year lifetime when converting cumulative to continuous exposure rather than 60 (70 minus the lag of 10 used for exposure in the POD derivation); i.e., do not correct for the lag of 10 for a 10-year lagged exposure, since the time of disease onset is not known in prevalence data."

> **EPA Response:** EPA revised its analyses based on SAB comments (see Section 5.2.2), and as a result, the primary model uses concentration; thus, it does not require the division by 70 to extrapolate to the full lifetime of 70 years. In the complementary analyses of the combined data from both health evaluations in Appendix E, analyses based on CE is divided by 70 (rather than 60) years, as recommended.

***SAB Inhalation Reference Concentration (RfC) #9*: [p. 4 Executive Summary]** "The uncertainty factors deserve additional consideration and analysis. A composite uncertainty factor

of 100 (an intraspecies uncertainty factor of 10 to account for human variability and sensitive subpopulations; and a database uncertainty factor of 10 to account for database deficiencies) was applied to the POD for derivation of the RfC. Although it may be difficult to identify specific data on LAA to support departure from the default value of 10 for human variability, concern for the impact on susceptible subpopulations, especially women and children, remains an issue. Consideration of additional data (Minnesota cohort and data on other amphiboles) might support a lower value, such as 3, for UF_D. In addition, a subchronic-to-chronic uncertainty factor higher than 1 may be used, given that the mean and maximum exposure duration in the study are well below the lifetime exposure of interest."

EPA Response: Please see response above to **Major SAB Recommendation *Letter #4***. In the revised analyses, the data set UF has been reduced to 3, while the subchronic-to-chronic UF has been increased to 10 based on the evaluation of the role of TSFE in determining LPT risk (see Section 5.2.2.6.2).

***SAB Inhalation Reference Concentration (RfC) #10*: [p. 5 Executive Summary]** "There also is concern that the BMR of 10% for a severe endpoint is not reflected by the choice of a LOAEL-to-NOAEL uncertainty factor (UF_L) of 1."

EPA Response: Please see response to **Major SAB Recommendation *Letter #4***. The LOAEL-to-NOAEL UF was retained at 1 because BMD modeling was used in derivation of the POD, rather than a LOAEL or NOAEL.

***SAB Inhalation Reference Concentration (RfC) #11*: [3.1.1 of the SAB Report, Recommendations, p. 9]** "An overall summary set of tables or figures describing the major cohorts (Libby workers, community, Marysville plant), the types/timelines of exposure, and the studies associated with each would help orient the readers of the document."

EPA Response: We have included a figure (see Figure 4-1) and text discussion summarizing the studies conducted in the three different locations (Montana, Ohio, and Minnesota), depicting the type of study population and type of health effect(s) examined. In addition, a table and text describing the three candidate principal studies (Alexander et al., 2012; Larson et al., 2012; Rohs et al., 2008) in Section 5.2.1, and more detailed tables of the demographic characteristics of the Marysville study population are included in Section 5.2.2.2.

***SAB Inhalation Reference Concentration (RfC) #12*: [3.1.1 of the SAB Report, Recommendations, p. 9]** "The draft document could be enhanced with quantitative comparison of the environmental exposures that have taken place in other geographic regions of the world (i.e., the Anatolia region of Turkey and Greece) (Metintas et al., 2012; Carbone et al., 2011; Metintas et al., 2010; Gogou et al., 2009; Constantopoulos, 2008; Metintas et al., 2008; Sichletidis et al., 2006) with the Libby, Montana, community with regard to airborne tremolite. This comparison should include numbers of fibers and fiber size distribution in relation to health effects."

EPA Response: A new Section has been added (see Section 4.1.5: Comparison with Other Asbestos Studies—Environmental Exposure Settings) that responds to these suggestions and includes a summary table describing exposure (fiber type, exposure level, and fiber size, where available) and health effects information for communities exposed in environmental or residential settings to tremolite or tremolite-chrysotile

mixtures and communities with environmental exposure to crocidolite, another type of amphibole asbestos. The health effects reported in these studies are consistent with those documented for workers exposed to commercial forms of asbestos.

***SAB Inhalation Reference Concentration (RfC) #13*: [3.2.3.1 of the SAB Report, p. 14]** "The rationale for the use of the Marysville, Ohio, cohort for development of the RfC was well described and scientifically supported. However, there are clear drawbacks to this cohort due to the lack of exposure sampling prior to 1972 when most of the cohort began work, the use of self-reported work histories, the end of Libby vermiculite use in 1980, and the mixture of vermiculite sources used throughout the life of the plant. These drawbacks are offset by the solely occupational exposure of this cohort, the use of better quality radiographs taken for research purposes, and the use of 2000 [International Labour Organization] ILO standards for reading radiographs. The selection of the subcohort for the main analysis has a clear and strong rationale. (There were 118 workers who began work in 1972 or later when exposure data were available and who had x-rays from the 2002−2005 exam.) The full cohort of 434 workers was used for analyses to substantiate the subcohort findings."

EPA Response: EPA acknowledges that the cohort of Marysville workers has both strengths and limitations, as identified in the SAB's above recommendation. EPA's primary analysis uses the subset of workers with more recent health evaluations and hired in 1972 or later to address some of these limitations (e.g., this subset was selected due to the availability of higher quality exposure information and more recent health evaluations); this strategy is supported by the SAB recommendation in ***SAB Inhalation Reference Concentration (RfC) #17***, below. EPA recognizes that the range of TSFE is limited in this subset; thus, EPA used the larger group of workers with more recent health evaluations (regardless of hire date) to estimate the effect of TSFE and included this in the primary modeling (see Section 5.2.2.6.2). In addition, modeling of the full cohort is described in Appendix E. The potential uncertainty due to the end of Libby vermiculite use in 1980 and the mixture of vermiculite sources used throughout the life of the plant is discussed in Section 5.3.1 and Appendix F.

***SAB Inhalation Reference Concentration (RfC) #14*: [3.2.3.1 of the SAB Report, p. 14]** "Although the SAB agrees that the Marysville subcohort represents the best population upon which to base the RfC, there was discussion about the need for additional analyses/cohorts to strengthen and support the RfC since the size of the Marysville subcohort was small. One suggestion is to use the Marysville cohort but include any x-ray abnormalities as the outcome (LPT, diffuse pleural thickening [DPT], or asbestosis). In addition, cause of death might be assessed for those who died between the two exams. Another suggestion for providing support and perspective to the Marysville findings is to conduct analogous analyses (to the extent the data permit) of pleural abnormalities among the Libby workers cohort (Larson et al., 2012) and among the Minneapolis exfoliation community cohort (Alexander et al., 2012; Adgate et al., 2011)."

EPA Response: Please see response to **Major SAB Recommendation *Letter #2*** and ***SAB Inhalation Reference Concentration (RfC) #2***.

***SAB Inhalation Reference Concentration (RfC) #15*: [3.2.3.1 of the SAB Report, p. 15]** "In addition to localized pleural thickening, the SAB also suggests that the EPA consider looking at LPT, DPT, and small opacity profusion score together as an outcome. There is evidence that

LPT is not always the first adverse effect that is detected on chest radiographs, and some individuals with LAA exposure can develop either DPT or increased profusion of small opacities without developing evidence of LPT. Combining outcomes is appropriate, since DPT and small opacity profusion also are effects of asbestos exposure and the goal is to define an exposure level below which LAA is unlikely to have adverse health effects."

EPA Response: Please see response to ***SAB Inhalation Reference Concentration (RfC) #2***.

***SAB Inhalation Reference Concentration (RfC) #16*: [3.2.3.1 of the SAB Report, Recommendation, p. 15]** "The SAB suggests the EPA assessment clarify the range of endpoints that generally can be used to derive an RfC."

EPA Response: EPA included in Section 4 a revised description of the radiographic endpoints evaluated in the relevant epidemiological studies. In Section 5, the selection of LPT as the critical endpoint is further explained (see Section 5.2.2.3); in brief, LPT is most likely to appear sooner after exposure, and at lower levels of exposure, making it the most sensitive of the available endpoints. In addition, EPA has conducted sensitivity analyses that included any pleural thickening and any radiographic changes as the critical effects (see Section 5.2.6).

***SAB Inhalation Reference Concentration (RfC) #17*: [3.2.3.1 of the SAB Report, Recommendation, p. 15]** "The agency should include a more detailed review of the literature to support the selection of LPT through detailing the studies that show the relationship between LPT and both pathologic and physiologic abnormalities, and also risk of other noncancer asbestos-related diseases."

EPA Response: In response to the specific SAB recommendation, EPA has conducted a more detailed and comprehensive review of the literature, and performed a meta-analysis of studies examining the relation between pleural plaques or LPT and pulmonary function measures. This work is presented in Appendix I as support for the selection of LPT as the critical effect. This analysis concluded that pleural plaques—and subsequently LPT—are associated with statistically significant decrements in both forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV_1).

***SAB Inhalation Reference Concentration (RfC) #18*: [3.2.3.1 of the SAB Report, Recommendation, p. 15]** "In addition to LPT, the document should include an analysis that uses all radiographic outcomes (LPT, DPT, and small opacities), recognizing this change may have little impact on the current analysis."

EPA Response: Please see response to ***Inhalation Reference Concentration (RfC) #2***.

***SAB Inhalation Reference Concentration (RfC) #19*: [3.2.5.1 of the SAB Report, Recommendation, p. 22]** "Consider sensitivity analyses of additional exposure metrics, particularly those weighting earlier life exposures more heavily."

EPA Response: EPA has evaluated different exposure metrics, including mean and RTW exposure metrics (see Section 5.2.2.6.2 and Appendix E.) in addition to the CE metric included in the ERD analyses. In the subcohort of Marysville workers hired in 1972 or later and evaluated in 2002−2005, the best fitting exposure metric was mean

exposure (C) (see Section 5.2.2.6.2), and this metric was carried forward for primary RfC derivation. This use of C is a change from the CE metric used in the ERD dated August 2011.

***SAB Inhalation Reference Concentration (RfC) #20*: [3.2.5.2 of the SAB Report, p. 22]** "This response focuses on the primary analysis of the Marysville subcohort. Additional comments on the analysis of this cohort can be found in response to Question 4 in Section 3.2.5.4. The SAB found that the various exposure-response models that were examined were reasonably well described. However, the SAB recommends a clearer description of how the 'best' model was chosen. It appears that EPA fits a series of quantal response models, retained models with adequate fit according to the Hosmer-Lemeshow test (presumably based on $p > 0.1$, but if so, this should be stated). Then, among the retained models, the authors selected the model with the lowest Akaike Information Criteria (AIC). From a statistical standpoint, this methodology can be justified. However, it is not clear how well aligned it is with the guidance for selection of the POD in the updated version of EPA's *Benchmark Dose Technical Guidance* (U.S. EPA, 2012). Thus the SAB recommends the EPA revise the approach to be better aligned with the *Benchmark Dose Technical Guidance* document."

EPA Response: Please see response to **Major SAB Recommendation *Letter #3***.

***SAB Inhalation Reference Concentration (RfC) #21*: [3.2.5.2 of the SAB Report, p. 23]** "Consistent with the tone of the *Benchmark Dose Technical Guidance* (U.S. EPA, 2012), the SAB recommends that a thoughtful approach to model selection be used, including consideration of biological/epidemiological plausibility, and desirable model features, combined with careful examination of the data, model fit, and application of the AIC. The SAB highlights the following points:

1) Model fit (visual comparison of model predictions to data and/or local smoother estimates from data) in the region of the benchmark response rate (BMR) should play a role in model selection.

2) The fitted Michaelis-Menten model has an upper plateau of 60% LPT incidence, while a study of highly exposed asbestos insulation workers reported a prevalence of 85% (Lilis et al., 1991). The Marysville cohort does not support precise estimation of the plateau. Thus, EPA should consider fixing the plateau at a level justified by the literature.

3) Other exposure metrics besides the simple cumulative exposure, such as time weighting of exposures, should be considered. The Dichotomous Hill model is attractive because it allows estimation of an exposure parameter (see b in Table 5-4), allowing the exposure effect to scale as covariates are added, the exposure metric changed, or the plateau fixed."

EPA Response: Please see response to **Major SAB Recommendation *Letter #3***. Based on the revised model considerations and selection process, the Dichotomous Hill model was chosen as the primary model for RfC derivation, largely for the reasons outlined by the SAB (see Section 5.2.2.6.1).

***SAB Inhalation Reference Concentration (RfC) #22*: [3.2.5.2 of the SAB Report, p. 23]** "The authors explain that their choice of a 10% Extra Risk (ER) as the BMR is in line with the EPA's *Benchmark Dose Technical Guidance*. However, that rate is generally considered to apply specifically to the analysis of quantal data sets from animal studies, which is the context in which

it was developed. In the EPA's *Benchmark Dose Technical Guidance*, it is mentioned that a BMR of 1% ER is typically used for human quantal response data because epidemiologic data often have greater sensitivities than bioassay data. The authors should explain what features of the data set or outcome variable led them to choose a BMR that is considerably greater than the norm for epidemiologic data."

EPA Response: Please see response to **Major SAB Recommendation *Letter #3***.

***SAB Inhalation Reference Concentration (RfC) #23*: [3.2.5.2 of the SAB Report, Recommendation, p. 23]** "Consider model features and balance plausibility, localized fit, and EPA's 2012 *Benchmark Dose Technical Guidance* (U.S. EPA, 2012) when choosing the best model and explain decisions in more detail."

EPA Response: Please see response to **Major SAB Recommendation *Letter #3.***

***SAB Inhalation Reference Concentration (RfC) #24*: [3.2.5.2 of the SAB Report, Recommendation, p. 23]** "In conjunction with updating and better justifying the primary analysis, evaluate the impact of different time weightings of the exposure metric."

EPA Response: Please see response to ***Inhalation Reference Concentration (RfC) #19***.

***SAB Inhalation Reference Concentration (RfC) #25*: [3.2.5.2 of the SAB Report, Recommendation, p. 23]** "Either lower the BMR to be more consistent with common practice for epidemiological data or provide more justification for the 10% BMR used to calculate the POD."

EPA Response: Please see response to **Major SAB Recommendation *Letter #3.***

***SAB Inhalation Reference Concentration (RfC) #26*: [3.2.5.3 of the SAB Report, p. 24]** "It is not clear that the scientific basis of using time since first exposure (TSFE) is well founded. EPA should consider what TSFE is supposed to be measuring and how it is related to other variables in the data set (specifically age and exposure). There is some suggestion in the draft document that in this data set it is a surrogate measure of intensity since people with larger TSFEs would be more likely to have been exposed to higher levels of LAA present during the early time periods. This perspective should help identify modeling options."

EPA Response: TSFE is the time between the first day of exposure and the day of the most recent health examination, which includes the duration of exposure and any time after exposure ceases until the day of the health examination. Results in the literature show that TSFE is a key determinant of prevalence, with prevalence increasing as TSFE increases (e.g., see Paris et al., 2009; Paris et al., 2008; Järvholm, 1992; Lilis et al., 1991). As discussed in the text in Appendix E, in the full cohort of all Marysville workers, there is a correlation between TSFE and CE because exposure was not constant over time but was highest in the early years when vermiculite ore was used. However, there are individual workers with high CE and low TSFE as well as workers with low CE and high TSFE, supporting the conclusion that TSFE is a key variable.

***SAB Inhalation Reference Concentration (RfC) #27*: [3.2.5.3 of the SAB Report, p. 24]** "The SAB also finds that the method for incorporating TSFE into the full cohort analysis is not well justified. Currently, the EPA uses TSFE as a predictor for the plateau in the Cumulative Normal

Michaelis-Menten model. No biological justification is given for why this maximum proportion would vary with TSFE."

> **EPA Response:** Upon further analysis in response to SAB comments, EPA is no longer relying on the Cumulative Normal Michaelis-Menten model in this assessment and instead has selected the Dichotomous Hill model, a minor variation on the Michaelis-Menten model, for the primary analysis. For alternative analysis (see Appendix E), EPA selected both the Dichotomous Hill model using mean occupational exposure concentration and a variant of the Dichotomous Hill model where TSFE is incorporated into the plateau term (the "cumulative normal" Dichotomous Hill model). With regard to use of a cumulative normal model form where TSFE is incorporated into the "plateau" term, the text has been modified to make clear that this form was evaluated because this is what plots of the raw data suggested.

***SAB Inhalation Reference Concentration (RfC) #28*: [3.2.5.3 of the SAB Report, p. 25]** "Improve the scientific justification for using TSFE in the full cohort analysis; this justification will include an explanation of its meaning in the context of this data set."

> **EPA Response:** As discussed above in response to ***SAB Inhalation Reference Concentration (RfC) #26***, Appendix E has been revised to incorporate the evidence from the literature that shows TSFE is an important explanatory variable; many studies show that prevalence increases as TSFE increases. With regard to use of a cumulative normal model form where TSFE is incorporated into the "plateau" term, the text has been modified to make clear that this form was evaluated because this is what plots of the raw data suggested.

***SAB Inhalation Reference Concentration (RfC) #29*: [3.2.5.3 of the SAB Report, p. 25]** "Revise the full cohort analysis to change the approach to incorporating TSFE, removing it from the model of the plateau. As part of the revision, the SAB suggests assessments be made to determine whether it is appropriate to use (a) the Dichotomous Hill model, (b) TSFE in the linear predictor alongside cumulative exposure and/or use an alternative exposure metric that explicitly incorporates TSFE, and (c) the approaches recommended for the subcohort such as a fixed plateau. As appropriate, such analyses should include assessment of the functional form of TSFE."

> **EPA Response:** As described in the response to **Major SAB Recommendation *Letter #3***, the analysis of the full cohort in the revised assessment evaluates a range of univariate and bivariate models and a range of exposure metrics including residence-time weighting that incorporates TSFE (see Appendix E). The analysis has been expanded to include a parallel detailed evaluation using the "cumulative normal" Dichotomous Hill model utilizing the cumulative exposure metric and TSFE, as well as the Dichotomous Hill model based on mean occupational exposure and TSFE, where TSFE is included alongside the exposure metric in the exponential term.

***SAB Inhalation Reference Concentration (RfC) #30*: [3.2.5.3 of the SAB Report, p. 25]** "The SAB recommends that the EPA present the lower 95% confidence limit of the benchmark concentration (BMCL) estimates from a set of reasonable and plausible models, and selections of data, which will both inform selection of a preferred model and illustrate the range of model uncertainty."

EPA Response: As discussed in response to ***SAB Inhalation Reference Concentration (RfC) #7***, EPA's revised analysis of the full cohort includes BMCL values for a wide range of alternative models, with special emphasis on the cumulative normal Dichotomous Hill model and the Dichotomous Hill model. Lower 95% confidence limits on the BMC were included in the presentation of the modeling results, for example, in Table 5-8.

***SAB Inhalation Reference Concentration (RfC) #31*: [3.2.5.4 of the SAB Report, p. 25]** "The SAB recommends a revised strategy for evaluation of covariates. The target of inference for the analyses of the Marysville cohort is the POD, which in this case is the BMCL. The evaluation of the various covariates should be made with respect to this target of inference. The SAB suggests the covariates fall into two classes: exposure-related covariates (various exposure metrics and TSFE) and nonexposure-related covariates (age, body mass index [BMI], gender, and smoking status). We provide recommended revised strategies for considering these two classes of covariates that follow directly from consideration of the target of inference."

EPA Response: Please see response to ***SAB Inhalation Reference Concentration (RfC) #7.***

***SAB Inhalation Reference Concentration (RfC) #32*: [3.2.5.4 of the SAB Report, p. 25]** "Nonexposure related covariates: A decision on whether to control for the nonexposure-related covariates should account for how the EPA wishes to determine and apply the RfC. The SAB suggests a BMCL most directly applicable to all members of the general population is most appropriate. This implies that the BMCL should be estimated from a model that includes exposure covariate(s), but that is otherwise unadjusted. This is the same approach used in the current draft document; only the rationale for the approach is different. The SAB suggests it would be informative to conduct sensitivity analyses to examine how the BMCL varies across subgroups defined by covariate values (e.g., older males or smokers). Because the Marysville subcohort is a small data set, it is difficult to conduct this evaluation exclusively in the subcohort. Therefore the SAB suggests that the EPA use the full cohort for the model selection and parameter estimation components of sensitivity analyses incorporating these covariates."

EPA Response: Please see response to ***SAB Inhalation Reference Concentration (RfC) #7***. There was no evidence that the potential confounders evaluated were significant predictors of LPT risk after adjusting for exposure to LAA and TSFE. Thus, there would be no significant effect modification (i.e., variation in risk across strata) from these factors.

***SAB Inhalation Reference Concentration (RfC) #33*: [3.2.5.4 of the SAB Report, p. 26]** "For this activity the EPA would use its selected final model after excluding all exposure variables (e.g., the Dichotomous Hill model with fixed background, fixed plateau, and after dropping exposure variables). After fitting a model with a specific set of nonexposure-related covariates in the full cohort, one can estimate a 'risk score' (i.e., the linear predictor for the nonexposure-related covariates). This risk score would be included as a single term (as either an unscaled offset or scaled by its estimated coefficient) in the subcohort analysis. Similar to the approach presented in Table E-5, these analyses can be used to produce a new table of subgroup-specific conditional BMCLs; these values will give some evidence of how the target of inference varies by subgroup. In addition, weighted averages of the conditional BMCLs can be computed to reflect population average BMCLs for specific covariate distributions in target

populations. For instance, Gaylor et al. (1998) gives a formula for the upper tail of a 95% confidence interval, and this formula can be extended to obtain BMCLs for weighted averages."

EPA Response: Please see responses to ***SAB Inhalation Reference Concentration (RfC) #7 and #32.***

***SAB Inhalation Reference Concentration (RfC) #34*: [3.2.5.4 of the SAB Report, p. 26]**
"Exposure-related covariates: The inclusion of exposure-related covariates in the model is fundamental to the inference. The EPA has done excellent preliminary work, and the SAB has provided recommendations in Sections 3.2.5.2 and 3.2.5.3 of this report about how to revise the approach. In addition, the SAB recommends that the EPA consider taking several further steps. First, alternative exposure metrics should be assessed directly in the subcohort data set to determine whether they fit the data better. In particular, alternative metrics (such as residence time-weighted exposure) that more heavily weight more distant exposure may be more biologically plausible because individuals exposed at an earlier age might be more susceptible to the damaging effects of asbestos. Second, TSFE should be considered for addition to the model. Since TSFE is complete and equally well estimated across all members of the cohort, the full cohort can be used to determine how to model this variable. Similar to the approach recommended for the sensitivity analyses discussed above, this would be done using the model intended for the subcohort, but omitting exposure variables other than TSFE. Then, the functional form of TSFE selected using the full cohort can be added to the subcohort analysis, either as an unscaled offset term or as a scaled covariate. Given biological understanding of the disease process, for models with both estimated exposure and TSFE included, it would be appropriate to report the BMCL conditional on a large TSFE."

EPA Response: As recommended by the SAB, EPA investigated alternative exposure metrics (cumulative, mean, RTW). In addition, EPA used the "hybrid" approach suggested by the SAB in which the effect of TSFE is estimated in a larger subset of Marysville workers (those with more recent health evaluations, regardless of hire date) and this effect is carried over into the primary modeling performed among those workers with more recent health evaluations and who were hired in 1972 or later (see Section 5.2.2.6.2). A parallel analysis based on the full cohort of Marysville workers is provided in Appendix E.

***SAB Inhalation Reference Concentration (RfC) #35*: [3.2.5.4 of the SAB Report, p. 26]**
"Additional comments on covariates: TSFE:

(1) TSFE deserves careful consideration for both biological and data set-specific reasons. It is an important determinant of LPT both because individuals' lung tissues exposed at an earlier age might be more susceptible to the damaging effects of asbestos and because asbestos' effect over time is increasingly damaging. It is correlated with exposure in this data set since subjects with the longest TSFE were exposed in the early years of the cohort when exposures were higher. It is also more accurately estimated than exposure. (2) The SAB does not agree with the use of the Cumulative Normal Michaelis-Menten model to adjust for TSFE because it makes the assumption that the TSFE only affects the plateau. This has not been justified biologically or in the context of features of this particular data set. Instead, the SAB recommends that EPA consider alternative approaches to account for TSFE."

EPA Response: Regarding (1): Please see responses to ***SAB Inhalation Reference Concentration (RfC) #34***. Regarding (2): For the analysis of the full cohort in

Appendix E, EPA investigated a variety of model forms that incorporated TSFE. These included bivariate log-logistic and bivariate Dichotomous Hill models in which TSFE was included as an independent predictor of prevalence alongside the exposure metric. EPA also investigated models in which TSFE was incorporated in the plateau term (Cumulative Normal Dichotomous Hill and Cumulative Normal Michaelis-Menten). EPA is no longer relying on the Cumulative Normal Michaelis-Menten model in this assessment.

***SAB Inhalation Reference Concentration (RfC) #36*: [3.2.5.4 of the SAB Report, p. 27]** Additional comments on covariates: Smoking:

"(1) Smoking is included in the follow-up by Rohs et al. (2008). However, the ever/never categorization of smoking is much less informative than the pack-year analysis of smoking used in the earlier study by Lockey et al. (1984). (2) There is an important discussion of the evidence linking pleural changes and smoking in footnote 34 on page 5-46. This information could be moved into the body of the report, and amplified somewhat. A table summarizing the relevant studies (irrespective of type of amphibole asbestos) summarizing the evidence regarding the role of smoking would be useful."

EPA Response: Please see response to ***SAB Inhalation Reference Concentration (RfC) #7***. Smoking was investigated along with other covariates, but in the revised analyses, was not found to be a potential confounder and was not significant in the final model. However, we have moved the information from the footnote to the main body of the text in the sections discussing uncertainty due to potential confounding (see Section 5.3.3).

***SAB Inhalation Reference Concentration (RfC) #37*: [3.2.5.4 of the SAB Report, p. 27]** Additional comments on covariates (Gender): "There is little discussion of gender, except in places where the number of females is listed as too few to analyze in any detail. The SAB did not regard this as a serious concern because it is reasonable to assume that females and males have similar probabilities of developing LPT."

EPA Response: Gender was investigated along with other covariates but, in the revised analyses, was not found to be a potential confounder and was not statistically significant in the final model (see Section 5.2.2.5.1). We agree with the SAB that risk of LPT is unlikely to vary greatly according to gender.

***SAB Inhalation Reference Concentration (RfC) #38*: [3.2.5.4 of the SAB Report, p.27]** "The SAB recommends that a table be included summarizing the results of the various sensitivity analyses and how they change the POD."

EPA Response: A section (with a table as suggested) summarizing the sensitivity analyses has been included at the end of Section 5 (see Section 5.3.6) and in Appendix E.

***SAB Inhalation Reference Concentration (RfC) #39*: [3.2.5.4 of the SAB Report, p. 27]** "Exposure-dependent censoring: The exposure-dependent censoring discussion is based on results from Rohs et al. (2008) that inappropriately separated deceased nonparticipants from the remaining nonparticipants. Once all nonparticipants are combined there is no evidence of exposure-dependent censoring. Furthermore, exposure-dependent sampling by itself does not lead to bias in risk estimates. The important issue for bias is whether two individuals with the same exposure, one diseased and the other not, are equally likely to participate in screening.

There has been no strong rationale presented that would indicate that such differential selection has occurred in this cohort."

EPA Response: EPA has rewritten the description of this study (see Section 4.1.2.2.2) to clarify that no exposure-dependent censoring is apparent when combining deceased and living nonparticipants.

***SAB Inhalation Reference Concentration (RfC) #40*: [3.2.5.4 of the SAB Report, Recommendation, p. 27]** "Revise consideration of covariates to focus on their impact on the target of inference.

1) For nonexposure-related covariates, this only alters the presentation; no additional primary analyses are needed. Sensitivity analyses conditional on subgroups defined by covariates can be added.

2) For exposure-related covariates, additional work is needed to refine the models to consider alternative exposure metrics, as well as the inclusion of TSFE or other time-related variables in analyses of the full cohort. The SAB encourages the EPA to either fully justify analyses based on the Cumulative Normal Michaelis-Menten model in the context of this particular data set, or replace them."

EPA Response: Regarding (1): Please see response to ***SAB Inhalation Reference Concentration (RfC) #24***. Regarding (2): Please see response to ***SAB Inhalation Reference Concentration (RfC)* #35**. EPA is no longer relying on the Cumulative Normal Michaelis-Menten model in this assessment.

***SAB Inhalation Reference Concentration (RfC) #41*: [3.2.5.4 of the SAB Report, Recommendation, p. 27]** "Revise this discussion of Rohs et al. (2008) to make note (perhaps in a revised table) that the dose distribution in participants is similar to the overall dose distribution of the original full cohort. Furthermore, revise the discussion of exposure dependent sampling to distinguish this from bias differential sampling in the sense above."

EPA Response: Please see response to ***SAB Inhalation Reference Concentration (RfC) #39.***

***SAB Inhalation Reference Concentration (RfC) #42*: [3.2.5.5 of the SAB Report, Recommendation, p. 28]** "The SAB recommends EPA indicate more clearly in Section 5.2.3.1. that 'year' is in the numerator in the exposure metric 'fibers/cc-year,' and to describe more clearly how cumulative exposure is derived."

EPA Response: The primary model for RfC derivation uses C (fiber/cc). As discussed in Section 1.1: "For LAA, the RfC is expressed as a lifetime daily exposure in fibers/cc (in units of the fibers as measured by PCM)."

Although the units of cumulative exposure are written as fibers/cc-year, in the epidemiologic literature, it actually means fibers/cc times years of exposure and could alternatively be written as (fibers/cc) × years. Details of how CE estimates were derived are in Appendix F, and the approach is summarized in Section 5.2.2.1: "In brief, occupational exposure was estimated for each worker and adjusted to a cumulative human equivalent exposure for continuous exposure, incorporating adjustments for different inhalation rates in working

versus nonworking time. These adjustments take into account the extensive seasonal changes in work hours at the Marysville facility (see Appendix F)."

***SAB Inhalation Reference Concentration (RfC) #43*: [3.2.5.6 of the SAB Report, p. 28]** "The use of a UF_H of at least 10 is standard in considering health protective levels based on effects in the workforce, which is generally healthier and less diverse than the general population. In fact, publications are available that discuss whether a factor of 10 is sufficient to cover all sensitive subpopulations, especially children (OEHHA, 2008; Dourson et al., 2002; Miller, 2002; Scheuplein et al., 2002; Hattis et al., 1999). Some treatment of the question of interindividual variability is offered in the later summary of conclusions (see Section 6 of the EPA document). There is no specific evidence on the relative sensitivity of children to the noncancer effects of Libby asbestos, although some indications with other amphiboles suggest the possibility of enhanced effects following exposure at younger ages (Bennett et al., 2008; Isaacs and Martonen, 2005; Haque et al., 1998; Haque et al., 1996). Overall, it seems unlikely that a departure from the default guideline value of $UF_H = 10$ could be justified within the existing guidelines, but concerns remain for the impact on susceptible subpopulations, especially women and children."

EPA Response: Please see response to **Major SAB Recommendation *Letter #4***. A UF for intrahuman variability of 10 is used in derivation of the RfC.

***SAB Inhalation Reference Concentration (RfC) #44*: [3.2.5.6 of the SAB Report, p. 29]** "EPA explains and justifies the selection of a UF_D of 10 based on the limited number of studies of exposure to Libby asbestos (Libby workers, [Agency for Toxic Substances and Disease Registry] ATSDR community study and Marysville workers) and the lack of evaluation of potentially more sensitive alternative endpoints. The SAB finds that this uncertainty factor would not be reduced even if improved exposure estimates allowed consideration of the full cohorts (or a larger fraction thereof)."

EPA Response: Please see response to **Major SAB Recommendation *Letter #4***. Briefly, in reevaluating uncertainty factors, EPA applied a UF_D of 3, recognizing the limited number of studies for LAA specifically, but also that LAA has been associated with autoimmune effects (see Section 5.2.3).

***SAB Inhalation Reference Concentration (RfC) #45*: [3.2.5.6 of the SAB Report, p. 29]** "However, some additional data have recently been published for the community surrounding a Minnesota expansion plant (Alexander et al., 2012; Adgate et al., 2011). Although there appears to be a rationale for at least an initial consideration of LAA as a unique material (to provide an unbiased comparison with other amphiboles), this SAB review has identified very substantial grounds for considering this material as having composition, physical properties, and biological effects that are very similar to those seen for other amphiboles. The most relevant comparison would be to tremolite, since Libby Amphibole is ~6% tremolite, an amphibole that is known to cause cancer and noncancer effects in human populations. However, it is uncertain how other components of Libby Amphibole (richterite and winchite) interact as a mixture with tremolite to modify toxicity. This consideration of data on other amphiboles is particularly pertinent to discussions of the mode of action, as well as the exposure-response relationships, for Libby Amphibole. In light of this similarity it appears reasonable, and indeed necessary, to at least debate the question of whether the available data on noncancer health effects of amphiboles are sufficient to mitigate the acknowledged data shortage for Libby Amphibole itself. Therefore, the

SAB considers that additional data (e.g., the Minnesota cohort and data on other amphiboles) might support a lower value, such as 3, for UF_D."

EPA Response: In EPA's revised assessment, a UF_D of 3 was selected; please see response to **Major SAB Recommendation *Letter #4*** and Section 5.2.3 for more details.

***SAB Inhalation Reference Concentration (RfC) #46*: [3.2.5.6 of the SAB Report, p. 29]** "On the other hand, there are substantial remaining uncertainties that are not addressed by these additional data, including those raised by consideration of the severity of the endpoint and the selection of the BMR (see below). This uncertainty should also be revisited by EPA in its judgement of an uncertainty factor of onefold for a LOAEL-to-NOAEL uncertainty factor (UFL). It can also be argued that a subchronic-to-chronic uncertainty factor (UFS) higher than 1 should be used, given that the mean and maximum exposure duration in this study are both well below the lifetime exposure of interest. This uncertainty should also be revisited for EPA in its judgement of an uncertainty factor of onefold for UF_S."

EPA Response: Please see response to **Major SAB Recommendation *Letter #4*** for more details. In the reevaluation of uncertainty factors, EPA retained a UF of 1 for LOAEL-to-NOAEL uncertainty, but increased the subchronic-to-chronic uncertainty factor to 10.

***SAB Inhalation Reference Concentration (RfC) #47*: [3.2.5.6 of the SAB Report, p. 29]** "It may be appropriate for EPA to select a value of 10 for UF_D, or a similar uncertainty spread across several factors, but EPA needs to reevaluate selection of this factor explicitly once all the additional information has been incorporated in the discussion."

EPA Response: In reevaluating uncertainty factors, EPA selected a UF_D of 3; for more details, please see Section 5.2.3 and the response to **Major SAB Recommendation *Letter #4***.

***SAB Inhalation Reference Concentration (RfC) #48*: [3.2.5.6 of the SAB Report, Recommendation, p. 30]** "Review additional data, in particular the exposure-response relationship for noncancer endpoints in the Minneapolis community cohort."

EPA Response: Please see response to **Major SAB Recommendation *Letter #2*** for more details; briefly, because of lack of TSFE data, the Minneapolis community cohort could not be used for exposure-response.

***SAB Inhalation Reference Concentration (RfC) #49*: [3.2.5.6 of the SAB Report, Recommendation, p. 30]** "Determine whether this new analysis supports the existing analysis based on the Marysville data, and if so whether this warrants reduction of the value of UF_D since the limited data basis for the original analysis has been expanded."

EPA Response: Please see response to **Major SAB Recommendation *Letter #4***.

***SAB Inhalation Reference Concentration (RfC) #50*: [3.2.5.6 of the SAB Report, Recommendation, p. 30]** "Reassess the selection of the BMR to reflect the severity of the chosen endpoint in the Marysville cohort and the precision available in the data. Whether or not the chosen BMR is changed, present this analysis in the document rather than simply asserting that a 'default' value for the BMR was chosen. Similar consideration should be applied to the

Minneapolis cohort to provide a valid comparison. This consideration needs to be linked to discussion of the selection of a value for UF_L as noted below."

EPA Response: Please see response to ***SAB Inhalation Reference Concentration (RfC) #6.*** In brief, EPA clarified the selection of the BMR in Section 5.2.2.5 and selected the BMR of 10% extra risk based on the characterization of LPT as having the lowest severity among available pleural outcomes.

***SAB Inhalation Reference Concentration (RfC) #51*: [3.2.5.6 of the SAB Report, Recommendation, p. 30]** "Review additional sources of uncertainty:

1) Timescale of cohort coverage, normally addressed by UF_S if this is a significant concern rather than including this as a component of UF_D which already has several major issues to account for.

2) Additional uncertainty resulting from target population diversity (including women and children, specific subpopulations of concern not represented in the cohort), and endpoint severity."

EPA Response: Please see response to **Major SAB Recommendation *Letter #4***. With respect to adjustment from subchronic data to chronic data, EPA reconsidered and did increase this uncertainty factor value from 1 to 10. This was despite the fact that the average duration of worker exposure in the key study was more than 7 years, which is often considered to represent a chronic exposure in humans. EPA concluded that an uncertainty factor of 10 is appropriate because the exposure-response modeling demonstrated that the range of time elapsed since first exposure (TSFE) in the Marysville workers may not be sufficiently long to appropriately describe the effects of a lifetime (i.e., 70 years) of exposure to LAA. EPA performed an analysis on the impact of TSFE and found that longer TSFE led to a substantial increase in the risk of LPT (see Section 5.2.2.), with an approximately 10-fold increase in risk when comparing a TSFE of 70 years (i.e., a lifetime of exposure) to a TSFE of 28 years (the median in the primary analytic data set). Based on this analysis, EPA concluded an uncertainty factor of 10 is appropriate to reflect that, with lifetime exposure, TSFE would increase as would its effect on lifetime prevalence or pleural abnormalities.

With respect to human variability, neither the SAB nor EPA concluded there was a basis for changing the uncertainty factor of 10 in EPA's External Review Draft. The Marysville data (and the Libby data) comprise occupational workers (primarily men) sufficiently healthy for full-time employment, and thus are not likely to capture the full range of human responses and potential sensitive subpopulations.

Finally, with respect to database uncertainty, EPA concluded that, while uncertainties remain, there is a basis to reduce the database uncertainty from 10 to 3. Since the release of the External Review Draft, two newly published studies provide further information on the pleural and parenchymal health effects of exposure to Libby amphibole asbestos (Alexander et al., 2012; Larson et al., 2012). Both of these studies support the derivation of the RfC based on pleural effects among Marysville workers. However, some uncertainty remains regarding autoimmune effects, and consequently, the database UF has been reduced to 3.

***SAB Inhalation Reference Concentration (RfC) #52*: [3.2.5.7 of the SAB Report, p. 30]** "In the report there are two sections on uncertainty for the RfC: an application of uncertainty factors following standard EPA practice (see Section 5.2.4), and a discussion of the uncertainties in the overall methodology and approach (see Section 5.3). This response focuses on the latter. Overall the SAB found the discussion to be thorough, detailed, and logical. The document can be improved by harmonizing the full set of uncertainty discussions, including both the discussion of RfC uncertainty and the related discussion of the IUR uncertainty (see the SAB response to question 5 under Section 3.2.6.5 below). In addition, the RfC uncertainty assessment can be strengthened. A key consideration of any assessment is whether the estimated RfC is adequately protective of public health. The SAB recommends that additional work be done to substantiate the RfC estimate through additional sensitivity analyses and discussion of results and insights from other data sets (e.g., cause of death for the deceased nonparticipants in Rohs et al. (2008) and the Minneapolis exfoliation community cohort (Alexander et al., 2012))."

EPA Response: EPA included numerous sensitivity analyses to address issues regarding the exposure metric, assumptions in exposure assignment, model form and assumptions, and the effect of covariates. These are described in the sections on uncertainty in Section 5.3 and in Appendix E.

***SAB Inhalation Reference Concentration (RfC) #53*: [3.2.5.7 of the SAB Report, p. 30]** "In considering other studies, the appropriate assumption is that LAA fibers have the same mechanisms of toxicity and quantitative risk relations as that of other asbestos fibers. In sensitivity analyses, consider alternative exposure metrics (prioritizing residence time-weighted metrics and excluding exposures after 1980), methods to fine-tune the RfC estimate from the subcohort (particularly fixing rather than estimating the plateau, allow the slope parameter to be estimated, use a lifetime of 70 regardless of the exposure metric), and added sensitivity analyses in the full cohort using suggestions from the SAB."

EPA Response: Please see response to ***SAB Inhalation Reference Concentration (RfC) #21***. The primary model for RfC derivation is the Dichotomous Hill model with plateau fixed at 85%, as suggested by the SAB.

***SAB Inhalation Reference Concentration (RfC) #54*: [3.2.5.7 of the SAB Report, Recommendation, p. 31]** "Harmonize the uncertainty discussions across the document."

EPA Response: EPA has made revisions to provide greater harmonization in the discussion of uncertainty for cancer and noncancer effects (see Sections 5.3 and 5.4.6). The uncertainty analyses pertaining to the derivation of the RfC are summarized in Table 5-17 and indicate that the uncertainty in the POD due to the factors examined (uncertainty in the exposure reconstruction, in the radiographic assessment of the critical effect, from potential confounding, in the effect of TSFE, in the endpoint definition, and in the choice of critical effect) is less than an order of magnitude.

***SAB Inhalation Reference Concentration (RfC) #55*: [3.2.5.7 of the SAB Report, Recommendation, p. 31]** "Substantiate the RfC estimate through

1) Additional sensitivity analyses of the subcohort;

2) Discussion of results from other studies;

3) Additional sensitivity analysis of the full cohort; and

4) Summarizing in tabular form the results of the various sensitivity analyses and model alternatives, to show how they affect the POD."

EPA Response: Please see response to ***SAB Inhalation Reference Concentration (RfC) #21.***

A.7. INHALATION UNIT RISK (IUR) – OTHER MAJOR SAB COMMENTS AND RECOMMENDATIONS WITH EPA RESPONSES:

***SAB Inhalation Unit Risk (IUR) #1*: [Overall Clarity, SAB Section 3.1.1, p. 8]** "A table comparing these results with the results from the earlier 1988 EPA analysis (U.S. EPA, 1988) on asbestos would be helpful."

EPA Response: Section 1.1.1 describes the IRIS Assessment for Asbestos (U.S. EPA, 1988) with specific results in Table 1-1, which can be compared with the results of the current assessment.

***SAB Inhalation Unit Risk (IUR) #2*: [Selection of Critical Study and Endpoint, SAB Section 3.2.4.3, p. 20]** "Tables 5-6 and 5-8 are mis-titled, since the tables include the number of deaths from mesothelioma and lung cancer as well as demographic and exposure data. The titles should either be changed and additional causes of death included in the tables or new tables should be created that focus on the causes of death. Provision of data on other major categories of mortality, including numbers of [chronic obstructive pulmonary disease] COPD, cardiovascular, colorectal cancer, and other cancer deaths, could provide useful information on the representativeness of the mortality experience of these cohorts."

EPA Response: The corresponding tables have been amended to include additional information on mortality from other causes and the titles have been changed. The new tables are titled:

Table 5-Cancer-1 (ERD Table 5-6). Demographic, mortality, and exposure characteristics of the Libby worker cohort

Table 5-Cancer-3 (ERD Table 5-8). Demographic, mortality, and exposure characteristics of the subset of the Libby worker subcohort hired after 1959.

***SAB Inhalation Unit Risk (IUR) #3*: [IUR Exposure-response Modeling, SAB Section 3.2.6.1, p. 33]** "Poisson regression analyses: the mathematical form of the regression function should be given, and discussion of whether the potential for over-dispersion was assessed."

EPA Response: The mathematical form has been provided as Equation 5-8. A discussion of the possibility of overdispersion (when the variance exceeds the mean in a Poisson distribution) has been included in Section 5.4.3.1 with results shown in Sections 5.4.3.2 and 5.4.3.5 indicating a lack of evidence for overdispersion in either the full cohort of all workers or the subcohort.

***SAB Inhalation Unit Risk (IUR) #4*: [IUR Exposure-response Modeling, SAB Section 3.2.6.1, p. 33]** "Cox proportional hazards modeling: the reasons should be given for not conducting a Bayesian analysis as was done for the Poisson regression model for mesothelioma."

EPA Response: EPA has clarified the reasoning in Section 5.4.3.3. The revised language is excerpted here: "While the Poisson model is appropriate for modeling very rare events, the standard form does not allow for inclusion of the time-varying nature of exposure. Lung cancer is more common than mesothelioma and does have a known background risk. Thus, modeling of lung cancer mortality is based on the relative risk rather than the absolute risk and was conducted in a frequentist framework, which is the standard methodology for epidemiologic analyses. A frequentist framework is an alternative method of inference drawing conclusions from sample data with the emphasis on the observed frequencies of the data."

***SAB Inhalation Unit Risk (IUR) #5*: [IUR Exposure-response Modeling, SAB Section 3.2.6.1, p. 33]** "Life-table analysis: the method used to estimate the hazard function for the exposed population should be clearly spelled out in the text. Was it based on a nonparametric estimate of the baseline hazard from the subcohort? Given that the SEER data were used to calculate the background incidence of lung cancer, it would seem more appropriate to use those data to estimate the baseline hazard and then to use the regression coefficient obtained from the Cox model applied to the subcohort data to obtain the hazard of the exposed group. Thus, the reasons for not using the SEER data to estimate the baseline hazard should be explained."

EPA Response: EPA has clarified that lung cancer hazard function is based on the nonparametric estimate of the baseline hazard from the subcohort, which was then applied to the background mortality rates for lung cancer from SEER. Given the potential for historical differences in the Libby subcohort compared with the U.S. population (i.e., the potential for cohort effects), EPA prefers to estimate the hazard on internal comparisons. As for projecting the expected disease burden going forward, EPA believes the observed hazard rates are best applied to more recent background rates. EPA has revised the description of the life-table analysis generally in Appendix G and Section 5.4.1 as well as specifically for mesothelioma in Section 5.4.5.1 and for lung cancer in Section 5.4.5.2.

***SAB Inhalation Unit Risk (IUR) #6*: [IUR Exposure-response Modeling, SAB Section 3.2.6.1, p. 33]** "Expand the discussion of model selection to explain the reliance on model fit criteria for model selection. In particular, why should the broader epidemiologic evidence on the time course of disease not argue at least for the presentation of more than one statistical model?"

EPA Response: As described in the previous response to **Major SAB Recommendation *Letter #7***, EPA has strengthened the presentation of the relative merits of alternative models and enhanced its justification of the selected models with revised text on models for mesothelioma in Section 5.4.3.1 and for lung cancer in Section 5.4.3.3.

***SAB Inhalation Unit Risk (IUR) #7*: [IUR Exposure-response Modeling, SAB Section 3.2.6.1, p. 34]** "In a tabular form, summarize the fit results, POD estimates, and IUR estimates from the full range of models considered in order to show the dependence of the IUR estimate on model selection."

EPA Response: Section 5.4.3.5 includes several new tables and figures summarizing the fit results along with the unit risk estimates for mesothelioma, lung cancer, and the combined IUR (see Section 5.4.5.3) to show the dependence of the IUR estimate on model selection.

***SAB Inhalation Unit Risk (IUR) #8*: [IUR Exposure-response Modeling, SAB Section 3.2.6.1, p. 34]** "Present the fit to data graphically for both the main models and for a broader range of models, including the Peto model. This step would provide a more thorough and transparent view of fit, particularly in the region of the BMR, than is allowed by examining summary statistical values alone."

EPA Response: New graphical presentations of model fits for mesothelioma, including the Peto model, are shown in Section 5.4.3.5, and model fits for lung cancer are shown in Section 5.4.3.6.

***SAB Inhalation Unit Risk (IUR) #9*: [IUR Exposure-response Modeling, SAB Section 3.2.6.1, p. 34]** "Provide in an appendix the details of the Nicholson/Peto model fit for which the text currently states 'data not shown'."

EPA Response: Details of the Peto model fit are included in Section 5.4.3.5, which includes additional results and descriptions of model fit, including new tables and figures.

***SAB Inhalation Unit Risk (IUR) #10*: [IUR Exposure-response Modeling, SAB Section 3.2.6.1, p. 34]** "Allow evaluation of the time dependence of disease by providing tabulations of mesothelioma mortality rates and lung cancer SMRs by time since first exposure, duration of exposure, and period of first exposure (for both the full and subcohorts of Libby workers)."

EPA Response: As noted in a previous response, EPA has added the recommended analyses of Libby worker full- and subcohorts for lung cancer, using both Montana and U.S. data for comparison, as well as parallel analyses of mesothelioma rates in the Libby worker full- and subcohorts. New tables on the rates of mesothelioma are shown in Sections 5.4.3.2 and 5.4.3.5. New tables on the rates of lung cancer and SMRs are shown in Sections 5.4.3.3 and 5.4.3.6.

***SAB Inhalation Unit Risk (IUR) #11*: [IUR Exposure-response Modeling, SAB Section 3.2.6.1, p. 34]** "Evaluate the feasibility of conducting an ancillary analysis of the full Libby data set, including hires before 1959, using interval statistics or other traditional censoring methods (not simple midpoint substitution). At a minimum, discuss the possible quantitative uncertainties associated with using the smaller subcohort."

EPA Response: New tables on the rates of mesothelioma and the rates and SMRs for lung cancer included all workers regardless of hire data as well as for those workers hired after 1959. The statistical tradeoff and possible quantitative uncertainties associated with using the smaller subcohort were discussed in Sections 5.4.3.4 and 5.4.6. These quantitative uncertainties included the lower number of cases of both cancers than in the whole cohort, the shorter follow-up time period for the subcohort, and the overall lower mortality rate due to the subcohort being younger. EPA carefully considered the SAB recommendation to use interval statistics or other traditional censoring methods and reviewed the references provided by SAB. EPA concluded that the use of the subcohort was most appropriate for quantitative analyses, particularly due to the availability of specific work histories and the higher percentage of exposure assignments based on actual measurements as opposed to missed values.

***SAB Inhalation Unit Risk (IUR) #12*: [IUR Exposure-response Modeling, SAB Section 3.2.6.2, p. 34]** "The numbers of COPD deaths (*n*) in the subcohort that were the basis for the analysis should be presented in the text."

EPA Response: The number of COPD deaths used in the analysis is shown in Section 5.4.2.4.

***SAB Inhalation Unit Risk (IUR) #13*: [IUR Exposure-response Modeling, SAB Section 3.2.6.2, p. 35]** "The statements about the evidence against confounding by smoking given by restriction of the cohort should be qualified by the assumptions required to justify them, or deleted."

EPA Response: The statements have been further qualified. The following text is shown in Section 5.4.3.4. "Thus, this restriction in the time period of hiring may make the cohort members more similar to each other, thereby possibly reducing the potential impact of any smoking-related confounding."

***SAB Inhalation Unit Risk (IUR) #14*: [IUR Exposure-response Modeling: p. 35]** "The SAB had no recommendations for further analyses" [with respect to the potential for lung cancer to confound risks of smoking in this cohort].

EPA Response: EPA accepts the SAB recommendations for no further analyses relevant to the potential for confounding of lung cancer risks by smoking.

***SAB Inhalation Unit Risk (IUR) #15*: [IUR Exposure-response Modeling, SAB Section 3.2.6.2, p. 35]** "The reference to three methods is confusing. There are actually only two, the restricted cohort and the Richardson analysis for which two exposure metrics are explored."

EPA Response: The discussion in Section 5.4.3.8 now refers to two methods, as noted in the recommendation.

***SAB Inhalation Unit Risk (IUR) #16*: [IUR Exposure-response Modeling, SAB Section 3.2.6.3, p. 35]** "The EPA should acknowledge that the assumption of independence is a theoretical limitation of the analysis, and should provide a fuller justification for this assumption. EPA has cited the NRC (1994) analysis as suggesting the impact of this issue is likely to be relatively small. This view is also echoed in U.S. EPA (2005a) *Guidelines for Carcinogen Risk Assessment*. These provide the basis for a default assumption. However, it would be preferable if this assessment discussed the evidence base and rationale for lung cancer and mesothelioma specifically."

EPA Response: EPA has acknowledged the assumption of independence in Section 5.4.5.3, and the revised text follows:

"It is important to mention here that the assumption of independence above is a theoretical assumption, as there is no data on independence of mesothelioma and cancer risks for LAA. However, in a somewhat similar context of different tumors in animals, NRC (1994) stated: '…a general assumption of statistical independence of tumor-type occurrences within animals is not likely to introduce substantial error in assessing carcinogenic potency.' To provide numerical bounding analysis of impact of this

assumption, EPA used results of Chiu and Crump (2012) on upper and lower limits on the ratio of the true probability of a tumor of any type and the corresponding probability assuming independence of tumors. The lower limit is $(1 - \min[p1,p2]) \div (1 - p1 \times p2)$ and upper limit is $\min(1,2 - p1 - p2) \div (1 - p1 \times p2)$. Substituting $p1$ = risk of lung cancer = 0.040 and $p2$ = risk of mesothelioma = 0.075, the lower limit is 0.963 and the upper limit is 1.003 (a value of 1.0 indicates independence). Because lower and upper values are both very close to the value of 1.0, this demonstrates that the assumption of independence in this case does not introduce substantial error consistent with what NRC (1994) has stated."

***SAB Inhalation Unit Risk (IUR) #17*: [IUR Exposure-response Modeling, SAB Section 3.2.6.3, p. 35]** "As a sensitivity analysis, the EPA should consider quantitatively accounting for dependence in the risks of mesothelioma and lung cancer mortality either using a method that models the dependence explicitly, or a bounding study that evaluates the numerical consequences of the assumption of independence."

EPA Response: As noted in the response above, EPA has provided a numerical bounding analysis to estimate the consequences of the assumption of independence. As explained in response to the preceding comment, in this analysis the assumption of independence does not introduce substantial error.

***SAB Inhalation Unit Risk (IUR) #18*: [IUR Exposure-response Modeling, SAB Section 3.2.6.5, p. 37]** "The SAB recommends that a more straightforward and transparent treatment of model uncertainty would be to estimate risks using a more complete set of plausible models for the exposure-response relationship (discussed in response to question 1 in Section 3.2.6.1), including the Poisson models. This sensitivity analysis would make the implications of these key model choices explicit."

EPA Response: EPA's standard practice is to investigate several modeling options to determine how to best empirically model the exposure-response relationship in the range of the observed data as well as to consider exposure-response models suggested in the epidemiologic literature. For lung cancer, a new discussion of potential alternative models has been included in Section 5.4.3.3, including Poisson, logistic, Cox, and multistage clonal expansion models. EPA selected the Cox model as the most appropriate model for exposure-response modeling based on the suitability of this model to the nature of the data set (e.g., time-dependent exposure information), the long history of this model usage in analyses of occupational cohorts, and the commonality of usage in other epidemiologic analyses of the Libby workers cohort. EPA's evaluation of alternative approaches found no other standard epidemiological model formulations that allow for the analysis of time-varying exposures in the manner achieved by the Cox proportional hazards model.

For mesothelioma, a new discussion of alternative models has been included in Section 5.4.3.1, including consideration of approaches such as parametric survival models. EPA concluded that the Peto model and variations of the Peto allowing for potential clearance are well supported in the epidemiologic literature. The Poisson model is an appropriate model for rare data. There are no examples of using other models for modeling mesothelioma in similar situations.

EPA presents results for sensitivity analyses that were conducted for both mesothelioma and lung cancer mortality in deriving combined inhalation unit risk in Section 5.4.5.3.

***SAB Inhalation Unit Risk (IUR) #19*: [IUR Exposure-response Modeling, SAB Section 3.2.6.5, p. 37]** "The SAB recommends that, as an initial step in conducting an integrated and comprehensive uncertainty analysis, the agency provide a tabular presentation and narrative evaluation of the IUR estimates based on a reasonable range of data selections (e.g., all or part of the earlier hires as well as the 'preferred' subcohort), model forms, and input assumptions (as discussed, in the response to question 1 in Section 3.2.5). These input assumptions should include *inter alia* exposure metrics and externally defined parameters, as discussed in the response to question 1 in Section 3.2.5. As noted in the current cancer risk assessment guidelines (U.S. EPA, 2005a page 3−29):

> The full extent of model uncertainty usually cannot be quantified; a partial characterization can be obtained by comparing the results of alternative models. Model uncertainty is expressed through comparison of separate analyses from each model, coupled with a subjective probability statement, where feasible and appropriate, of the likelihood that each model might be correct (NRC, 1994).

The SAB notes that ideally, the agency would develop a quantitative characterization of the overall uncertainty in its IUR estimates by incorporating the major sources of uncertainty the agency has identified in its evaluation. However, the SAB recognizes the challenge of conducting such an analysis, and is not recommending that it be undertaken at this time."

> **EPA Response:** Section 5.4.3.4 describes the challenges EPA faced in analyses of the full cohort, attributing the difficulties to the lack of accurate information on job code and job department among 71% of workers hired prior to 1960. In contrast, among those workers hired after 1959, only 1% of workers lacked specific work histories. EPA evaluated the feasibility of conducting an ancillary analysis of the full Libby data set to include hires before 1959. As described previously, EPA added a discussion of the quantitative uncertainties connected to the use of a smaller subcohort in Sections 5.4.3.4 and 5.4.6, as recommended by SAB. EPA determined that the use of higher quality personal exposure information outweighs the limitations caused by a smaller size of the subcohort because the use of poor exposure data leads to large measurement error and results in the underestimation of the regression coefficient of the dose response (cf. Bateson and Kopylev, 2014; Lenters et al., 2012; Lenters et al., 2011).

SECTION A.8 RESPONDS TO PUBLIC COMMENTS WITH EACH SUBSECTION ADDRESSING A DIFFERENT GENERAL TOPIC.

A.8. PUBLIC COMMENTS

A.8.1. Mineralogy - Summary of Major Public Comments with EPA Responses:

None.

A.8.2. Fiber Toxicokinetics – Summary of Major Public Comments and EPA Response:

Toxicokinetics Public Comment #1 **(Paraphrased):** Commenter requested inclusion of specific peer-reviewed, published literature on LAA and further discussion of the comparative toxicity of LAA and other amphiboles.

> **EPA Response:** EPA has included summaries of the peer-reviewed published literature on LAA through March 2014 in the appropriate section of the Toxicological Review (see Section 4.2 for in vivo, see Section 4.3 for in vitro) and full study descriptions in Appendix D. As this Toxicological Review is specific to LAA, studies on other amphiboles that do not make up the LAA mixture are not included in these summaries or in Appendix D. However, a discussion of the determinants of fiber toxicity has been included in Section 3 to discuss what is known about the comparative toxicity of various fiber characteristics for all amphiboles. Further, the revised section on MOA includes discussion of hypothesized MOA for other amphiboles in comparison to LAA.

A.8.3. Noncancer Health Effects – Summary of Major Public Comments with EPA Responses:

Noncancer Health Effects Public Comment #1 **(Paraphrased):** Several commenters stated that EPA failed to demonstrate an association between LPT and decreased lung function, so that any lung function decrease that might be associated is "insignificant" and thus LPT is not adverse by EPA's own definition of "adverse."

> **EPA response:** EPA has provided an expanded description of the selection of the critical effect for the derivation of the RfC in Section 5.2.2.3. EPA also conducted a systematic review and meta-analysis of studies examining the relation between LPT and pulmonary function measures. This work is presented in Appendix I.
>
> This additional literature review and analysis demonstrates that pleural plaques (a subset of LPT) are associated with a decrease in two key measures of lung function, and that these decreases are unlikely to be due to other factors such as excess body fat or undetected changes in lung tissue (other than the pleural plaques) that might have also been caused by exposure to asbestos. Thus, these additional references and analysis support the EPA's conclusions in its External Review Draft, and the SAB advice to EPA, that LPT is an appropriate health endpoint for the derivation of the inhalation reference concentration.
>
> EPA's literature search identified epidemiology studies examining lung function in asbestos-exposed populations with and without pleural plaques; 20 studies relating changes in forced vital capacity (FVC) to presence of pleural plaques and 15 studies relating changes in forced expiratory volume in 1 second (FEV_1) to presence of pleural plaques were included in a meta-analysis.
>
> A meta-analysis of the identified studies conducted by EPA estimated a statistically significant decrement of 4.09 (95% CI: −5.86, −2.31) and 1.99 (95% CI: −3.77, −0.22)

percentage points respectively in predicted FVC and FEV_1 attributable to the presence of pleural plaques.

The definition of "adverse" in EPA's IRIS Glossary states that an adverse effect "…affects the performance of the whole organism or reduces an organism's ability to respond to an additional environmental challenge." EPA analysis shows that the LPT causes a statistically significant lung function decrease; such lung function decreases reduce an organism's ability to withstand those additional environmental challenges that further reduce lung function.

Another EPA definition of adversity for epidemiologic data states that reductions in lung function such as FEV_1 are considered adverse respiratory health effects (U.S. EPA, 1994).

Additional analyses indicated that the decrements associated with the presence of LPT are not likely to be due to limitations in the study designs or conduct, undetected subclinical fibrosis or misidentification of pleural plaques due to subpleural fat pads. Only several studies controlled for exposure, but the largest best controlled HRCT study that also controlled for exposure found decrease in lung function similar to the decreases above.

Further, the extent of plaques was found to correlate with the degree of lung function decrement, and longitudinal studies indicate that decrements increase with longer follow-up.

These findings support the conclusion that pleural plaques, and thus LPT, is an appropriate health endpoint for the derivation of the RfC.

Noncancer Health Effects Public Comment #2 **(Paraphrased):** Several commenters stated that EPA did not consider all of the scientific literature on LPT and that it confuses LPT with DPT.

EPA response: In response to the SAB's identification of additional references and recommendation that the Agency include a more detailed review of the literature, EPA conducted a more detailed review of the literature examining the relationship between lung function measures and localized pleural thickening (LPT) or pleural plaques ("pleural plaques" as defined in some, particularly older, studies is a subset of LPT). That systematic review not only included the additional references noted by the Science Advisory Board, but comprises a systematic and well-documented literature search and review of the published literature through the date of December 2013. This work is presented in Appendix I and discussed in Section 5.2.2.3.

In a meta-analysis presented in Appendix I, EPA considered only studies that considered pleural plaques (a subset of LPT) in groups that did not contain any DPT or parenchymal abnormalities, so that there would not be confusion of LPT with DPT.

Noncancer Health Effects Public Comment #3: "A new peer reviewed study published in Chest (Clark et al., In Press) (Clark, KA; Flynn, JJ III; Goodman, JE; Zu, K; Karmaus, WJ; Mohr, LC. 2014. "Pleural plaques and their effect on lung function in Libby vermiculite miners." Chest doi: 10.1378/chest.l4-0043, http://journal.publications.chestnet.org/article.aspx?articleid=1868832.) analyzes historic health data from the Libby, Montana vermiculite miners and finds that plaques alone did not cause lung

function deficits among miners exposed to LAA. No statistically significant difference in lung function was found between miners with pleural plaques alone and those with no radiography findings (using High Resolution Computed Tomography ("HRCT")). EPA should evaluate and account for this study because it analyzes Libby-specific data, making it one of the most relevant studies for this LAA assessment to consider. Moreover, this study thoughtfully addresses bias and seeks to eliminate confounders present in many other studies. This study uses the most reliable diagnostic methods: HRCT and multiple pulmonary function test parameters. It is well accepted in the medical community that x-ray radiography is prone to misdiagnosis of pleural plaques (e.g., extrapleural fat can be mistakenly identified as plaques) and underdiagnosis of other lung abnormalities (e.g., fibrosis) that affect lung function. The HRCT data used in this study provide superior contrast sensitivity and cross-sectional imaging format, and thus minimize the potential for bias from relying upon x-rays. The study quality also is enhanced because it evaluates multiple pulmonary function test parameters to distinguish among different types of lung decrements (such as obstructive lung disease that is unlikely to be related to asbestos). In contrast to this new study, many other studies that EPA has relied on reflect bias from reliance upon less accurate x-rays and limited lung function testing.)" [Comment received by EPA on June 25, 2014.]

EPA response: In response to **Major SAB Recommendation *Letter #1***, EPA conducted a systematic review and meta-analysis of the influence of localized pleural thickening on lung function, including a separate meta-analysis of HRCT studies. Although the Clark et al. (In Press) was published after the cut-off date of December 31, 2013 for the systematic review and meta-analysis, EPA evaluated the Clark et al. (In Press) study as it relates to the meta-analysis. EPA found that inclusion of Clark et al. (In Press) would not materially change EPA's conclusions and in fact, the new paper is supportive of EPA's conclusion (i.e., the summary estimate in the meta-analysis of HRCT studies shows even greater decreases in lung function associated with LPT and the uncertainty associated with the decrease is diminished with the inclusion of additional data from Clark et al. (In Press) as noted by the decrease in the width of the confidence interval).

	Appendix I Meta-Analysis	Meta-Analysis *if* Including Clark paper
FVC	-3.30% (-5.25; -1.34)	-3.59% (-5.08, -2.10)
FEV_1	-1.96% (-6.01; 2.09)	-2.60% (-5.94; 0.74)

Noncancer Health Effects Public Comment #4: "A second peer reviewed study (Moolgavkar et al., 2014) (Moolgavkar, SH; Anderson, EL; Chang, ET; Lau, EC; Turnham, P; Hoel, DG. 2014. "A review and critique of U.S. EPA's risk assessments for asbestos." Crit. Rev Toxicol. doi: 10.31109/10408444.2014.902423. http://informahealthcare.com/doi/abs/ 10.3 1 09/1 0408444.2014.902423) rigorously assesses the body of literature that the Draft Assessment relies upon, and concludes that: ... in light of the serious methodological limitations and inconsistent findings of these collective studies, the overall weight of evidence does not establish an independent adverse effect of pleural plaques on pulmonary function. This study quotes and then applies EPA-established criteria as follows: "by the Agency's own definitions, for an effect to be considered adverse, the presence of biological or pathologic changes is not sufficient.

Rather, these changes must additionally affect the performance of the whole organism or compromise the organism's ability to respond to environmental changes."

"EPA should evaluate and account for this study because it assesses sources of bias and confounders present in the body of literature that the LAA Draft Assessment relies upon." [Comment received by EPA on June 25, 2014.]

EPA response: The publication by Moolgavkar et al. (2014) reviews the literature quoted in the 2011 External Review Draft. Their review is nonquantitative in nature and only evaluates a small part of the overall literature. In response to **Major SAB Recommendation *Letter #1***, EPA conducted a systematic review and meta-analysis of the influence of localized pleural thickening on lung function and concluded that localized pleural thickening is associated with statistically significant decrease in lung function measures (see Appendix I). In Appendix I, EPA formally evaluated the limitations of each study and conducted sensitivity analyses that confirmed the overall conclusions.

The remainder of the article repeats a number of public comments submitted to the SAB and to EPA by the authors of Moolgavkar et al. (2014). EPA has responded to these public comments in revisions of the assessment and/or elsewhere in Appendix A.

A.8.4. Carcinogenicity – Summary of Major Public Comments and EPA Response

***Carcinogenicity Public Comment #1* (Paraphrased):** Commenters raised an issue with the consideration of the cancer mode of action (MOA) and the possibility of nonlinearity in exposure-response.

EPA Response: The MOA section of the Toxicological Review (see Section 4.6) has been revised to include a formal carcinogenic MOA analysis. Further discussion of the mechanistic data in support of the MOA for amphibole asbestos in general has been included in Section 4.4. Data gaps still remain to satisfactorily characterize specific mechanisms involved in LAA-induced disease. The formal mode-of-carcinogenic-action analysis demonstrated that there are insufficient data to determine an MOA for LAA given available data. Therefore, EPA determined that a linear low-dose extrapolation was appropriate. In the absence of a well-defined MOA, linearity of exposure-response below the POD is assumed in the derivation of the IUR (EPA's *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a)).

A.8.5. Inhalation Reference Concentration (RfC) – Summary of Major Public Comments and EPA Response

***Inhalation Reference Concentration (RfC) Public Comment #1*:** Suresh Moolgavkar stated "The noncancer risk assessment is based on a cohort of workers at a Marysville, Ohio plant in which Libby vermiculite was processed. The endpoint of interest was pleural abnormalities (pleural thickening) on chest radiographs. The original data set considered by Rohs et al. (2008)

consisted of 280 workers with 80 cases of abnormalities on chest radiography. The Agency assessment was based on 119 workers with 12 cases of abnormalities. Thus, the Agency discards 85% of cases for this assessment. The reasons given for this drastic reduction in the cohort size are not tenable."

There were several related comments on the selection of the critical study for the derivation of the RfC. Several commenters thought that the critical study population was too small and that the full Marysville, OH cohort should be used.

EPA Response: EPA focused on the subset of workers who had the highest quality exposure data and more recent health evaluations for the derivation of the RfC.

EPA has used the modeling approach recommended by the SAB, which relies on the larger subset of workers with more recent health evaluations (regardless of hire date), to estimate the effect of TSFE on the risk of LPT and has combined this information with the highest quality exposure data in the primary modeling performed in the subcohort to derive the RfC.

EPA has also performed modeling based on the fuller data set of all health evaluations performed in 1980 and 2002−2005. That analysis is presented in Appendix E. The primary and this complementary modeling of the full cohort yield a comparable RfC.

Inhalation Reference Concentration (RfC) Public Comment #2: Suresh Moolgavkar stated "There is no evidence of a monotonic increasing exposure-response relationship for pleural thickening in either the full cohort or the subcohort chosen for analysis by the Agency."

EPA Response: Monotonicity in the observed exposure-response data is not a requirement for RfC derivation and may be sensitive to the number of strata into which the data are divided.

In the analysis of the primary subcohort of workers from Marysville, OH, hired in 1972 or afterwards, the exposure-response relationship between mean intensity of exposure and the risk of LPT is plotted in two different ways (see Figure 5-3). The two ways divide the data into quartiles and quintiles and plot the exposure-response relationship. These show increasing risk with increasing exposure. Plots of the exposure-response relationship for the full cohort are shown in Appendix E and also show increasing risk with increasing exposure. Figure 5-3 shows that the prevalence of LPT increases with increasing exposure.

The monotonic models used to derive the exposure-response relationship adequately fit the data (see Tables 5-4 and 5-9).

***Inhalation Reference Concentration (RfC) Public Comment #3*:** Public comments were raised regarding the source of data on Marysville workers exposed between 1971 and 1973. For example, Suresh Moolgavkar stated: "The Agency says, '…more accurate exposure data are considered to be those from 1972 and later, as these data were based on analytical measurements.' Based on these considerations, the Agency chose from the Rohs cohort the subcohort consisting of workers who began work in 1972 or later. The radiographic examination of these workers was conducted over the period 2002−2005. However, in their paper, Rohs et al. (2008) identified 1973, not 1971, as the year after which '…more comprehensive environmental

exposures were available…' The subcohort of workers hired after 1973 consists of 94 individuals with 10 cases of pleural abnormalities. I have the Rohs database and it includes an identifier for workers hired after 1973 but not for those hired after 1971. The report does not explain this discrepancy."

EPA Response: Additional work (i.e., after publication of the Rohs et al. (2008) paper) was done by the University of Cincinnati to refine and update the exposure estimates. Please see Appendix F for details.

***Inhalation Reference Concentration (RfC) Public Comment #4*:** Public commenters raised the issue of potential confounders in the epidemiologic analyses. For example, Suresh Moolgavkar stated: "I analyzed the data in the subcohort of individuals in the Rohs cohort who were first employed after 1973.… With the usual assumption of a logit-linear relationship between exposure and response in the logistic model, the coefficient for cumulative exposure is statistically significant at the 0.05 level of significance. If, however, either age or body mass index (BMI) are considered as confounders in a joint analysis, the coefficient for cumulative exposure becomes insignificant. One of the important criteria enunciated by the Agency for study selection for noncancer risk assessment is that the exposure-response relationship be robust to adjustment for potential confounders. Thus, on page 5-11, the report states 'Amandus et al. (1987) report that although cumulative exposure and age are both significant predictors of small opacities, cumulative exposure was not significantly related to pleural abnormalities when age is included in the model, thus limiting the usefulness of these data for RfC derivation based on pleural abnormalities.' In listing the advantages of the Rohs subcohort the Agency used, the report on page 5-14 (number 6) clearly states that it considers the absence of any evidence of confounding in this data set a distinct advantage. I do not have access to the exact data used by the Agency, but I have analyzed a closely related data set as described above and there is strong evidence of confounding by both age and BMI. By its own criteria, the Agency should not be using this data set for derivation of an RfC."

EPA Response: The commenter's concern is related to the potential for confounding of the relationship between exposure to LAA and the risk of LPT. EPA evaluated confounding using both a theory-based method (to ascertain whether the potential confounder is associated with both the exposure and with the outcome; see Section 5.2.2.6.1) as well as a data-based method (by including each potential confounder in the final model to assess its statistical significance; see Section 5.3.3). No evidence of confounding was found in either case. Comparable modeling of the full cohort is described in Appendix E.

It is possible that the differences in interpretations of potential confounding are related to difference in the exact data used by EPA and by the commenter.

EPA did assess the potential for confounding by age and by BMI using two different approaches and did not identify such confounding of the exposure-response relationship used to derive the RfC.

***Inhalation Reference Concentration (RfC) Public Comment #5*:** Suresh Moolgavkar commented "…the Agency uses various lags in the analyses of the subcohort. The use of lags for the analyses of pleural abnormalities makes no sense. Lags, although I do not generally favor them, can be used in analyses of hazard or incidence functions when the diagnosis of an end-point, such as cancer, is made at a well-defined point in time. It makes absolutely no sense

to use lags in the analyses of prevalent conditions, which could have occurred many years before the condition was noted. In the Rohs database all radiography was performed between 2002 and 2005 when pleural abnormalities were noted. These could have occurred many years before the radiography was done. What is the interpretation of a lag in this situation?"

> **EPA Response:** EPA agrees with the commenter that lack of information on the timing of the initial occurrence of the pleural changes makes it difficult to interpret lagged exposures given the cross-sectional nature of the x-ray data. In the revised IRIS draft assessment, EPA did not include lagged exposure metrics for this reason when modeling the noncancer outcomes. Please also see response to ***SAB Inhalation Reference Concentration (RfC) #8***. Lags were evaluated for the lung cancer and mesothelioma risk modeling because for these cancers there is data available on the date of death which is expected to be closely related to the date of cancer incidence due to the short survival time for these cancers (see Section 5.4.2.2 for more details).

Inhalation Reference Concentration (RfC) Public Comment #6 **(Paraphrased):** One commenter noted that the exposure metric for the derivation of the RfC should be mean concentration rather than cumulative exposure.

> **EPA Response:** EPA reconsidered the justification for model selection and the selected exposure metric. EPA evaluated different exposure metrics, including mean and RTW (see Section 5.2.2.6 and Appendix E) in addition to the CE metric included in the ERD analyses. The recommended examination of alternative metrics of exposure has resulted in a change from the use of CE in the draft to the use of C in the revision. Please also see the response to **Major SAB Recommendation** ***Letter #3*** comment.

Inhalation Reference Concentration (RfC) Public Comment #7 **(Paraphrased):** There were several comments on the selection of the model for the derivation of the RfC. Comments stated that the model selection criteria were unclear, that the Michaelis-Menten model should not be used to derive the RfC, and that the merits of some models could not be appropriately distinguished based on model fit. Other specific comments regarding the modeling included mention of background prevalence of localized pleural thickening and the plateau parameters.

> **EPA Response:** The SAB also commented that EPA should include biological and epidemiological characteristics of the different models in the model selection. As noted in the EPA Response to **Major SAB Recommendation** ***Letter #3***, EPA provides a more thorough explanation of its selection of the best model for noncancer exposure-response analysis in Section 5.2.2.6 and in Appendix E.
>
> Following the guidance in the updated *Benchmark Dose Technical Guidance* (U.S. EPA, 2012), EPA explained that there are several stages of exposure-response modeling. Once the appropriate data set(s), endpoint(s) and BMR are determined, an appropriate set of statistical model forms is selected and evaluated for model fit to determine which models adequately represent the data. Among those models with adequate fit, one or more models are selected to derive a point of departure for the RfC. Regarding the selection of models to evaluate, the *Benchmark Dose Technical Guidance* notes that additional criteria may be used, "governed by the nature of the measurement that represents the endpoint of interest and the experimental design used to generate the data" (page 26). When modeling the Marysville data, certain biological and epidemiological features must be considered, including the nature of the data set, ability to estimate the effects of

exposure and of important covariate(s), the existence of a plateau or theoretical maximum response rate in a population, and the ability to estimate a background rate of the outcome in a population.

For the primary modeling in Section 5.2.2.6., EPA selected the Dichotomous Hill model, (a minor variation on the Michaelis-Menten model proposed in its External Review Draft) because it allowed fuller consideration of the biological and epidemiological features described above.

While EPA presents the results from the Michaelis-Menten model for purposes of comparison, the final assessment does not rely upon the Michaelis-Menten model. EPA explains in the final assessment how, based on advice from the SAB, it selected preferred model forms and evaluated those forms, with evaluations of different exposure metrics, with statistical comparisons, goodness-of-fit criteria, and graphical comparisons with aggregated data. This is described in a revised Section 5.2.2.6 concerning model considerations (including background prevalence, plateau, and ability to control for potential confounders), model selection, and selection of the BMR, taking into account EPA's newly available updated *Benchmark Dose Technical Guidance* (U.S. EPA, 2012). Please also see response to **Major SAB Recommendation *Letter #3*** comment.

***Inhalation Reference Concentration (RfC) Public Comment #8* (Paraphrased):** One commenter noted that the justification of the uncertainty factors was inadequate.

EPA Response: EPA has reconsidered the choice of UFs in light of the revised analyses and newly available published studies. Consequently, the database UF has been reduced to 3, while the subchronic-to-chronic UF has been increased to 10 based on the evaluation of the role TSFE on LPT risk in the Marysville data. Increasing the LOAEL-to-NOAEL UF is unnecessary because the POD is based on BMD modeling. The basis for those decisions is explained in a revised Section 5.2.3. Please also see response to the **Major SAB Recommendation *Letter #4*** comment.

***Inhalation Reference Concentration (RfC) Public Comment #9* (Paraphrased):** There were several comments that the RfC would be below background concentrations, that the RfC would be used for other amphiboles, and that it would be unfeasible to measure fiber concentration at the RfC level.

EPA Response: This assessment is quantifying the toxicity of LAA. Background or naturally-occurring levels of many material vary considerably across the US (reference current USGS report). A discussion of varying geogenic levels of materials such as asbestos has little relevance in a summary of toxicological data.

There are instances in which exposure to a substance either poses health risks, or at least cannot be determined to be unlikely to pose health risks, at commonly found "background" levels. Thus, there is nothing inherently contradictory if an RfC is below common environmental or other "background" exposures. EPA is unaware of a basis for bounding this assessment based on background exposures at any Superfund site. In addition, the RfC of 9x10-5 f/cc is above average ambient air concentrations currently measured in Libby, MT.

When there are practical implementation concerns about reference values below detection limits or below background, those concerns are best addressed in the context of risk management decisions. Many EPA programs have policies as to how they make risk management decisions in such contexts; thus, those concerns are best addressed in the risk management decision-making context.

A.8.6. Inhalation Unit Risk (IUR)—Major Public Comments with EPA Responses:

***Inhalation Unit Risk (IUR) Public Comment #1*:** Public comments were received on the importance of evaluating the quality of exposure assessments made in epidemiology studies and as a consideration in selected studies to use for asbestos toxicity assessment. For example, Terry Spear stated: "Asbestos risk assessments are sensitive to small changes in decisions about which data to include or exclude. The following abstract from Burdorf and Heederik (2011) illustrates this point: 'Mesothelioma deaths due to environmental exposure to asbestos in The Netherlands led to parliamentary concern that exposure guidelines were not strict enough. The Health Council of the Netherlands was asked for advice. Its report has recently been published. The question of quality of the exposure estimates was studied more systematically than in previous asbestos meta-analyses. Five criteria of quality of exposure information were applied, and cohort studies that failed to meet these were excluded. For lung cancer, this decreased the number of cohorts included from 19 to 3 and increased the risk estimate three- to six fold, with the requirements for good historical data on exposure and job history having the largest effects. It also suggested that the apparent differences in lung cancer potency between amphiboles and chrysotile may be produced by lower quality studies. A similar pattern was seen for mesothelioma. As a result, the Health Council has proposed that the occupational exposure limit be reduced from 10,000 fibers m^{-3} (all types) to 250 fibers m^{-3} (amphiboles), 1,300 fibers m^{-3} (mixed fibres), and 2,000 fibers m^{-3} (chrysotile). The process illustrates the importance of evaluating quality of exposure in epidemiology, since poor quality of exposure data will lead to underestimated risk.' "

> **EPA Response:** EPA agrees on the importance of evaluating the quality of exposure data as part of evaluating epidemiology studies. EPA cites the work cited by the commenter by Burdorf and Heederik (2011) and follow-up work by Lenters et al. (2011) and Lenters et al. (2012) when EPA discusses the importance of evaluating the quality of the exposure data. EPA has cited these works as part of the justification for EPA's decision to base its cancer risk estimates on the selected subcohort for which there is the best exposure information (see Section 5.4.3.4).

***Inhalation Unit Risk (IUR) Public Comment #2*:** Public comments were received on the use of the smaller subcohort from the Libby worker study for quantitative risk assessment. For example, Suresh Moolgavkar stated "The data set chosen for the cancer risk assessment is a small subcohort of the full cohort of Libby miners. This subcohort discards the vast majority of lung cancers and mesotheliomas in the Libby cohort, particularly in individuals over the age of 65. Thus, Agency risk assessments are based largely on younger individuals in the cohort and ignore the ages at which cancer is most common."

> **EPA Response:** EPA evaluated the potential uncertainties in basing the quantitative analyses on a subcohort, and concluded that the availability of higher quality exposure information outweighed the limitations caused by the smaller size of the cohort (see also the response to ***SAB Inhalation Unit Risk (IUR) #19***.

The concern of the commenter that the subcohort analysis does not include individuals of all ages can be evaluated by reviewing EPA's presentation of the primary results in comparison to those in the published literature of the full Libby worker cohort, which includes individuals of all ages. These analyses are presented in Tables 5-52 and 5-53 in Section 5.4.5.3.1. EPA believes that the estimates of cancer exposure-response based on the subcohort provide better estimates due to the higher quality of exposure data.

In addition, the SAB stated that the "…use of the subcohort post-1959 for quantification may be reasonable due to the lack of exposure information for many of the workers in earlier years; out of 991 workers hired before 1960, 706 had all department and job assignments listed as unknown."

***Inhalation Unit Risk (IUR) Public Comment #3*:** Public comments were received regarding the statistical methods used for inhalation unit risk derivation. For example, Suresh Moolgavkar stated: "The Agency uses inappropriate statistical methods for analyses of the data on lung cancer and mesothelioma. In particular the importance of duration of exposure in determining risk is ignored. In the lung cancer analysis effect modification by age, which is strongly evident in the Libby cohort, is not addressed."

EPA Response: The commenter states that the EPA used inappropriate statistical methods for the analysis of lung cancer and mesothelioma; however, in later comments, the same commenter states that "the proportional hazards model used by the Agency for analysis of lung cancer in the Libby miners' cohort is standard."

The commenter states that the importance of duration is ignored; however, for lung cancer, the time-varying proportional hazards model does account for duration of exposure and is the same model form used by the commenter in other asbestos analyses of lung cancer risk (Moolgavkar et al., 2010).

The commenter makes the point that the observed lack of proportionality in the full cohort analysis of lung cancer may be due to effect modification by age and cites an analysis by Richardson (2009). Effect modification by age is a possible explanation of the lack of proportionality in the modeling of lung cancer mortality as has been noted by Richardson (2009) in a two-stage clonal expansion model of a cohort of asbestos-exposed workers. However, similar modeling of lung cancer risk in the same cohort of workers by other investigators (Zeka et al., 2011) was unable to replicate that finding. EPA did evaluate the possibility of effect modification of the lung cancer mortality risk by age in the Libby workers subcohort and did not identify such a phenomenon as summarized in Section 5.4.3.5.

***Inhalation unit risk (IUR) Public Comment #4*:** Public comments were made regarding the potential impact of exposure error on risk estimates. For example, Suresh Moolgavkar stated: "The Agency repeats the old canard (page 5-78 of the report) about nondifferential covariate measurement errors leading to risk estimates biased towards the null. This statement, although widely repeated by epidemiologists, is incorrect. First, not only must the misclassification be nondifferential, it must satisfy other conditions (e.g., Jurek et al., 2005) for the result to hold. Second, the statement applies to the expectation of the risk estimate, not to the value of the estimate from any single study. Thus, it is possible to have nondifferential misclassification that satisfies all the required conditions but the result of a single study may actually overestimate the risk. As Jurek et al. (2005) state, '…exposure misclassification can spuriously increase the

observed strength of an association even when the misclassification process is nondifferential and the bias it produced is towards the null.' Similar discussion is provided by Thomas (1995) and Weinberg et al. (1995)."

A related comment by Terry Spear stated that it is difficult or impossible to find true associations between exposure and effect when exposure misclassification exists in epidemiological studies. Systematic misclassifications will create falsely high- or low-risk estimates while random misclassification may mask true associations altogether.

> **EPA Response:** The commenter (Moolgavkar) is correct that, under certain conditions, nondifferential measurement error can yield results away from the null in a single study. However, under general conditions of nondifferential exposure measurement error, the expectation of the risk estimate is biased towards the null. According to a highly regarded textbook, nondifferential exposure error typically results in bias towards the null (Rothman and Greenland, 1998).
>
> The commenter has not provided any information to suggest that, in this case, one would expect no bias or a bias in the other direction due to the inclusion of the early hires in the Libby workers cohort for whom the majority had no data on work histories and thus no specific data on their exposures.
>
> As described in the discussion of uncertainties in the cancer exposure-response (see Section 5.4.6.1.2.4), uncertainties related to exposure measurement error are considered unrelated to disease status and the general result is likely to be an attenuation in risk estimates towards the null (i.e., the addition of random noise to a clear signal tends to reduce the clarity of the observed signal, and the avoidance of random noise results in a stronger observed signal).
>
> Issues of the misclassification of exposure in general may also be considered for the noncancer exposure-response analyses. In the Marysville data used to support the derivation of the primary RfC, there is no evidence of systematic misclassification of exposure. In addition, EPA focused on the subset of workers with the highest quality exposure data to derive the RfC, reducing the probability of exposure misclassification. Similarly, for the IUR, selection of the subcohort minimizes exposure misclassification as described in Section 5.4.5.3.1.
>
> While EPA agrees that significant systematic exposure misclassification can make it more difficult to derive accurate risk estimates, EPA did not find evidence that systematic misclassification is an issue in the derivation of the RfC or IUR.

Inhalation Unit Risk (IUR) Public Comment #5 **(Paraphrased):** Suresh Moolgavkar stated that estimated half-lives for lung cancer and mesothelioma appear too short—especially for mesothelioma.

> **EPA Response:** EPA reviewed the epidemiologic literature and has noted that half-lives have been used to predict cancer risks associated with asbestos. EPA evaluated the fit of models with and without half-lives and found that for mesothelioma, the models based on a half-life applied to cumulative exposure fit better than models without a half-life. Half-lives also have been used for modeling the Wittenoom, Australia amphibole

asbestos cohort (Berry et al., 2012). Berry and colleagues found similar half-lives for amphibole asbestos-related mesothelioma as EPA found for LAA and mesothelioma.

For lung cancer unit risk, EPA selected the cumulative exposure metric which does not involve half-lives.

Inhalation Unit Risk (IUR) Public Comment #6 **(Paraphrased):** There were several comments on the selection of the model for the derivation of the IUR. Commenters questioned the use of the Poisson model for mesothelioma instead of the traditional use of the Peto model and suggested the use of two-stage clonal expansion models for lung cancer instead of the traditional Cox proportional hazards model.

EPA Response: As responded to SAB comment ***SAB Inhalation Unit Risk (IUR)*** **#18**, EPA's standard practice is to investigate several modeling options to determine how best to empirically model the exposure-response relationship in the range of the observed data as well as consider exposure-response models suggested in the epidemiologic literature. For lung cancer, a new discussion of potential alternative models has been included in Section 5.4.3.3, including Poisson, logistic, Cox, and multistage clonal expansion models. EPA selected the Cox model as the most appropriate model for exposure-response modeling based on the suitability of this model to the nature of the data set (e.g., time-dependent exposure information), the long history of this model usage in analyses of occupational cohorts, and the commonality of usage in other epidemiologic analyses of the Libby workers cohort. EPA's evaluation of alternative approaches found no other standard epidemiological model formulations that allow for the analysis of time-varying exposures in the manner achieved by the Cox proportional hazards model.

For mesothelioma, a new discussion of alternative models has been included in Section 5.4.3.1, including consideration of approaches such as parametric survival models. EPA concluded that the Peto model and variations of the Peto allowing for potential clearance are well supported in the epidemiologic literature. The Poisson model is an appropriate model for rare data. There are no examples of using other models for modeling mesothelioma in similar situations.

EPA presents results for sensitivity analyses that were conducted for both mesothelioma and lung cancer mortality in deriving combined inhalation unit risk in Section 5.4.5.3.

A.9. OTHER GENERAL PUBLIC COMMENTS TO THE SAB WITH EPA RESPONSES:

Other Public Comment #1 **(Paraphrased):** Some commenters recommended EPA have an additional round of public comment and peer review.

EPA Response: EPA considered whether the revisions to the draft assessment warranted additional peer review and concluded that the changes made were in response to peer review advice and public comments and did not of themselves need a new additional round of public comment or peer review.

Other Public Comment #2 **(Paraphrased):** There were several comments on the SAB process such as that more time should be allowed for public speakers to make comments; that there was no opportunity for meaningful interaction between the public speakers and the SAB panel; that

SAB should avoid policy recommendations; that the panel should include all panelists' opinions; that there was not enough statistical experience on the panel; that the panel process was too rushed; and that the panel was unaware of EPA guidance.

> **EPA Response:** The review of this assessment went through the standard SAB peer-review process and was consistent with the EPA Peer-Review Guidance. There were numerous opportunities for external parties to submit comments. External parties were invited to submit comments to the docket during a 60-day public comment period from August 25 to October 24, 2011 as noted in the Federal Register. All public comments to the docket were provided to the SAB for review. External parties were also invited to present analyses and viewpoints to the EPA assessment staff and managers at a "Public Listening Session" held on October 6, 2011. External parties had further opportunities to make presentations and provide written input to the SAB review panel and the full SAB during the initial SAB Panel meeting February 6−8, 2012 and at subsequent teleconference meetings on May 1, May 8, July 25, and September 25, 2013.
>
> The SAB Panel was constituted according to the process established by the SAB with public comment on the expertise of the panel members and oversight by the full SAB.

***Other Public Comment #3*:** The Sections 5.2.3.3 through 5.4.6.2 deal with statistical modeling (pages 5-28 to 5-122). In these sections statistical models and complex equations are used to analyze data from Libby Amphibole asbestos studies. If the reader of this section doesn't have at least a degree in statistics then the contents are very unclear and difficult to understand or analyze for accuracy of conclusions. Since releasing the initial draft at a town meeting in Libby on May 3, has anyone been able understand this section of it? In this section a large quantity of information on asbestos illness is derived from statistics. Sections 5.2.3.3 through 5.4.6.2 should be deleted.

> **EPA Response:** EPA has added overview text intended to provide a simpler explanation of the basis for the assessment. EPA has rewritten the sections on model considerations and selection to provide more clarity. EPA has also provided graphics that were not in the External Review Draft. For purposes of transparency so that statistically-trained readers can understand how EPA addressed methodological issues, the detailed statistical information and explanations in the assessment are needed.

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PARTICLE SIZE DISTRIBUTION DATA FOR LIBBY AMPHIBOLE STRUCTURES OBSERVED IN AIR AT THE LIBBY ASBESTOS SUPERFUND SITE

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Prepared by:

U.S. Environmental Protection Agency

Region 8

Denver, CO

With Technical Assistance from:

SRC, Inc.

Denver, CO

APPROVAL PAGE

This report, *Particle Size Distribution Data for Libby Amphibole Structures Observed in Air at the Libby Asbestos Superfund Site*, is approved for distribution.

Bonita Lavelle
U.S. EPA, Region 8

7/19/10
Date

PARTICLE SIZE DISTRIBUTION DATA FOR LIBBY AMPHIBOLE STRUCTURES OBSERVED IN AIR AT THE LIBBY ASBESTOS SUPERFUND SITE

1.0 INTRODUCTION

Libby is a community in northwestern Montana that is located near a large open-pit vermiculite mine. Vermiculite from this mine contains varying levels of a form of asbestos referred to as Libby Amphibole (LA). In 1999, EPA Region 8 initiated environmental investigations in the town of Libby and in February, 2002, EPA listed the Libby Asbestos Site (the Site) on the National Priorities List. The Site includes the former vermiculite mine and residential homes, commercial businesses, schools and parks that may have become contaminated with asbestos fibers as a result of vermiculite mining and processing conducted in and around Libby as well as other areas in the vicinity that may have been impacted by mining-related releases of asbestos. Historic mining, milling, and processing operations at the Site, as well as bulk transfer of mining-related materials, tailings, and waste to locations throughout Libby Valley, are known to have resulted in releases of vermiculite and LA to the environment.

As part of the response actions taken pursuant to the Comprehensive Environmental Response, Compensation and Liability Act, EPA has performed a number of investigations to characterize the nature and extent of LA contamination of air, soil, dust and other media in and around the community of Libby. Because available information suggests that the toxicity of asbestos is at least partially influenced by the size of the inhaled asbestos particles, these investigations have included the measurement of the dimensions (length and width) of LA particles observed in samples collected from the Libby site.

The purpose of this report is to summarize size distribution data for LA particles that have been observed in air samples collected at the site, and to utilize these data to make comparisons between various subsets of the data to determine if any important differences in particles size distributions can be recognized.

2.0 METHODS

2.1 Data Overview

EPA has been collecting samples of air since 2001 at the Libby site. Table 1 provides an overview of the sampling programs that have generated these data. The raw data for the air samples included in this assessment are provided in Appendix A.

Most of the samples that have been collected have been analyzed for asbestos by transmission electron microscopy (TEM) using either ISO 10312 (1995) or AHERA (1986) counting rules, as modified by site-specific modifications as described in modifications forms LB-000016 and LB-000031 (provided in Appendix B). In all cases, the data that are recorded during the analysis

of a sample include the length, width and aspect ratio (length/width) of all particles that meet the counting rules specified for the analysis.

2.2 Data Presentation

One convenient method for comparing the size distributions of two different sets of LA particles is through a graph that plots the cumulative distribution function (CDF) for each particle set. This graphical format shows the fraction of all particles that have a dimension less than some specified value. This format is used in this document to present the distributions of length, width and aspect ratio.

There are a number of statistical tests that can be used to compare two distributions in order to support a statistical statement about whether the distributions are "same" or "different". Such comparisons are complicated by the fact that the distributions may be similar over some intervals and dissimilar over other intervals. However, at present, data are not sufficient to know which parts of the distribution are most important from a toxicological perspective. Therefore, this document relies upon simple visual inspection to assess the degree of difference between various regions of differing distributions.

3.0 RESULTS

3.1 Data Validation

The Libby2 database and Libby OU3 database have a number of built-in quality control checks to identify unexpected or unallowable data values during upload into the database. Any issues identified by these automatic upload checks were resolved by consultation with the analytical laboratory before entry of the data into the database. After entry of the data into the database, several additional data verification steps were taken to ensure the data were recorded and entered correctly. A total of 29,504 LA structures are included in Table 1. Of these structures, 25% have undergone data validation in accord with standard site-wide operating procedures (SRC, 2008) to ensure that data for length, width, particle type, and mineral class are correct. Of the structures that have undergone validation, only 39 of 7,464 (0.5%) structures had errors in length, width, or mineral class. These errors were corrected and the database updated as appropriate.

3.2 Consolidated Data Set

Originally, most samples of air at Libby were analyzed using a counting rule based on a fiber aspect ratio of 5:1. More recently, most air samples are counted using an aspect ratio rule of 3:1. Because this rule has varied over time, Libby-specific laboratory modifications LB-000016 and LB-000031 (see Attachment 1) were created to document the historic modifications and instructions that laboratories have followed throughout the Libby program.

Figure 3-1 presents the particle size distributions for 29,504 LA particles observed to date[1] in air samples collected at the Libby Asbestos Superfund site that have an aspect ratio of 5:1 or more, along with the distributions for 11,451 particles that were counted using an aspect ratio rule of 3:1. As seen, the distributions are very similar. This is because the number LA particles that have an aspect ratio > 3:1 and < 5:1 is a relatively small fraction of the total (7%).

For simplicity, all remaining analyses focus on the set of particles with an aspect ratio of 5:1 or more.

3.3 Frequency of Complex Structures

Asbestos particles occur not only as fibers but also in more complex structures including bundles, clusters, and matrix complexes. The frequency of these structure types in air samples from Libby are summarized below:

[1]Based on a query of the Libby2 database on 12/08/09 and the Libby OU3 database on 2/9/10.

Type[2]	Number	Frequency
Fiber	23,933	81%
Bundle	2,366	8%
Matrix	3,150	11%
Cluster	54	0.2%
Total	29,504	100%

As shown, most (81%) of the enumerated structures are fibers, with less than 20 % complex structures.

3.4 Comparisons of Stratified Data Sets

The data sets shown in Figure 3-1 are based on air samples that were collected at a number of different locations around the site, and which were analyzed by several different methods. In order to investigate whether there are any important differences in size distributions between operable units, sampling locations (indoor, outdoor), activity (e.g., active or passive), and /or analytical method, the consolidated data set was partitioned into a number of subsets, as follows:

Figure	Comparison
3-2	LA particles observed in air stratified by structure type
3-3	LA particles observed in air stratified by Operable Unit
3-4	LA particles observed in air stratified by sample type (ambient, indoor, outdoor ABS)
3-5	LA particles observed in air stratified by preparation method (direct vs indirect)
3-6	LA particles observed in air stratified by analysis method (ISO vs AHERA)

Figure 3-2 is a comparison of different structure types (fiber, bundles, and matrices). Clusters were not included because there were too few for a distribution to be meaningful. As seen, the length distribution for matrix particles is somewhat left-shifted compared to fibers. This is perhaps expected because some portion of the fiber length in matrix fibers is obscured by the matrix particle. In contrast, the length and thickness distributions for bundles are right-shifted compared to fibers. This is expected because a bundle is several fibers lying in parallel.

Figure 3-3 compares the size distributions of LA at different operable units (OUs) at the site. As seen, there appears to be little difference in structures from the different OUs.

[2]In some cases, the structure type assignment provided by the laboratory was not a valid choice according to the recording rules for the specified analysis method. Table A-1 in Appendix A presents the types of invalid structure types and the structure class assumption that was made in order to include the structure in this report.

Figure 3-4 shows the distribution of structure sizes for different types of air samples. Samples have been placed into three groups: ambient air, indoor ABS, and outdoor ABS. As shown, the length and width distributions for indoor and outdoor ABS samples are relatively similar, while the length and width distribution for ambient air samples appear to be right shifted. However, this observation should be considered to be relatively uncertain because of the small number (136) of particles that constitute the ambient air data set.

Figure 3-5 compares the size distributions for samples using direct and indirect preparation methods. As shown, there is little difference in the distributions or either length of width, suggesting that preparation method does not have a significant impact on particle size.

Figure 3-6 compares the particle size distributions as a function of analytical counting rules. As shown, the length and width distributions for particles analyzed using AHERA rules tend to be somewhat right-shifted relative to the distributions for particles analyzed using ISO 10312 rules. This apparent difference might be related either to differences in counting rules between methods, or possibly to differences in the nature of samples analyzed by each method. In either event, the difference between methods appears to be relatively small.

4.0 SUMMARY

Particle size data are available for nearly 30,000 LA structures that have been observed in air samples collected at the Libby Asbestos Superfund site. Most (about 80%) LA particles are fibers, with less than 20% complex structures (bundles, clusters, or matrices). LA particle lengths typically range from a little less than 1 μm up to 20-30 μm, and occasionally higher. The average length is about 7 μm. Thicknesses typically range from about 0.1 μm up to about 2 μm, with an average of about 0.5 μm. Although some variations occur, particle size distributions are generally similar between different locations and between different types of samples.

APPENDIX A

RAW DATA: LA STRUCTURE DATA FROM THE LIBBY 2 DATABASE AND THE LIBBY OU3 DATABASE

Libby2DB based on a download date of 12/8/09
Libby OU3 DB based on a download date of 2/9/10

See attached compact disc.

APPENDIX B.

LIBBY-SPECIFIC LABORATORY MODIFICATION FORMS

LB-000016
LB-000031

Table 1. Air Sample Collection Programs

Program	Program Description	Program Date Range	Sampling and Analysis Plan (s)	Number of LA Structures [a]
Phase 1	Initial investigation sampling to assess nature and extent of potential contamination. Includes source areas (e.g., screening plant, export plant), commercial buildings, and residential properties.	Dec 1999−present	U.S. EPA (2000)	328
Phase 1R	Monitoring and confirmation sampling as part of clean-up activities.	Jun 2000−present	U.S. EPA (2000)	18,525
Phase 2	Activity-based sampling (ABS) included four scenarios: 1) routine indoor activities, 2) active cleaning, 3) simulated remodeling disturbances, 4) garden rototilling.	Mar−Nov 2001	U.S. EPA (2001)	867
Phase 2R	Monitoring and confirmation sampling as part of Phase 2	Apr 2008−Nov 2009		1,717
CSS	Contaminant Screening Study of Libby properties to determine need for remediation.	Apr 2003−Oct 2006	U.S. EPA (2002)	3
SQAPP	Sampling to address risk assessment data gaps. Included indoor ABS (routine activities) and outdoor ABS (raking, mowing, playing), as well as clean-up evaluation samples.	Jun 2005−Oct 2006	U.S. EPA (2005)	1,456
Ambient Air (AA)	Ambient air monitoring program for 14 stations in OU4, 2 stations in OU2, 2 stations in OU6. Samples represent long-term (continuous 5-day) collection periods.	Oct 2006−Jun 2008	U.S. EPA (2006); (2007c)	136
OU4 Indoor/ Outdoor ABS	Sampling to assess exposures during indoor ABS (passive & active activities) and outdoor ABS (raking, mowing, playing) in OU4.	Jul 2007−Jun 2008	U.S. EPA (2007b); (2007a)	5,603
Indoor Schools	Stationary air sample collection from within Libby public schools	Dec 2008	U.S. EPA (2008a)	2
Outdoor Schools	Outdoor ABS sampling from Libby public schools simulating exposures to students and maintenance staff.	Jul−Sept 2009	U.S. EPA (2009a)	5
Phase 2 (OU3)	Ambient air sampling. Samples represent long-term (continuous 5-day) collection periods.	July−Oct 2008	U.S. EPA (2008b)	67
Phase 3 (OU3)	ABS air sampling of ATV riding, hiking, camp fire construction	Aug−Nov 2009	U.S. EPA (2009b)	59
Clean-up Evaluation	Sampling to monitor air and dust levels after completion of clean-up activities at 31 properties.	Nov 2003−Feb 2004	U.S. EPA (2003)	5
Other	Includes various site-specific sampling investigations (e.g., Stimson Lumber, Flyway, BNSF) and smaller-scale sampling programs.	Aug 2001−present	various	731

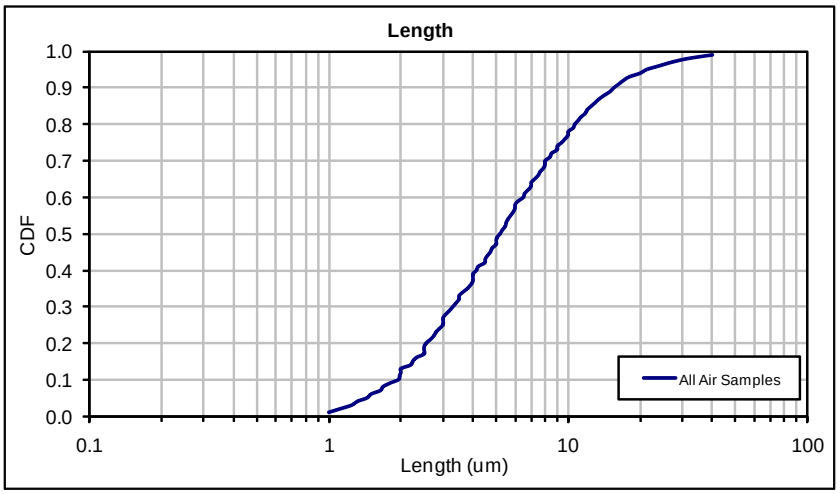
(a) Restricted to LA structures recorded in accordance with a 5:1 aspect ratio rule.

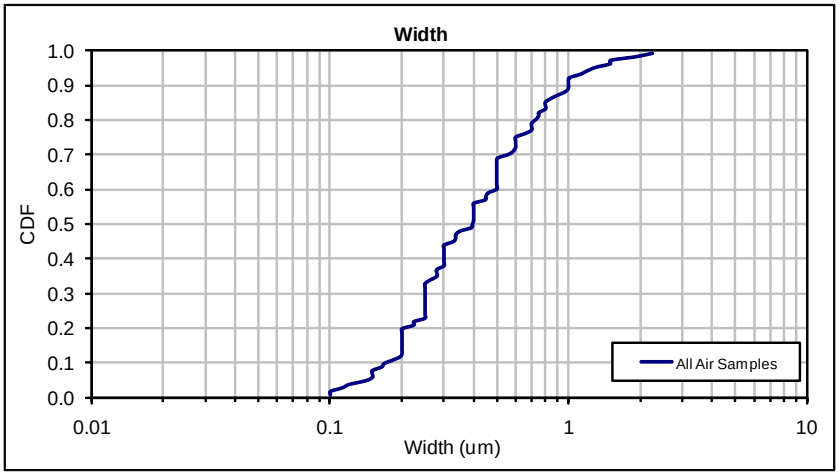
LA structure counts are based on a download of Libby 2DB performed on 12-8-09 and the Libby OU3 DB on 2-9-10.

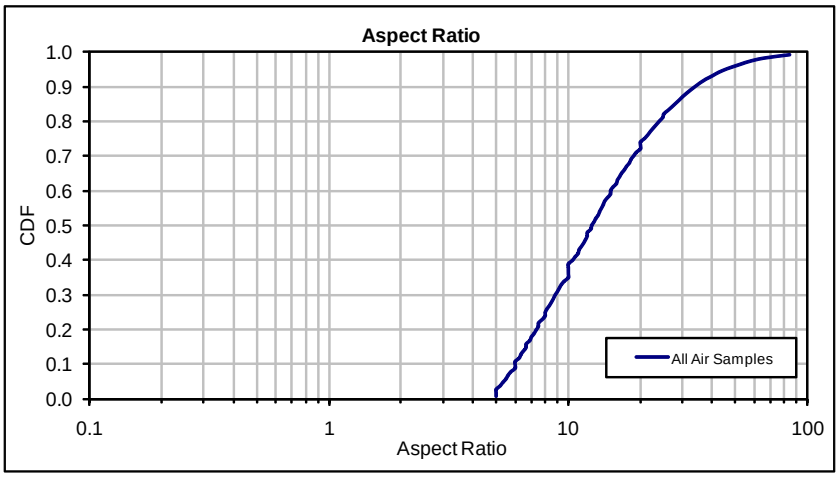
Other		
Program	LA Structures	Description

1A	9	AIRS Site (418 Mineral Ave)
BN	17	BNSF
CR	3	Cumulative Risk Study
DM	1	Demolition Sampling from 2006 only
E1	1	BNSF Rail Yard Exclusion Zones
EP	104	Export Plant
FC	184	Flower Creek
FL	146	WR Grace (Flyway site)
SL	266	Stimson Lumber

Figure 3-1. Particle Size Distributions of LA Particles in Libby Air Samples





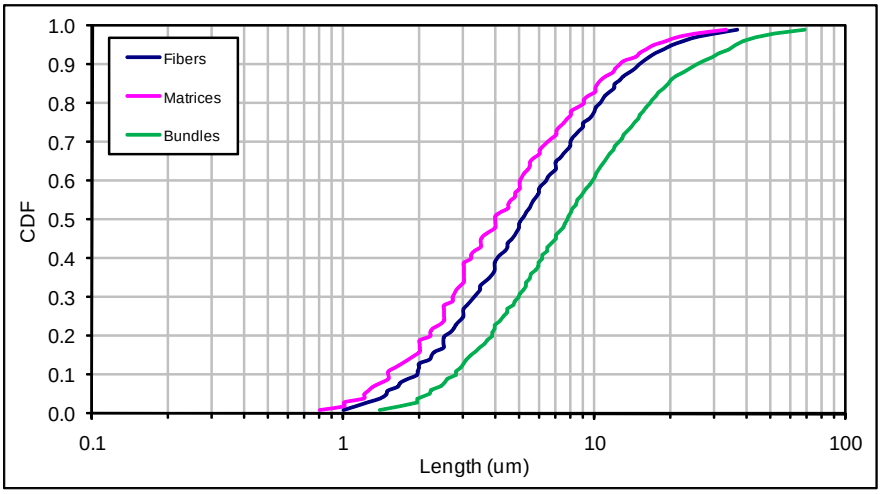


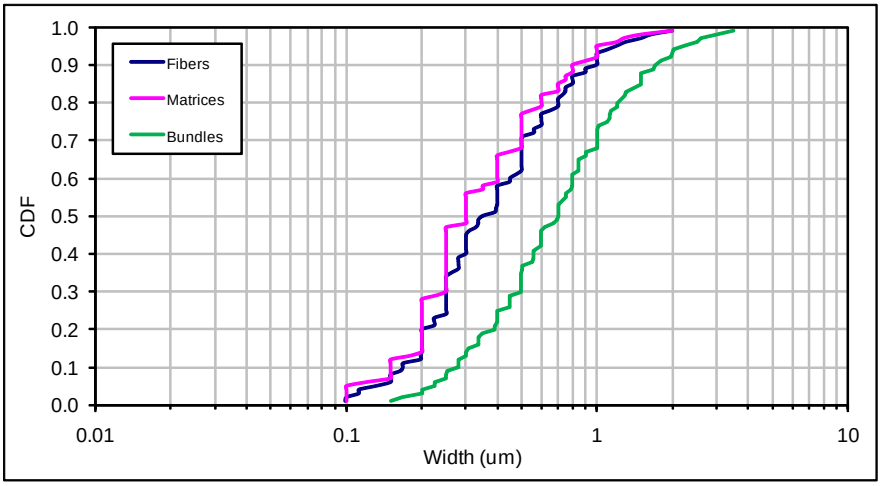
Data are based on a download of Libby 2DB performed on 12-8-09 and the Libby OU3 DB on 2-9-10.

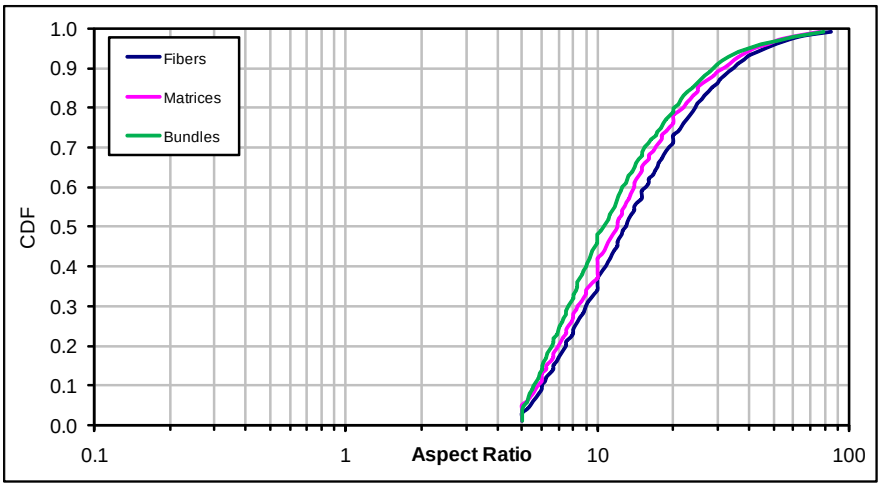
All Air Samples

Number of Structures (29,504)		
Type	Number	Frequency
F	23,933	81%
B	2,366	8%
M	3,150	11%
C	54	0.2%

Figure 3-2. Particle Size Distributions of LA Particles in Libby Air Samples by Structure Type





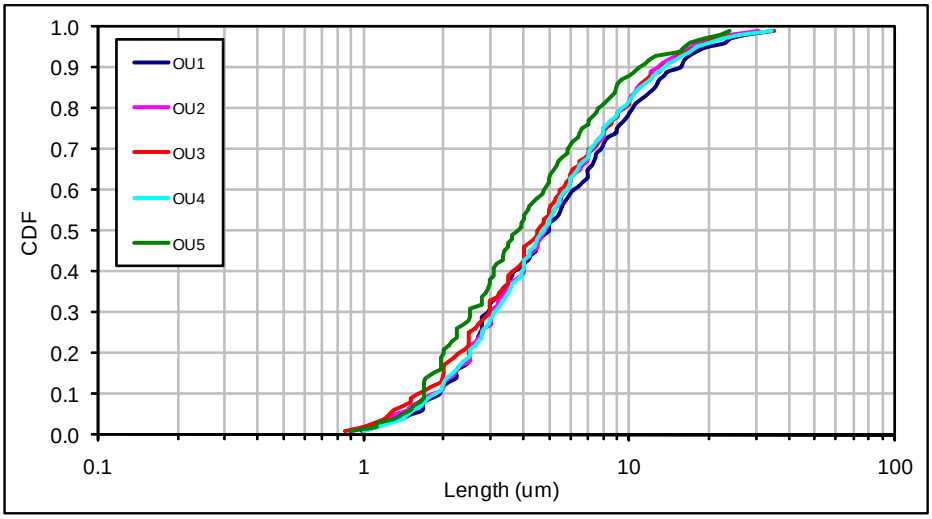


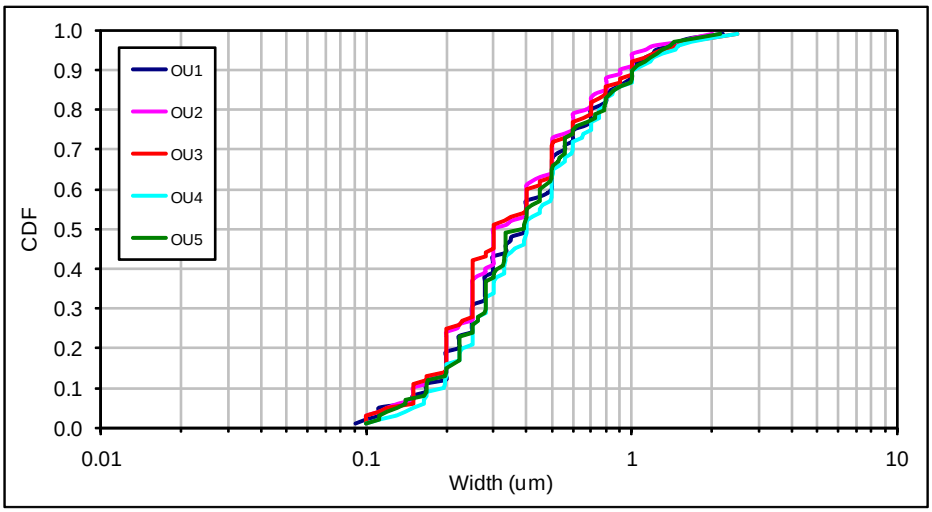
Data are based on a download of Libby 2DB performed on 12-8-09 and the Libby OU3 DB on 2-9-10.

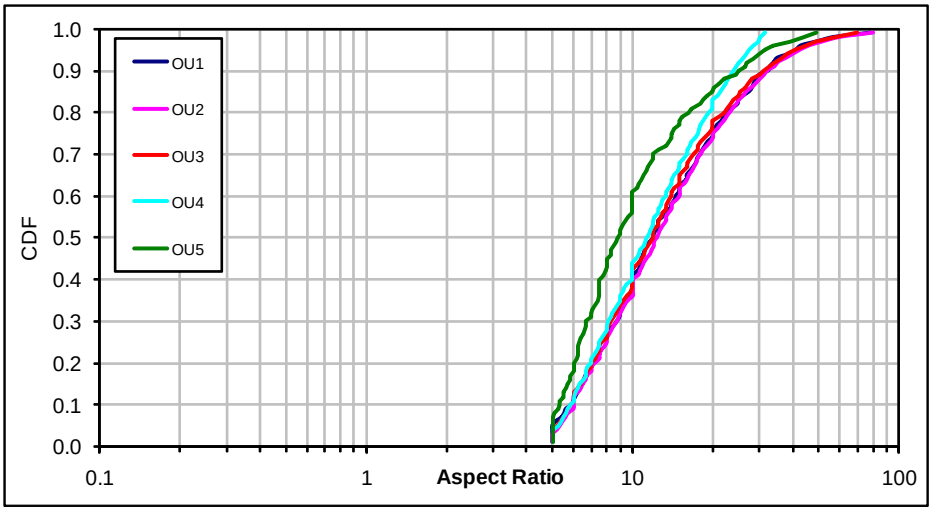
Structure Type	N Structures
F	23,933
B	2,366
M	3,150

Clusters have not been included in this figure because N = 54 and this in not believed to be a suffficient number of structures.

Figure 3-3. Particle Size Distributions of LA Particles in Libby Air Samples by Operable Unit (OU)



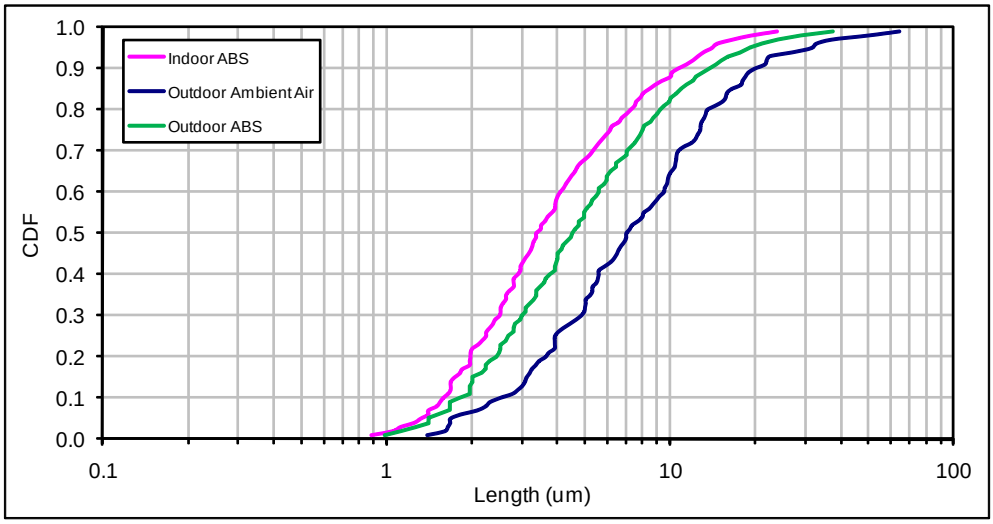


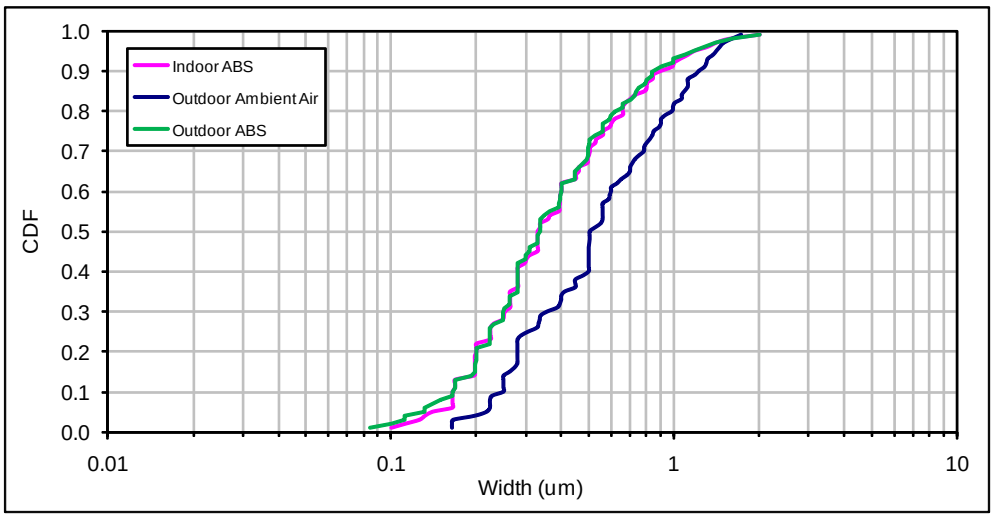


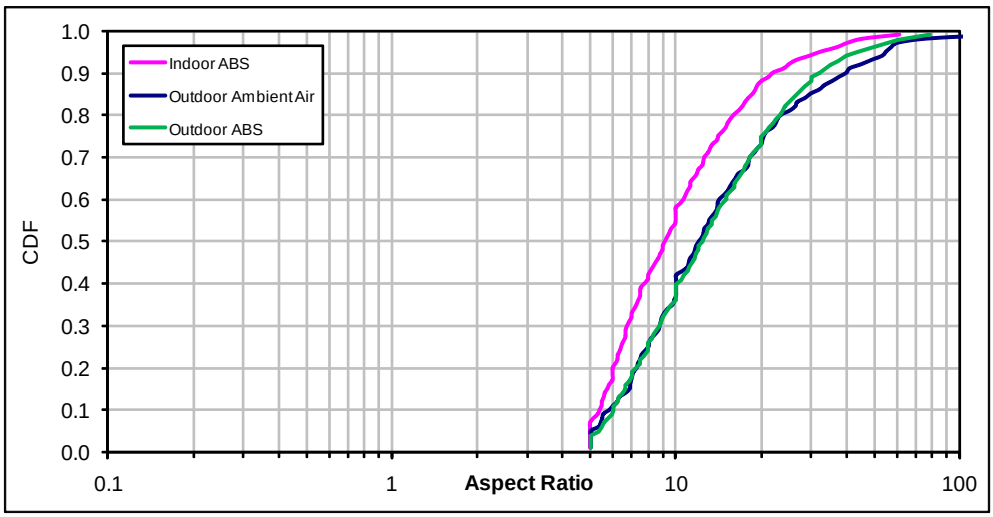
Data are based on a download of Libby 2DB performed on 12-8-09 and the Libby OU3 DB on 2-9-10.

OU	N Structures
1	447
2	7,421
3	4,382
4	13,005
5	335

Figure 3-4. Particle Size Distributions of LA Particles in Libby Air Samplesby Air Type



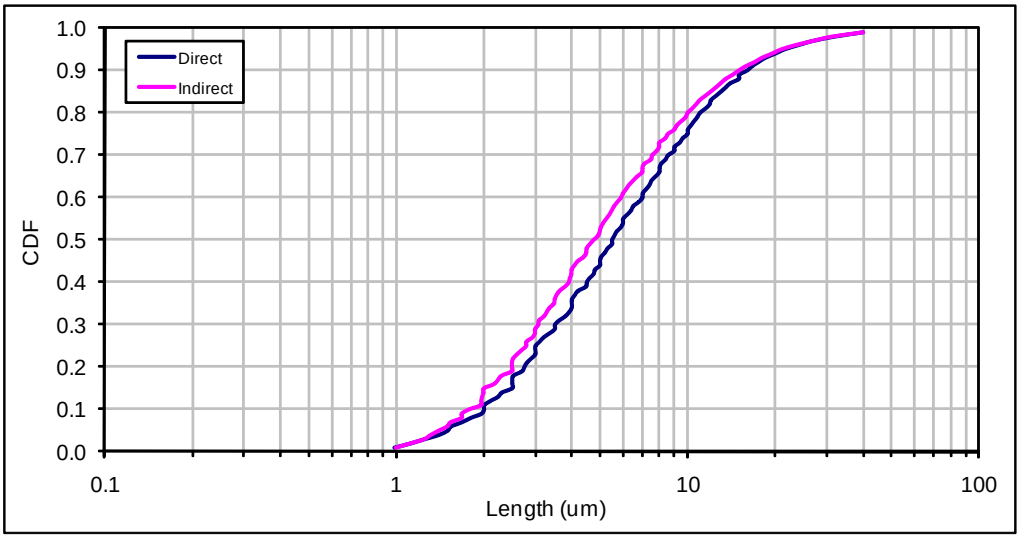


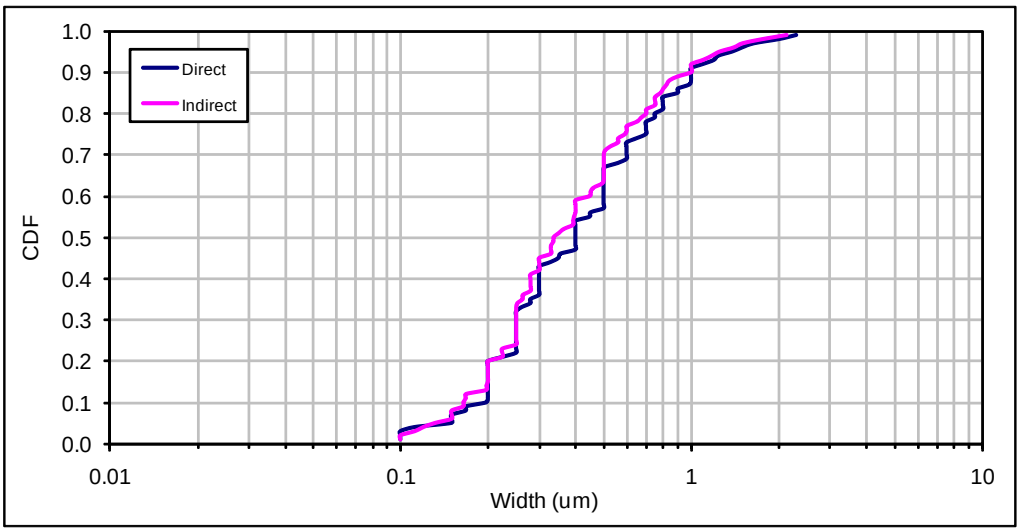


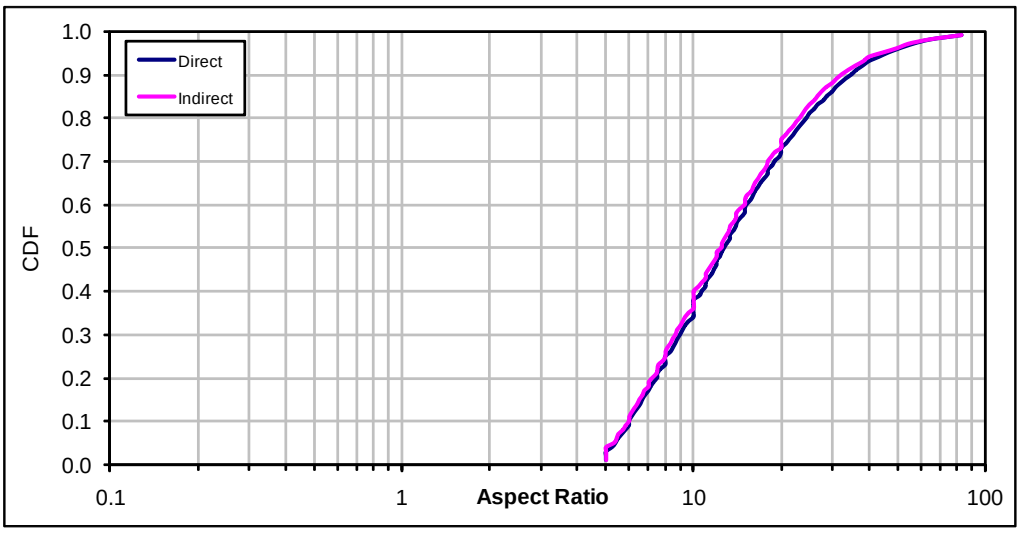
Data are based on a download of Libby 2DB performed on 12-8-09 and the Libby OU3 DB on 2-9-10.

Samples Source	N Structures
Ambient Air	136
Indoor ABS	891
Outdoor ABS	5,953

Figure 3-5. Particle Size Distributions of LA Particles in Libby Air Samples by Preparation Method



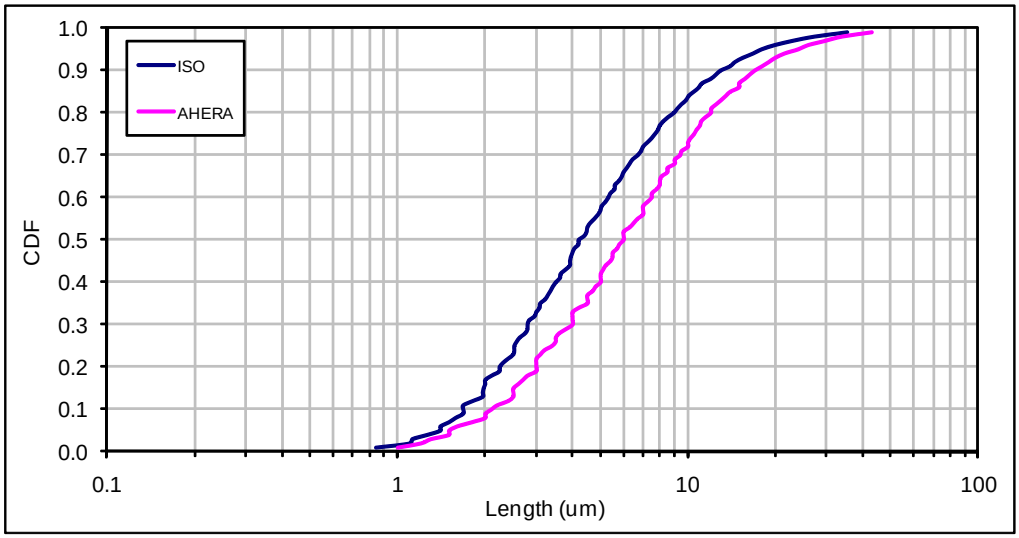


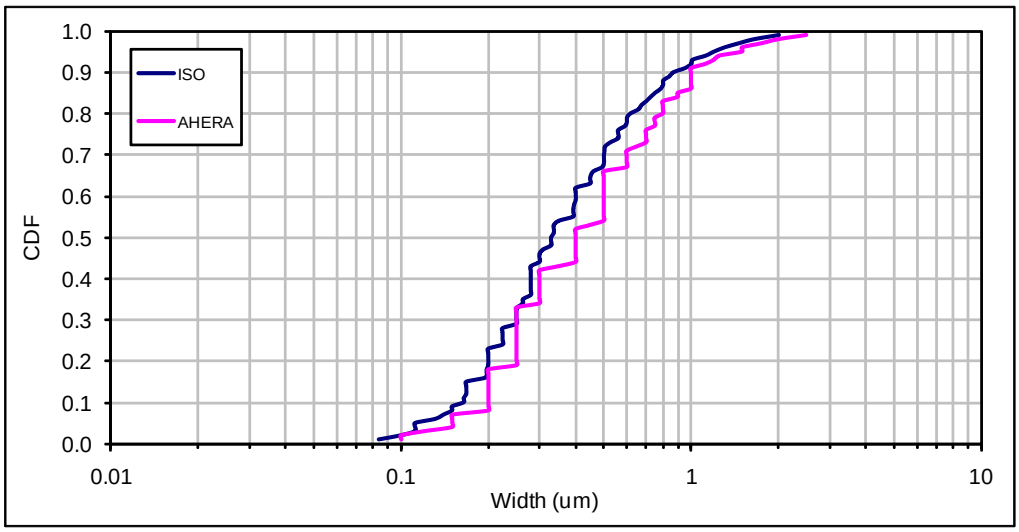


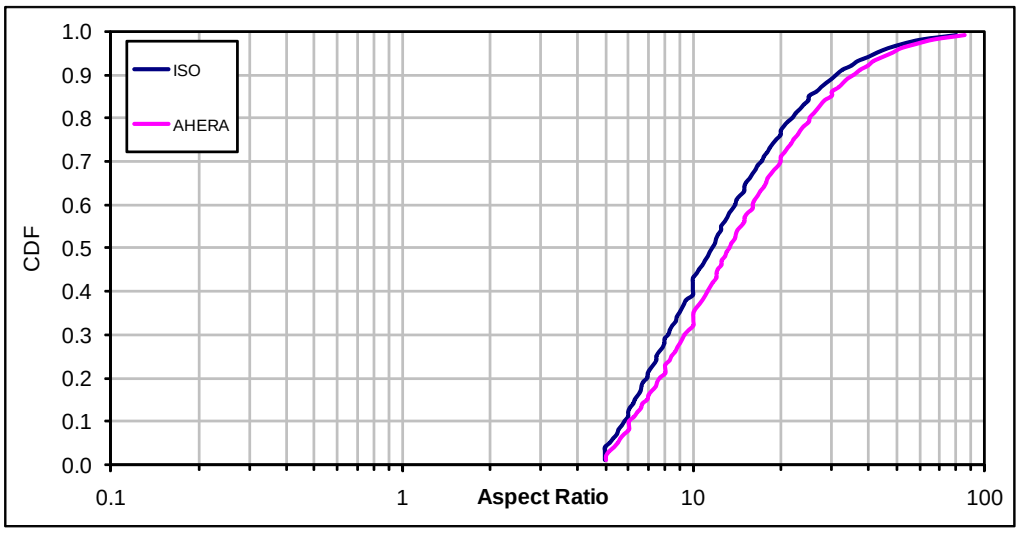
Data are based on a download of Libby 2DB performed on 12-8-09 and the Libby OU3 DB on 2-9-10.

Preparation	N Structures
Direct	17,578
Indirect	11,926

Figure 3-6. Particle Size Distributions of LA Particles in Libby Air Samples by Analysis Method







Data are based on a download of Libby 2DB performed on 12-8-09 and the Libby OU3 DB on 2-9-10.

Analysis Method	N Structures
ISO	12,657
AHERA	16,847

5.0 REFERENCES

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ISO (International Organization for Standardization). (1995). Ambient air -- Determination of asbestos fibres - Direct transfer transmission electron microscopy method [Standard]. (ISO 10312:1995). Geneva, Switzerland: International Organization for Standardization (ISO). http://www.iso.org/iso/iso_catalogue/catalogue_tc/catalogue_detail.htm?csnumber=18358

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APPENDIX C. CHARACTERIZATION OF AMPHIBOLE FIBERS FROM ORE ORIGINATING FROM LIBBY, MONTANA, LOUISA COUNTY, VIRGINIA, ENOREE, SOUTH CAROLINA, AND PALABORA, REPUBLIC OF SOUTH AFRICA

The O.M. Scott plant in Marysville, Ohio manufactured a number of products including fertilizers, dyes, and pesticides that were bound to a vermiculite carrier as a delivery vehicle. The plant received ore from Enoree, South Carolina, Louisa County, Virginia, Libby, Montana, and Palabora, Republic of South Africa which was processed in an exfoliation furnace to produce vermiculite used in the manufacture of their commercial products. Only ore from South Carolina was used in 1957 and 1958. From 1959 to 1971, ores from South Carolina and Libby were used. From 1972 to 1980, ores from Libby, South Africa, and Virginia were used. No ore from Libby was used after 1980. Only ore from South Africa and Virginia were used after 1980 (see Appendix F).

EPA Region 8 obtained samples of ore from Libby, South Africa, and Virginia from Dr. James Lockey, University of Cincinnati, and analyzed the samples to determine the particle size distribution (length, width, and aspect ratio) using transmission electron microscopy and energy dispersive spectroscopy to identify the mineral composition of the amphibole fibers. Dr. Lockey obtained the South African and Virginia ore samples from the Marysville facility in 1980 and the Libby ore (Libby #3 ore) from an expansion plant in Salt Lake City, Utah, in 1981. EPA received a sample of ore from Enoree, South Carolina from the USGS historical collection, Denver, CO (Vermiculite Ore [BO-4], approximately 10% gangue, Zonolite Co. Mine, Travelers Rest, South Carolina 8/27/58).

The ore from the Rainey Creek complex (Vermiculite Mountain Mine, Libby, Montana) resides in large ultramafic intrusive bodies that are rich in biotite, pyroxenite, and biotitite, a rock comprised Meeker et al. (2003) of almost pure biotite. The ultramafic intrusions are cut by deposits of syenite and carbonatite and much of the biotite has been hydrothermally altered to hydrobiotite and vermiculite (Meeker et al., 2003; Frank and Edmund, 2001). The pyroxenite has been altered to fibrous soda-rich amphiboles and contacts with pyroxenite surrounding the biotitite contain the vermiculite ore zone containing diopside, hydrobiotite and apatite. Fibrous and nonfibrous amphiboles are located in both veins and disseminated throughout the intrusive rock along cleavage planes of pyroxene. Amphiboles from Vermiculite Mountain had been referred to as soda tremolite, richterite, soda-rich tremolite, tremolite asbestos, and richterite asbestos by a number of investigators. In 2000, Wylie and Verkouteren (2000) identified winchite as the principle amphibole in the Vermiculite Mountain deposit based on chemical investigation referencing the classification system of Leake et al. (1997) and optical properties. Meeker et al. (2003) investigated amphibole types from the mine complex using electron probe microanalysis and x-ray diffraction analysis and reported the presence of winchite, richterite, tremolite, and magnesioriebeckite. Magnesio-arfvedsonite and edenite were detected in low

abundance. The amphibole composition of the Libby Amphiboles is roughly winchite, richterite, tremolite, magnesio-riebeckite, magnesio-arfvedsonite, and edenite (84:11:6:<1:<1:<1). The O.M. Scott facility received ore from the Vermiculite Mountain Mine complex, Libby, Montana from 1959 through 1980.

The Palabora Igneous Complex located near Phalaborwa, Republic of South Africa is the location of the Palabora mine. The Palabora ore deposit shares many features with the Vermiculite Mountain mine complex including zoned deposits with ultramafic rocks (pyroxenite) and intrusion by alkalic rock primarily syenite. The primary mica at Palabora is phlogopite rather than biotite and the primary alteration product that forms vermiculite ore is hydrophlogopite rather than hydrobiotite (Schoeman, 1989).

The Palabora ore is reported to contain little or no asbestiform fibers based on polarized light microscopy by the Institute of Occupational Medicine in Edinburgh (IOM Consulting, 2008). Crude vermiculte from the Palabora complex was also reported to be free of asbestiform fiber by polarized light microscopy (IOM, 2006). In both reports, the analysis by polarized light microscopy were conducted with a detection limit of 1 ppm and since no chrysotile or amphibole structures were detected, no further analysis by electron microscopy and x-ray diffraction were conducted.

The ore from the Virginia Vermiculite mine in Louisa County, Virginia is described as mafic rock intruded by a series of small pegmatites (Gooch, 1957). Meisinger (1979) classified the deposits as Type 3, similar to the ores from Enoree, South Carolina. The formations consist of potassic ultramafic bodies primarily biotite. The vermiculite ores are found primarily in hydrobiotite portions of the biotite intrusions. The hydrobiotite deposits are preferentially mined because of better commercial properties compared to vermiculite.

There is limited information on the asbestos content of the ores from the Louisa deposit. Rohl and Langer (1977) reported both chrysotile and amphibole fibers in six ore samples from the Louisa deposit. The chrysotile was reported and fibers and bundles while the amphibole was described as widely composed with most of the fibers classified as actinolite. Moatamed et al. (1986) analyzed the Virginia, Palaboroa, and Libby ore samples and reported traces of fibrous amphibole asbestos identified as actinolite and actinolite in the form of cleavage fragments having low aspect ratios. Amphibole content for both unexfoliated and exfoliated ores ranged up to 1.3 % amphibole asbestos.

Ores from the Enoree, South Carolina deposits are primarily hydrobiotite and biotite in origin. Fluroapatite is a common mineral collocated with the hydrobiotite. Zircon is also widely dispersed throughout the plutons along with minor accessory minerals including talc, chlorite, chromite, rutile, titanite, corundum, anatase, and amphibole asbestos (Hunter, 1950). The amphibole asbestos identified in the vermiculite deposit at Enoree has been classified as tremolite (Libby, 1975).

Briefly, samples of ore and vermiculite were prepared following the procedure outlined by Bern et al. (2002). Samples were dried, ground with a Wylie mill and mortar and pestle and sieved through a 230 µm (60 mesh) sieve. Samples (exactly 2.0 gms) were mixed with 18 gms of analytical silica sand and placed in a fluidized bed asbestos segregator vessel to load 25 mm MCE air sampling filters (0.8 µ pore size) (Januch et al., 2013). The fluidized bed asbestos segregator was run for 3 minutes to load the filter cassettes with sufficient fibers for analysis by transmission electron microscopy (TEM). The fluidized bed asbestos segregator preparation method allows for analytical sensitivity for fiber detection in the range of 0.002% by mass (Januch et al., 2013). Three filters were loaded for each of the ore and vermiculite samples. After loading, the filters were prepared for TEM analysis by mounting on copper girds, carbon coating, and subjected to TEM analysis (TEM-ISO 10312 method).

The laboratories followed fiber counting rules detailed in the Sampling and Analysis Plan for the specific study. Total amphibole fibers and Phase Contrast Microscopy equivalent (PCMe) fibers were counted for each of the ore/vermiculite samples. A total of 1.0 mm^2 area or a total of approximately 100 grid openings were counted for each filter to achieve the desired analytical sensitivity. Energy dispersive spectroscopy (EDS) was performed on selected samples from each of the vermiculite/ore samples to provide mineral characterization of individual fibers. Fiber counts were recorded on NADES data sheets for further analysis. Only the Libby vermiculite and Libby ore samples had sufficient fibers detected to perform a fiber size distribution.

Fiber counts were determined by counting fiber numbers for a specific area of the filter grid or a specific number of grid openings (whichever was achieved first) to determine total fibers present. As shown in Table C-1, the number of fibers for the test materials varied greatly depending on the source.

Table C-1. Fiber detected in ore and expanded product

		Structures counted			Concentration (s/g)		
Sample type	**Grid openings**	**LA**	**OA**	**C**	**LA**	**OA**	**C**
Enoree (BO-4) ore	285	6	1	0	14,300	3,400	0
Virginia ore	146	0	0	0	0	0	0
Virginia expanded	146	1	0	0	4,336	0	0
South Africa ore	146	1	0	2	4,401	0	8,801
South Africa expanded	146	0	0	0	0	0	0
Libby # 3 ore	148	320	0	0	1,393,873	0	0
Libby expanded	153	108	0	0	468,213	0	0

LA = Libby amphibole; OA = Other amphibole; C = Chrysotile.
Note: the designation of fibers as LA in this instance reflects only a qualitative morphological comparison to amphiboles of the Libby series.

The Libby #3 ore and the Libby #3 expanded material contained the greatest number of fibers both in fiber counts on the filters and in calculated structures per gram of material. Virginia expanded and South African ore contain amphibole structures represented by low fiber counts. South African ore also contained chrysotile fibers as determined by morphology and EDS analysis. The estimation of structures per gram of material indicated that there were 4,000 amphibole fibers per gram of material which was lower than the Libby ore samples. Enoree ore contained amphibole fibers determined to be actinolite and anthophyllite based on morphology and EDS analysis. Based on fluidized bed preparation, the ore contained approximately 18,000 structures per gram of material which was lower than the Libby ore samples. Numerous nonasbestiform minerals were also detected including biotite, micas, and pyroxenes.

Amphiboles are a complex group of minerals characterized by double chains of silicate tetrahedra and the generic chemical formula of: $A_{0-1}B_2C_5T_8O_{22}[OH]_2$ where A, B, C, and T represent the various cations. The modern classification system of amphiboles is described in Leake et al. (1997). To classify the mineral species of the amphibole, it is not sufficient to determine its composition; the various cations must be assigned to the specific A, B, C, and T sites. The cutoffs of the compositional ranges allowed for each amphibole mineral species are based on the number of the cations in the various sites. The methodology to classify an amphibole is to first determine its elemental compositions (e.g., as expressed as weight percentage oxide for each element or as atomic percentage for each element). Then a normalized routine is applied to the raw elemental measurements to calculate the number of each of the cations contained in one formula unit. (This is a simple arithmetic calculation since the cation

percentage have been measured and the stoichiometry must balance the charges of the cations and anions.) Generally, one formula unit is assumed to contain 23 oxygens. Next the sites are filled up by assigning cations to them subsequently, specifically:

T: Si^{4+}, Al^{3+}, and Ti^{4+}

C: Al^{3+} and Ti_{4+} (only after the T sites are filled first) and then Mg^{2+}, Fe^{2+}, Fe^{3+}, and then Mn^{2+}.

B: Any remaining Mg^{2+}, Fe^{2+}, and Mn^{2+} (after the C sites are filled), all Ca^{2+}, then Na^{+} if there is any room left.

A: Na^{+} and K^{+} only

Once the cations are assigned to their sites, it is a simple matter to classify the minerals based on the cutoffs of the compositions field allowed for each mineral.

The Libby amphibole group of minerals is a complex group of amphiboles consisting of six minerals:

- Winchite, $CaNa[Mg, Fe^{2+}]_4[Al, Fe^{3+}]Si_8O_{22}[OH]_2$
- Richterite, $NaCaNa [Mg, Fe^{2+}, Mn, Fe^{3+}]_5Si_8O_{22}[OH]_2$
- Tremolite, $Ca_2Mg_5Si_8O_{22}[OH]_2$
- Magnesio-riebeckite $Na_2[Mg_3, Fe^{3+}_2]Si_8O_{22}[OH]_2$
- Magnesio-arfvedsonite $NaNa_2[Mg_4,Fe^{3+}]Si_8O_{22}[OH]_2$
- Edenite $NaCa_2Mg_5Si_7AlO_{22}[OH]_2$

Although this looks complex, the matter is simplified by the fortunate fact that all Libby amphibole is characterized by a low amount of Al in the T site (and a correspondingly high Si content). So, according to Leake's classification, if the Si (expressed as apfu) is at least 7.5 and Al content in the T site is <0.5, all six Libby amphibole types can be plotted on a graph of Na content of the B site versus the (Na + K) content in the A site. This approach was described by Meeker et al. (2003) for the Rainy Creek complex.

Quantitative EDS spectra (TEM/EDS) were collected from all amphibole fibers found in the South Africa, South Carolina, and Virginia samples, and six randomly-selected LA fibers in each of the Libby ore and Libby expanded samples. Two bundles of asbestiform serpentine (chrysotile) were found in the South Africa ore sample. EDS spectra were collected for one of the bundles. The chemical formula of serpentine is: $Mg_3Si_2O_5[OH]_4$. The EDS software package collected and summarized each spectrum to determine the atomic percentage of each element of interest.

Several assumptions were made in the treatment of the EDS data:

1) Numbers of cations per formula unit are calculated on the basis of 23 oxygens. This may or may not be correct, since an (OH) site in the amphibole crystal can be occupied by either OH^-, F^-, Cl^-, or O^{2-}. The calculated cation numbers will be affected if a significant quantity of O^{2-} is in the OH site.

2) A persistent problem with amphiboles is that they can contain both ferric (3+) and ferrous (2+) iron in the same crystal. For the purposes of this report all Fe was assumed to be Fe^{2+}. A routine for calculating the ratio of Fe^{2+} to Fe^{3+} is described in Leake et al. (1997) but it is very complex, applies to polished sections, and was not attempted for this report.

3) For the purposes of this report, the T sites were filled completely full to 8 apfu with all Si and then Al and Ti. The C sites were then filled to 5 apfu with any remaining Al and/or Ti and then with Mg and Fe^{2+}. All Ca and any Mg and, Fe remaining after the C site was full were then assigned to the B site. Next, Na was assigned to the B site until it was full (apfu), then any remaining Na and all K was assigned to the A site. Quantitative EDS measurements were calibrated with the USGS's BIR-1G basalt glass standard and the feldspar minerals albite and orthoclase.

Application of these assumptions to the TEM/EDS data produces a useable graph of the Na and K content of the amphibole fibers. As shown in Figure C-1, Libby #3 ore and Libby #3 Expanded amphiboles were characteristic of winchite, richterite, edenite, and tremolite-actinolite. Virginia Expanded and South African ore both contained amphibole fibers characteristic of non-Libby (Na and K negative) in the tremolite series. Compositions of amphibole fibers from the Libby Starting Material, which is a mixture of LA minerals traceable from the mine at Libby and used as a reference material by environmental laboratories, is shown on Figure C-1 for comparison.

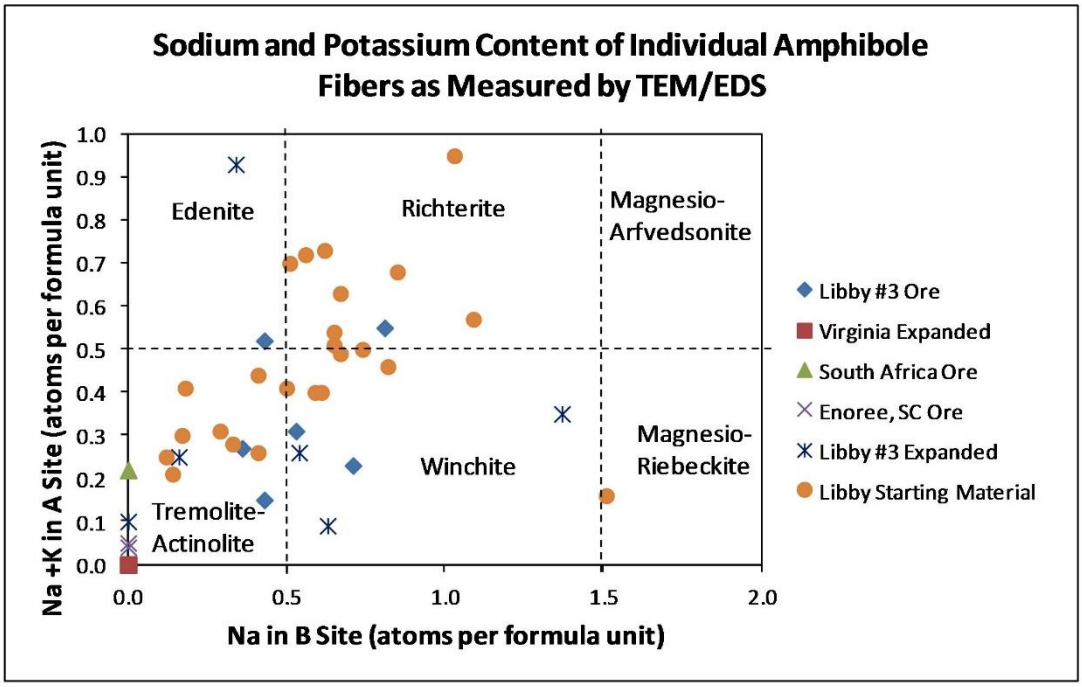

Figure C-1. Cation values for Na in the B site and the Na + K in the A site from individual amphibole fibers.

Following all assumptions described above and the approach of plotting Na in the B-site versus Na + K in the A site as described by Meeker et al. (2003), the mineral species of the Marysville fibers can be described as:

- The single Virginia amphibole asbestos fiber is an actinolite
- The single South African amphibole fiber is a tremolite
- Six of the Enoree amphibole fibers are actinolite and one is anthophyllite (OA)
- Five of the LA fibers from Libby are winchite
- One of the LA fibers is a richterite
- Two of the LA fibers are edenite
- Four of the LA fibers from Libby are actinolite

Actinolite, which has the chemical formula of $Ca_2(Mg,Fe^{2+})_5Si_8O_{22}[OH]_2$, is part of a solid solution series with tremolite and occurs when some Mg is substituted by Fe^{2+}. Actinolite was not found in Meeker et al. (2003) analyses of samples from the mine at Libby, however, some of those tremolite analyses would be classified as actinolite if all Fe was treated as Fe^{2+} (Meeker et al., 2003), which is how the analyses described above were treated.

Fiber size distributions for amphibole fibers from the Libby #3 ore and Libby #3 Expanded sources were conducted on the fibers counted during the TEM analysis of the filter

grids (see Figure C-2). Due to the low number of fibers detected in the Virginia and South Africa sources, it was not possible to develop a fiber size distribution for these fibers. The LA fiber size data were plotted as a cumulative distribution frequency for fiber length, fiber width, and aspect ratio. These data were compared to LA fibers collected in Libby as part of EPA's ongoing ambient air monitoring program. The Libby ore and expanded material showed an increased frequency of longer and wider fibers than the fibers from the Libby ambient air sampling program. Aspect ratios were nearly identical. The differences between the length and width frequency were not outside of the expected range for LA fibers and were consistent with fiber size distributions for soil activity-based-sampling data from Libby.

Based on the TEM morphological analysis of filter grids, TEM/EDS analysis for the fiber mineralogy, and the fiber size distribution data, it can be concluded that the amphibole fibers detected in the Libby #3 ore samples from the Salt Lake Expansion facility are consistent with data from authentic Libby amphibole fibers (Meeker et al., 2003) found in Libby, Montana. Further, ore samples from Virginia and South Africa contained amphibole and chrysotile fibers but at a much lower frequency of detection than the Libby amphibole ore.

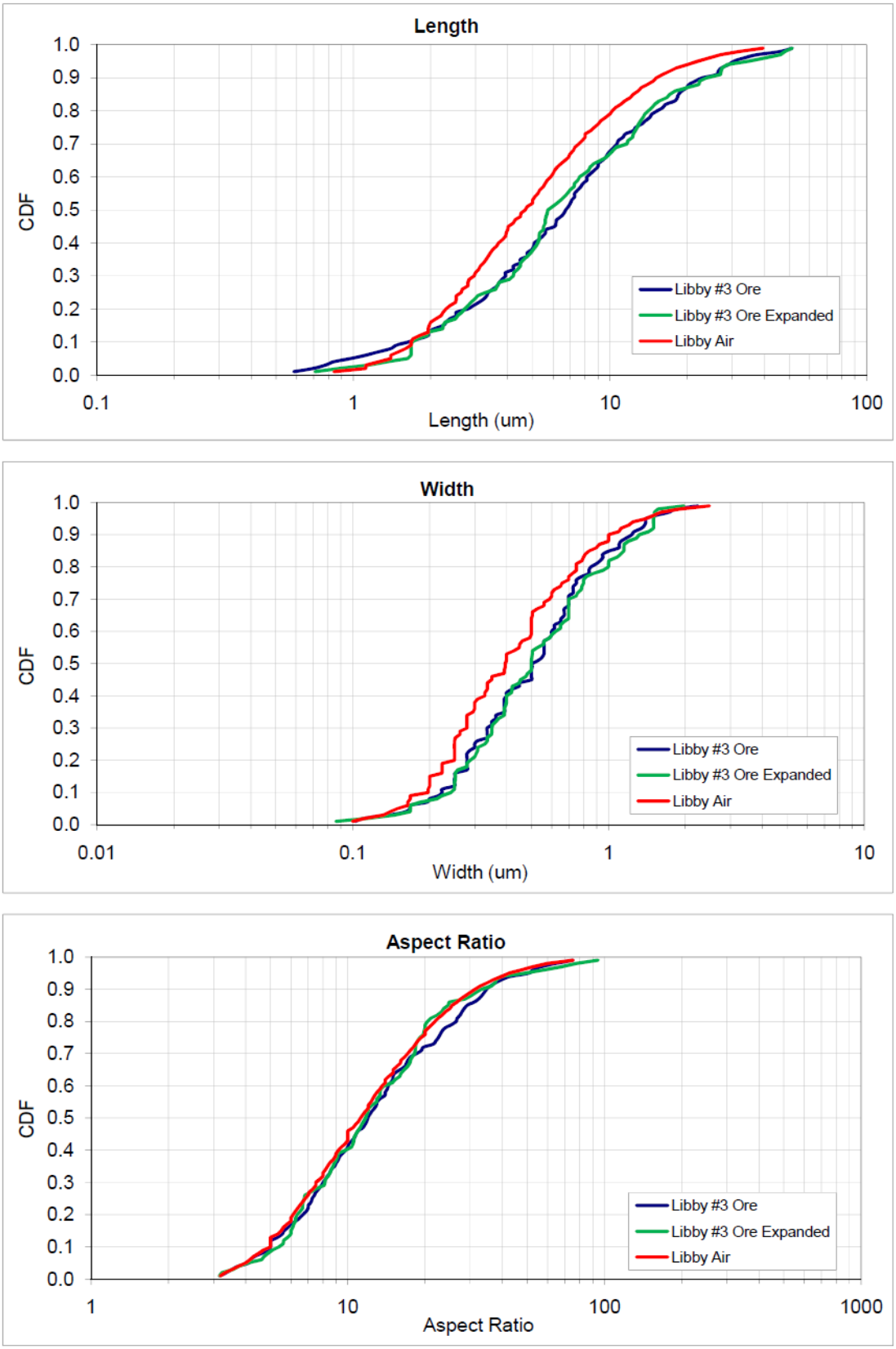

Figure C-2. Particle size distribution of LA amphiboles.

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APPENDIX D. ANALYSIS OF SUBCHRONIC- AND CHRONIC-DURATION STUDIES AND CANCER BIOASSAYS IN ANIMALS AND MECHANISTIC STUDIES

D.1. SUBCHRONIC- AND CHRONIC-DURATION STUDIES AND CANCER BIOASSAYS

D.2. INHALATION

Davis et al. (1985) performed a chronic-duration inhalation study examining response to tremolite asbestos. Specific-pathogen-free (SPF) male Wistar rats (n = 48) were exposed in a chamber to 10 mg/m^3 (~1,600 fibers/mL, >5 μm) of commercially mined tremolite (South Korea) for a total of 224 days (7 hours per day, 5 days per week) over a 12-month period. The tremolite sample contained approximately 50% fibers 10 to 100 μm long, using a fiber definition of length ≥5 μm, diameter ≤3 μm, and aspect ratio >3:1. The results of the inhalation study produced very high levels of pulmonary fibrosis, as well as 16 carcinomas and 2 mesotheliomas, among the 39 tremolite-exposed animals (see Tables D-1 and D-2). No pulmonary tumors were observed in the controls.

Although Davis et al. (1985) did not describe the chrysotile data, the difference between tremolite and chrysotile was stated to be statistically significant, with tremolite exposure inducing more fibrotic and carcinogenic lesions (see Table D-1). These results show that rats exposed to tremolite exhibited increased numbers of pulmonary lesions and tumors. Tumors observed in other organ systems are also listed in Table D-2 and appear to be unrelated to exposure. Although a method for an injection study is described in Davis et al. (1985), only the inhalation results are presented. The injection study referenced in Davis et al. (1985) may be the intraperitoneal injection experiments (Davis et al., 1991) using the same tremolite material.

Table D-1. Pulmonary fibrosis and irregular alveolar wall thickening produced by tremolite exposure

Time after start of exposure (number of rats examined)	12 mo (n = 3)	18 mo (n = 4)	27–29 mo (n = 12)
Peribronchiolar fibrosis (SD)[a]	23.0 (21.4–24.2)	13.4 (9.7–18.9)	–
Irregular alveolar wall thickening (SD)[b]	35.2 (27.7–41.0)	27.7 (20.8–35.4)	–
Interstitial fibrosis (SD)[b]	0	3.0 (0–5.6)	14.5 (3.8–26.9)

SD = standard deviation.
[a]Percentage of 100 squares counted in lung tissue area.
[b]Percentage of total lung tissue area.

Source: Adapted from Davis et al. (1985).

Table D-2. Tumors (benign and malignant) produced by tremolite exposure

Tumor site	Control (*n* = 36)	Tremolite (*n* = 39)
Pulmonary		
Adenomas	0	2
Adenocarcinomas	0	8
Squamous carcinomas	0	8
Mesotheliomas	0	2
Other organ systems		
Digestive/peritoneal	5	3
Urinogenital	3	1
Endocrine	3	5
Musculoskeletal, integumentary	5	5
Reticuloendothelial/vascular	20	15

Source: Adapted from Davis et al. (1985).

Wistar rats were exposed for 13 consecutive weeks (6 hours per day, 5 days per week) to either Calidria chrysotile asbestos or tremolite asbestos in a flow-past, nose-only inhalation study (Bernstein et al., 2003) (see Table D-3). The tremolite samples had fiber counts of 100 fibers/mL of fibers longer than 20 μm present in the exposure aerosol. Fibers were defined as any object with an aspect ratio >3:1, length ≥5 μm, and diameter ≤3 μm, and all other objects were considered nonfibrous particles. Counting was stopped when nonfibrous particle counts reached 30, and fiber counting was stopped at 500 with length ≥5 μm, diameter ≤3 μm; a total of 1,000 fibers and nonfibrous particles were recorded (Bernstein et al., 2003). Lung tissue and associated lymph nodes were examined by histopathology following tissue digestion. Associated lymph nodes showed erythrophagocytosis (minimal severity) in one animal at all-time points, compared to chrysotile and the control, which showed erythrophagocytosis (minimal severity) only at 180 days.

Table D-3. Chrysotile and tremolite fiber characteristics of fibers used in inhalation exposure studies in rats

Fiber type	Mean no. fibers evaluated	Mean no. total fibers/mL	Mean % total fibers, >20 µm length	Mean diameter µm ± SD	Mean length µm ± SD	Diameter range (µm)	Length range (µm)
Chrysotile	2,016	48,343.2	0.4	0.08 ± 0.07	3.61 ± 7.37	0.02−0.7	0.07−37.6
Tremolite	1,627	3,128.1	3.4	0.32 ± 3.52	5.49 ± 13.97	0.1−3.7	0.9−75

Source: Bernstein et al. (2003).

Table D-3 shows the comparison of number, concentration, and mean size distribution of fibers used in this study. Note that the mean tremolite fiber diameter and length are much greater than those of chrysotile, but the size ranges do overlap somewhat (Bernstein et al., 2003).

The long-term effects from the same exposure and counting methods discussed above were described in Bernstein et al. (2005), who present the full results through 1 year after cessation of tremolite exposure in Wistar rats (n = 56). The long tremolite fibers, once deposited in the lung, remain throughout the rat's lifetime. Even the shorter fibers, following early clearance, remain with no dissolution or additional removal. At 365 days postexposure, the mean lung burden was 0.5 million tremolite fibers >20 µm long and 7 million fibers 5−20 µm long with a total mean lung burden of 19.6 million tremolite fibers. The tremolite-exposed rats showed a pronounced inflammatory response in the lung as early as 1 day postexposure, with the rapid development of granulomas (1 day postexposure) followed by the development of pulmonary fibrosis characterized by collagen deposition within the granulomas. Increases in alveolar macrophages and granulomas were observed at all-time points (1, 2, 14, 90, and 180 days) measured except 365 days. Pulmonary fibrosis increased starting at 14 days and continued to be observed for up to 365 days. Slight interstitial fibrosis also was observed, but only at 90 and 180 days postexposure. This study demonstrates that tremolite exposure leads to pronounced inflammation and fibrosis (Bernstein et al., 2006). Tumors were not observed in this study, and is a consistent observation with the time frame observed in other studies (i.e., 1 year postexposure Smith, 1978).

D.2.1. Intratracheal Instillation

A study by Putnam et al. (2008) was designed to explore gene–environment interactions in the development of asbestos-related diseases. C57Bl/6 mice were exposed once via intratracheal instillation to Libby Amphibole asbestos (LAA)[3] (Six Mix; 100 µg), crocidolite

[3]The term "Libby Amphibole asbestos" is used in this document to identify the mixture of amphibole mineral fibers of varying elemental composition (e.g., winchite, richterite, tremolite, etc.) that have been identified in the Rainy Creek complex near Libby, MT. It is further described in Section 2.2.

(100 μg), or saline (30 μL). Characteristics of fibers are described in Table D-4. Animals were sacrificed, and the lungs were harvested 6 months postinstillation. The left lung was used for ribonucleic acid (RNA) isolation, and the right lung was used for histology (email from E. Putnam [University of Montana] to M. Gwinn [U.S. EPA] dated 02/26/09). Histology on mouse lungs from each treatment group demonstrated an increase in fibrosis, as viewed by Gomori's trichrome staining, following exposure to crocidolite and, to a lesser extent, LAA. Histologic tissue was also exposed to Lucifer Yellow stain to further analyze variability in collagen following exposure. Lucifer Yellow staining revealed an increase in collagen following exposure to both crocidolite and LAA, but only crocidolite exposure led to a statistically significant increase ($p < 0.05$). RNA was isolated from homogenized lungs and purified for use in microarray analysis. Pooled RNA samples from mice in each exposure group were analyzed on a 10K-element mouse oligonucleotide array (MWG Biotech), and expression was compared to a mouse reference standard RNA. Gene-expression results were analyzed by GO Miner, and genes exhibiting at least 1.25-fold upregulation or downregulation in treated lungs were described. These included genes involved in membrane transport, signal transduction, epidermal growth factor signaling, and calcium regulation for both crocidolite and LAA exposures, which support the increase in collagen observed above. Some limitations to this study are the use of a standard reference for gene-expression comparisons (as opposed to the saline controls), the practice of describing genes only if a greater than twofold difference in expression is observed and the use of pooled samples of homogenized whole lung that, in some cases, could dilute variability among different areas of exposed lung (different lobes, fibrotic versus nonfibrotic).

Table D-4. Fiber characteristics for intratracheal instillation studies in mice

Material	Diameter (μm)	Length (μm)	Aspect ratio
LAA (Six Mix)	0.61 ± 1.22	7.21 ± 7.01	22.52 ± 22.87
Crocidolite	0.16 ± 0.09	4.59 ± 4.22	34.05 ± 43.29

Source: Smartt et al. (2010); Blake et al. (2007); Blake et al. (2008); Putnam et al. (2008).

A follow-up paper to Putnam et al. (2008) prepared by Smartt et al. (2010) examined the increase of collagen in C57Bl/6 mouse lung following exposure to crocidolite or LAA. The paper also examined a few specific gene alterations by quantitative reverse transcription polymerase chain reaction (RT-PCR). Animals (n = 3 to 6 mice per group) were dosed with the same samples (see fiber characteristics in Table D-4) as described above (Putnam et al., 2008) but were euthanized at 1 week, 1 month, and 3 months postinstillation. Treated mice were then divided into two groups, with the left lung from the first group used for RNA isolation and the right lung used for histology. The lungs from the second group were used for protein isolation

and hydroxyproline assay (email from E. Putnam [University of Montana] to M. Gwinn [U.S. EPA] dated 02/26/09). Similar to results from Putnam et al. (2008), Gomori's staining demonstrated increased collagen and inflammation at the airways in lungs of mice exposed to either LAA or crocidolite. These results were similar following exposure to both amphiboles, with crocidolite effects appearing more severe at all-time points examined. No changes in the pleura of the lungs that were indicative of potential mesothelioma were observed; such changes, however, would not be expected in such a short time frame. This study also examined severity of inflammation and found that, on average, crocidolite-exposed animals demonstrated minimal inflammation at 1 week postinstillation, which then progressively worsened at 1 and 3 months postinstillation. Although both asbestos exposures led to increased inflammation, LAA exposure demonstrated minimal inflammation, which did not progress in the time points examined. Gene-expression alterations were measured by quantitative RT-PCR for genes involved in collagen accumulation and scar formation (*Col1A1*, *Col1A2*, and *Col3A1*). Although exposure to both forms of asbestos at 1 week and 1 month postinstillation led to increased Col gene expression, the levels and subtypes varied. LAA exposure led to increased gene expression of *Col1A2* at 1 week postinstillation and *Col3A1* at 1 month postexposure, while crocidolite led to no significant alterations in the expression of these genes. Both crocidolite and LAA exposure led to increased *Col1A1* gene expression as compared to the saline control at 1 week and 1 month postexposure. Due to these differences in expression, the authors also examined the collagen protein levels in the lungs to compare with the gene-expression changes. Total collagen content was determined by measuring the hydroxyproline content in the caudal aspect of the left lung. As compared to saline-exposed mice, a significant increase in hydroxyproline was observed at 1 week and 1 month following exposure to both crocidolite and LAA; however, only lungs from crocidolite-exposed animals demonstrated a significant increase at 3 months postexposure. These studies demonstrate that exposure to LAA lead to inflammation and fibrosis, although with differences in the time and level of response from those of crocidolite.

Shannahan et al. (2011a) exposed two rat models of human cardiovascular disease (CVD) to LAA[4] to determine if the preexisting CVD in these models would impact lung injury and inflammation following exposure. Healthy Wistar Kyoto (WKY) rats were compared to spontaneously hypertensive (SH) and spontaneously hypertensive heart failure (SHHF) rats following exposure. These rat models demonstrate pulmonary iron homeostasis dysregulation (Shannahan et al., 2010). All rats (male only) were exposed to 0, 0.25, or 1.0 mg/rat via intratracheal instillation and were examined at 1 day, 1 week, and 1 month postexposure. No changes were observed histopathologically, however, changes were observed in markers of homeostasis, inflammation, and oxidative stress. Bronchoalveolar lavage fluid (BALF) protein was significantly increased in both the SH and SHHF rat models as compared to controls as early

[4]Median fiber dimensions as determined by TEM: length = 3.59 µm; width = 0.23 µm; aspect ratio ≥5:1.

as 1 week postexposure. γ-Glutamyl transferase (GGT) activity was increased in a concentration-dependent manner with exposure to LAA at the earliest time point measured (1 day), and was more pronounced in WKY rats as compared to SH and SHHF rats. Lactate dehydrogenase (LDH) activity was also elevated in all strains but was more pronounced in the SHHF rat model. Neutrophil increases were observed following exposure in all strains, peaking at 1 day postexposure in all strains and persisting in the SH and SHHF rats until 1 month postexposure. Macrophages showed similar results but persisted only in the SH rat model until 1 month postexposure. In order to determine any impact of exposure on iron homeostasis, BALF ferritin and transferrin levels were measured in the lung. Increases in ferritin and transferrin were observed in both SH and SHHF rats as compared to WKY controls. Nonheme iron was also observed to be increased in only the SH rats at 1 day and 1 week postexposure. Markers of inflammation (macrophage inflammatory protein [MIP]-2) and oxidative stress (heme oxygenase-1 [HO-1]) were elevated in both SH and SHHF as compared to WKY rats at baseline, but limited exposure-related differences were observed. Limited changes were also observed in ascorbate and glutathione (GSH) levels in BALF and lung tissue. Inflammation and cell injury were observed in all strains (Shannahan et al., 2011a). In conclusion, this study showed the potential for population variability related to CVD in response to exposure to LAA, including markers of cellular injury, iron homeostasis, and inflammation.

Shannahan et al. (2011b) tested the hypothesis that LAA[5] will bind iron and increase the inflammogenic activity of fibers in vitro and acute lung injury and inflammation in vivo. The authors examined the ability of LAA to bind exogeneous iron in an acellular system and evaluated iron-related alterations in the production of reactive oxygen species (ROS). The authors also investigated the role of iron in the acute inflammogenic response in vitro, using human bronchiolar epithelial cells, and in vivo using SH rats by modulating fiber-associated iron concentrations. In a cell-free medium, LAA bound about 16 µg of iron/mg of fiber and increased ROS generation about threefold. Generation of ROS was reduced by treatment with deferoxamine (DEF), an iron chelator. To determine the role of iron in LAA ROS generation and inflammation, BEAS2B cells (bronchiolar epithelial cell line) were exposed to LAA (50 µg), iron-loaded LAA, or LAA treated with DEF. No conditions altered HO-1 or ferritin mRNA expression. LAA by itself markedly increased IL-8 gene expression, which was significantly reduced by iron-loaded LAA, but increased with LAA treated with DEF. To determine the role of iron in LAA-induced lung injury in vivo, spontaneously hypertensive rats were exposed intratracheally to either saline (300 µL), DEF (1 mg), ferric chloride (21 µg), LAA (0.5 mg), iron-loaded LAA (0.5 mg), or LAA plus DEF (0.5 mg). Neither ferric chloride nor DEF increased BALF neutrophils compared to saline at 24 hours after treatment. LAA exposure led to a statistically significant increase in BALF neutrophils ($p < 0.05$). Loading of iron on LAA,

[5]Median fiber dimensions as determined by TEM: length = 3.59 µm; width = 0.23 µm; aspect ratio ≥5:1.

but not chelation, slightly decreased inflammation (LAA + DEF > LAA > iron-loaded LAA). At 4 hours after exposure, LAA-exposed lung mRNA expression of MIP-2 was significantly reduced in rats exposed to iron-loaded LAA, but increased by DEF (LAA + DEF > LAA > iron-loaded LAA). Ferritin mRNA expression was elevated in rats exposed to iron-loaded LAA compared to the LAA control. HO-1 expression was unchanged following treatment with LAA. The study authors concluded that the acute inflammatory response following exposure to LAA might be modified by the fiber's ability to complex iron, rather than redox cycling of fiber-associated iron. The authors further concluded that iron overload conditions may influence susceptibility to LAA-induced pulmonary disease.

Shannahan et al. (2012a) identified a number of serum biomarkers in healthy and CVD rats following varying durations of exposure to LAA. These studies were conducted to determine if asbestos-exposed healthy rats presented with biomarkers upregulated to CVD rats. Rats were intratracheally instilled with 0, 0.25, 0.5, 1.0, or 5.0 mg in 300 μL. Four separate study designs were employed. In the first study, WKY (healthy), SH (CVD), and SHHF (CVD) rats were exposed to a single intratracheal instillation, and biomarkers were assessed 1 day and 3 months postexposure. In the second study, F344 rats were instilled once and samples were collected 3 months and 1 year postexposure. In the third study, F344 rats were instilled biweekly for 13 weeks and samples were collected 1 day and 2 weeks following the final instillation. In the fourth study, WKY rats were instilled weekly for 4 weeks and serum samples were analyzed 1 day and 1 month following the final instillation. Acute-phase response (APR) molecules that are involved in inflammatory responses such as α2-macroglobulin were upregulated 1 day after a single instillation of 1 mg LAA in WKY and SH rats. In addition, 5 mg LAA increased α2-macroglobulin 1 day and 2 weeks after the 13-week exposure. All other doses and exposure endpoints did not affect α2-macroglobulin. Another APR molecule, α1-acid glycoprotein, was increased in WKY, SH, and SHHF rats 1 day following a single instillation and 3 months postexposure in SH rats. In addition, α1-acid glycoprotein was also increased 1 day and 2 weeks after a 13-week exposure to 5.0 mg LAA in F344 rats. WKY rats also had non-dose-responsive increases in α1-acid glycoprotein 1 day after a 4-week exposure to 0.25 and 0.5 mg LAA. The metabolic molecule lipocalin-2 was increased 1 day after a single instillation in WKY, SH, and SHHF rats and 1 day and 1 month after a 4-week exposure. Biomarkers for cancer were largely unaffected by LAA exposure. An exception to this was at 1 day after a single instillation in WKY and SH rats, mesothelin was reduced in the serum. Altogether, the data suggest that the modification of biomarker expression generally occurs rapidly and returns to homeostatic levels 1 day after instillation, regardless of duration.

In another study, Shannahan et al. (2012c) conducted a series of experiments to determine the effect of LAA-induced pulmonary damage on the development of CVD, and to identify early markers of lung and CVD in asbestos-exposed individuals. Three separate study designs were utilized. In the first study, WKY, SH, and SHHF rats were instilled once with 0,

0.25, or 1 mg LAA and examined 1 day, 1 week, 1 month, and 3 months postexposure. In the second study, F344 rats were instilled once with 0, 0.15, 0.5, 1.5, or 5 mg LAA and examined 1 day, 3 days, 1 week, 2 weeks, 3 months, 1 year, and 2 years postexposure. In the third study, F344 rats were instilled biweekly for 13 weeks with 0, 0.15, 0.5, 1.5, or 5 mg LAA and examined 1 day, 2 weeks, and 2 years postexposure. WKY rats instilled with 1 mg LAA showed a decreased rate of ADP-induced aggregation after 1 week, 1 month, and 3 months of exposure. LAA at 1.5 and 5.0 mg increased platelet disaggregation 1 year postexposure in F344 rats. The matrix metalloproteinase TIMP-2 showed a dose-dependent increase at 3 months postexposure in F344 rats exposed to 0.25 and 1.0 mg LAA, but TIMP-2 was decreased in SH rats following exposure to 1.0 mg LAA. Endothelial nitric oxide synthase and endothelin receptor-A (both markers of vasoconstriction) were decreased and increased, respectively, in WKY rats at 1.0 mg LAA. No other dose-responsive effects were noted for other inflammatory or vasoconstriction markers. Altogether, these data suggest that LAA exposure may change the expression of some biomarkers in healthy rats to resemble expression levels of cardiovascular compromised rats.

The role of inflammasome activation and iron in the development of LAA-induced fibrosis was studied in Shannahan et al. (2012d). Male SH rats were instilled with a single exposure to 0 or 0.5 mg LAA, DEF, 21 μg $FeCl_3$, 0.5 mg LAA + 21 μg $FeCl_3$, or 0.5 mg LAA + 1 mg DEF. Tissues were collected 4 hours and 1 day postexposure. LAA instillation increased gene expression in the lung of the inflammasome-related molecules *cathepsin B, Nalp3, NF-kβ, apoptosis-associated speck-like protein containing a CARD (ASC), IL-1β,* and *IL-6* expression 4 hours postexposure. Lung tissue expression of inflammatory cytokines *CCL-7, Cox-2, CCL-2,* and *CXCL-3* was increased 4 hours following LAA exposure. Conversely, LAA exposure reduced *IL-4* and *CXCl-1* in the BALF. Finally, the ratio of *pERK/ERK*, which is an upstream activator of the inflammasome cascade, was increased in the lung of LAA-exposed rats 1 day postexposure. Rats treated with LAA + DEF or LAA + $FeCl_3$ had significantly different levels of *Cox-2* in the BALF and *IL-6* in lung tissue, but all other endpoints were not significantly different. These data suggest that the concentration of iron does not impact the activation of the inflammasome cascade and cytokines downstream of the pathway in LAA-exposed animals.

In another study examining the role of iron in lung disease, Shannahan et al. (2012b) evaluated the effect of Fe overload on LAA-induced lung injury in rats with CVD. WKY, SH, and SHHF male rats were instilled once with 0, 0.25, or 1.0 mg of LAA. Blood, BALF, and lung tissue were collected 1 week, 1 month, and 3 months postexposure. Gene array analysis demonstrated that LAA exposure upregulated inflammatory-related genes such as *NF-kβ* and cell cycle regulating genes such as *matrix metalloproteinase-9* in WKY rats but inhibited these same clusters of genes in SH and SHHF animals 3 months after instillation. Histological examination of lung sections observed greater Fe staining of macrophages in SHHF rats compared to WKY and SH rats at 1 and 3 months postexposure; however, no differences in the progression of

pulmonary fibrosis were noted among the three strains. Altogether, these data do not suggest that the iron overload conditions that are characteristic of the CVD strains amplify the pulmonary effects of LAA.

Padilla-Carlin et al. (2011) investigated pulmonary and histopathological changes in male F344 rats following exposure to LAA.[6] The rats were administered a single dose of saline, amosite (AM), (0.65 mg/rat), or LAA (0.65 or 6.5 mg/rat) by intratracheal instillation. At time from 1 day to 3 months after exposure, bronchoalveolar lavage (BAL) was performed and the right and left lung was removed for Rt−PCR and histopathological analysis, respectively. The results showed that amosite exposure (0.65 mg/rat) resulted in a higher degree of pulmonary injury, inflammation, and fibrotic events than the same mass dose of LAA. Both amosite and LAA resulted in higher levels of cellular permeability and injury, inflammatory enzymes, and iron-binding protein in both BALF and lung tissue compared to saline controls. In addition, histopathological examination showed notable thickening of interstitial areas surrounding the alveolar and terminal bronchioles in response to amosite and LAA. However, mRNA levels for some growth factors (e.g., PDGF-A and TGF-1β), which contribute to fibrosis, were downregulated at several time points. The authors concluded from this study that on a mass basis, amosite produced greater acute and persistent lung injury.

In a continuation of the previous study, Cyphert et al. (2012b) compared the long-term lung effects of LAA with amosite asbestos in the F344 rat. Male F344 rats were intratracheally instilled with 0.65 or 6.5 mg LAA or 0.65 mg amosite in a single dose and monitored for 2 years. At 2 years postexposure, there was a trend of increased collagen gene expression, a marker for fibrosis, in all asbestos-exposed animals, but only the 0.65 mg dose of LAA reached statistical significance. Mesothelioma markers, mesothelin (Msln) and Wilms' tumor gene (WT1), were similarly increased in the lung at 1 year and 1 and 2 years postexposure to the low dose of LAA, respectively. Epidermal growth factor receptor (EGFR) was increased in the lung at both doses of LAA 2 years after instillation. Histological analysis noted a time-dependent and dose-responsive increase in fibrosis scarring in LAA-exposed rats, but inflammation scoring did not consistently induce dose-responsive or time-dependent increases in LAA-treated animals. Fibrosis was significantly greater in the amosite-exposed animals at both 1 and 2 years postinstillation. The data do not suggest that LAA induces significantly different types of effects on carcinogenic, inflammatory, or fibrotic markers compared to amosite.

In another study establishing the pulmonary effects of different asbestos fibers, Cyphert et al. (2012a) compared the effects of LAA with chrysotile and tremolite fibers on pulmonary function in male F344 rats. Animals (eight/group) were treated with a single intratracheal instillation of LAA (0.5 mg or 1.5 mg/rat), tremolite (0.5 mg or 1.5 mg/rat), and chrysotile (0.5 mg or 1.5 mg/rat), and several markers of lung inflammation and injury were examined

[6]Median fiber dimensions as determined by TEM: length = 3.59 μm; width = 0.23 μm; aspect ratio ≥5.

1 day and 3 months postexposure. After both, 1 day and 3 month exposures, both doses of LAA exposure significantly increased the number of neutrophils in the BALF and biomarkers of lung injury such as total protein, albumin, and LDH, relative to the control; however, the lung alterations after 3-month exposures were greatly reduced relative to the 1-day data. Minimal and mild levels of fibrosis were observed in the lung histopathology after 3 months in the low- and high-dose levels of LAA. Relative to other fibers tested in these series of experiments, the LAA fibers induced less fibrosis than the chrysotile fibers but were more pathogenic than the tremolite sample. The study concluded that the severity of fibrosis is correlated to the length and aspect ratio of the fibers.

In an early study, Sahu et al. (1975) described histological changes in the lungs of mice exposed individually to amosite, anthophyllite, and tremolite. Fibers were described only as <30-μm long. Groups of 20 male albino Swiss mice were exposed to amosite, anthophyllite, and tremolite at a single dose of 5 mg, and two animals from each group were sacrificed at 1, 2, 7, 15, 30, 60, 90, 120, and 150 days postexposure. Microscopic results following exposure to tremolite showed acute inflammation of the lungs at 7 days postexposure, including macrophage proliferation and phagocytosis similar to that observed with amosite and anthophyllite. Limited progression of fibrotic response was observed at 60 and 90 days postexposure, with no further progression of fibrotic response.

Blake et al. (2008) and Pfau et al. (2008) examined the role of amphibole asbestos in autoimmunity with both in vitro and in vivo assays. Blake et al. (2008) performed in vitro assays with LAA, and both studies performed the in vivo assays with tremolite. C57BL/6 mice were instilled intratracheally for a total of two doses each of 60 μg saline and wollastonite or Korean tremolite sonicated in sterile phosphate buffered saline (PBS), given 1 week apart in the first 2 weeks of a 7-month experiment. Detailed fiber characteristics were described in Blake et al. (2007) for wollastonite and LAA, but not for Korean tremolite (see Table D-4; wollastonite and Korean tremolite not shown).

Blake et al. (2008) described autoantibody production following exposure to wollastonite or tremolite, monitored biweekly with blood samples from saphenous vein bleeds and then by cardiac puncture following euthanization. Specific autoantibodies were identified by immunoblotting with known nuclear antigens. These autoantibodies were then incubated with murine macrophage cells previously exposed to LAA, wollastonite, or vehicle control (binding buffer containing 0.01 M HEPES, 0.14 M NaCl and 2.5 mM $CaCl_2$). Only sera from mice exposed to tremolite showed antibody binding colocalized with SSA/Ro52 on the surface of apoptotic blebs (Blake et al., 2008).

In Pfau et al. (2008), serum and urine samples were collected and checked for protein biweekly for 7 months following exposure to wollastonite or tremolite. By 26 weeks, the tremolite-exposed animals had a significantly higher frequency of positive antinuclear antibody tests compared to wollastinate and saline. Most of the tests were positive for dsDNA and

SSA/Ro52. Serum isotyping showed no major changes in immunoglobulin subclasses (IgG, IgA, IgM), but serum IgG in tremolite-exposed mice decreased overall. Furthermore, IgG immune complex deposition in the kidneys increased, with abnormalities suggestive of glomerulonephritis. No increased proteinuria was observed during the course of the study. Local immunologic response was further studied on the cervical lymph nodes. Although total cell numbers and lymph-node size were significantly increased following exposure to tremolite, percentages of T- and B-cells did not significantly change. Because tremolite is part of the makeup of LAA (6%), using tremolite-exposed mice might yield a similar response to LAA-exposed mice. This same effect has been demonstrated following exposure to ultraviolet radiation in skin cells, suggesting a similar mechanism (Saegusa et al., 2002).

Salazar et al. (2013; 2012) conducted a series of studies to establish the effects of LAA exposure on autoimmune disease. The first set of studies utilized the collagen-induced arthritis (CIA) and peptidoglycan-polysaccharide (PG-PS) models of rheumatoid arthritis to determine whether LAA exposure increased the onset, or prolonged or intensified, the joint inflammation characteristic of the disease (Salazar et al., 2012). Female Lewis rats were instilled biweekly for 13 weeks with a total dose of 0, 0.15, 0.5, 1.5, and 5.0 mg LAA followed by induction with either model of arthritis. LAA at 5.0 mg reduced the magnitude of the swelling response in the cell-mediated PG-PS model; however, neither the onset nor the duration of swelling was affected by LAA exposure. LAA at 1.5 and 5.0 mg and amosite at 0.5 and 1.5 mg reduced total serum IgM. LAA at 5.0 mg and amosite at 1.5 mg reduced anti-PG-PS IgG in the serum 17 weeks after the final instillation. Finally, the number of rats positive for antinuclear antibodies (ANA) was increased only at the low exposure concentrations of LAA in PG-PS-treated and nonarthritic rats. These results suggest that LAA may have a modest inhibitory effect on the PG-PS rat model but may enhance responses to other systemic autoimmune diseases (SAID).

In a follow-up study, Salazar et al. (2013) explored in greater detail the effect of LAA exposure on ANA over time and the antigen specificity of the ANA. Female Lewis rats were intratracheally instilled under the conditions in the previous study (described above). Serum samples were analyzed every 4 weeks from the beginning of the instillations up to termination at Week 28. Because elevated ANA are commonly associated with kidney disease, proteinuria was assessed every 3 weeks beginning at Week 6 until termination of the experiment. Histopathological analysis was also performed on the kidneys. ANA were increased 8 weeks postexposure to LAA at 5.0 mg. By Week 28, all doses of LAA except 1.5 mg increased ANA in the serum. Analysis of the antigen specificity found that only the LAA at 1.5 mg significantly increased antibodies specific for extractable nuclear antigens (ENA) and the Jo-1 antigen. Urinalysis found that all doses of LAA exposure induced moderate levels of proteinuria, but this effect was not dose responsive. No dose-related histopathological effects were observed. Altogether, these data suggest that LAA exposure increases autoimmune antibodies in the serum but that no evidence of autoimmune disease is identifiable. However, the lack of SAID in the

Lewis rat may be due to strain-specific factors, suggesting that other animal models may be more appropriate for studying the autoimmune effects of LAA.

D.2.2. Injection/Implantation

LVG:LAK hamsters were intrapleurally injected with tremolite obtained from the Libby, MT, mine in an unpublished study by Smith (1978) prepared for W.R. Grace and Company. These samples were identified as tremolite (22260p5; Sample 60) and 50% tremolite + 50% vermiculite (22263p2, Sample 63). Both fiber samples were measured by optical phase microscopy, and fibers were described as amorphous, irregularly shaped particles of about 5−15 μm diameter, with Sample 60 (tremolite) also containing the occasional fiber up to 30 μm long. Fiber size for Sample 60 (tremolite) was also measured by scanning electron microscopy (SEM) and determined to have a geometric mean length of 2.07 μm, a geometric mean diameter of 0.2 μm, and an average aspect ratio of 10.36:1. Twenty-five milligrams of each of the two samples were individually injected intrapleurally in LVG:LAK hamsters. Pathology was examined at approximately 3 months postexposure in 10 animals from each group, with the remaining animals observed until death, or 600 days postexposure, depending on the health of the animal. Average survivorships were 410, 445, and 421 days in groups exposed to Sample 60, Sample 63, and saline, respectively (see Table D-5). Pleural fibrosis was observed 3 months postexposure, and mesothelioma was observed in both treatment groups between 350 and 600 days postexposure, with no mesotheliomas in control groups.

Table D-5. Pleural adhesions and tumors following intrapleural injection exposure in LVG:LAK hamsters (25 mg)

Endpoint	Control	Sample 60 (tremolite)	Sample 63 (tremolite and vermiculite)
Average adhesion rating[a,b]	0 (*n* = 10)	3.3 (*n* = 10)	3.6 (*n* = 10)
Total tumors/animals[c]	8/59	8/58	16/61
Benign	3/59	2/58	5/61
Malignant	5/59	6/58	9/61
Mesothelioma	0/59	5/58	5/61

[a]As analyzed in first group sacrificed (between 41 and 92 days postexposure).
[b]Rating for pleural adhesions: 0 = no adhesions; 1 = minimal adhesions; 4 = extensive adhesions.
[c]These include adrenal adenoma, adrenal adenocarcinoma, lymphoma, pulmonary adenocarcinoma, adrenal and salivary carcinoma, mesothelioma, rhabdomyosarcoma, hepatoma, thyroid carcinoma, subcutaneous carcinoma, and malignant melanoma.

Source: Smith (1978).

A subsequent study (Smith et al. (1979)) was designed to determine whether mesothelioma is a nonspecific result of mesothelial cells trapped in fibrous pleural adhesions, occurring regardless of fiber type. Earlier studies by this group suggested that fibrosis and tumors resulting from fiber exposure (chrysotile or glass) were related to fiber dimensions (>20-μm long, >0.75 μm in diameter) (Smith and Hubert, 1974). Injected fibrous talc (FD-14) was used as a negative control in earlier studies and led to limited fibrosis and no tumor formation. The characteristics of the FD-14 sample are described in the proceedings of Smith and Hubert (1974). No further information could be found on the characteristics of the samples used in this study.[7] Because the talc contained 50% tremolite, 35% talc, 10% antigorite, and 5% chlorite, it was considered a tremolite sample by Smith (1978). When the sample was later analyzed independently by Wylie et al. (1993), only 64 (12.8%) of 500 tremolite particles measured met the National Institute for Occupational Safety and Health definition of a fiber (≥3:1 aspect ratio). Wylie et al. (1993) note, however, the sample consisted of very long fibers of the mineral talc, with narrow widths and a fibrillar structure. A second tremolite sample (Sample 275) used by Smith et al. (1979) was described as similar to FD-14, although no details were given. The last two samples were prepared from a deposit of tremolitic talc from the western United States (Sample 31) and from a specimen of asbestiform tremolite (Sample 72).[8]

Each of the four samples was examined microscopically, although the data were not reported in the paper by Smith et al. (1979). The average fibers in Sample 72 were long, thin, crystalline fibers (>20 μm long, 0.4 μm in diameter). Sample 31 appeared to have fewer long, thin fibers than Sample 72, and many of the fibers in this sample were acicular. The characteristics of the FD-14 sample were determined by phase microscopy (Smith and Hubert, 1974), but no characterization method was reported for the other three samples in this study. Other samples used by this group have been analyzed by both optical and electron microscopy (Smith, 1978; Smith and Hubert, 1974). The limited information on the fiber characteristics of the samples used in these studies is provided in Table D-6. Note that no information was provided confirming the presence or absence of particles or fibers less than 5 μm in length in any of the three papers by Smith and Hubert (1974) or Smith et al. (1979) and Smith (1978). These data deficiencies limit the interpretation of results from this study.

[7]This fiber is also analyzed in Wylie et al. (1993) and Stanton et al. (1981).

[8]Although the source of this material is not reported, these studies parallel those in the unpublished study performed by Smith et al. (1979) for W.R. Grace that used material from Libby, MT. Whether Sample 72 is material from Libby, MT, or another location is unknown.

Table D-6. Fiber characteristics and numbers of resulting tumors following intrapleural injection of 10 or 25 mg fiber samples into LVG:LAK hamsters

Sample	Average length[a] µm	Average diameter[a] (µm)	Tumors/survivors at 10 mg[b]			Tumors/survivors at 25 mg[b]		
			350 d	500 d	600 d	350 d	500 d	600 d
FD-14	5.7	1.6	N/D	N/D	N/D	0/35	0/26	0/20
275	N/D	N/D	0/34	0/14	0/6	0/31	0/15	0/3
31	>20	<0.4	1/41	1/19	1/11	2/28	4/9	6/5
72	>20	<0.4	0/13	1/6	3/2	3/20	5/6	5/1

N/D = not described.
[a]Although average length and diameter are reported, what range of fibers was counted is unclear. Smith (1978) (unpublished) states that only fibers greater than 5 µm long are included. No other information is provided for these samples.
[b]Numerator = cumulative number of animals with tumors; denominator = number of survivors.

Source: Smith et al. (1979); Smith (1978); Smith and Hubert (1974).

Following analysis of LVG:LAK intrapleurally injected with 10 or 25 mg of each of the four samples of tremolite, Smith (1978) reported tumors at 350 days postexposure (25 mg) and 600 days postexposure (10 mg) for Samples 31 and 72 (see Table D-6). Although the number of animals was not provided by Smith et al. (1979), previous studies by these authors reported using 50 animals per exposure group (Smith, 1978; Smith and Hubert, 1974). The results in Table D-6 present the cumulative number of tumors (numerator) at each time point analyzed over the remaining survivors (denominator). The survival rate without tumor presentation was decreased for animals exposed to Samples 72, 31, and 275. Smith et al. (1979) concluded that the FD-14 and 275 samples were noncarcinogenic, and Sample 31 was less carcinogenic than Sample 72. Hamsters exposed to Sample 72 had extensive pleural fibrosis, which was observed to a lesser degree in hamsters exposed to the other samples (Sample 72 > Sample 31 > Sample 275 = FD-14). No statistical information was reported for these results, and because the number of background tumors in control animals was not provided, no statistical analysis can be performed.

Both studies demonstrate that intrapleural injections of amphibole asbestos (tremolite or LAA[9]) lead to an increase in pleural fibrosis and mesothelioma in hamsters compared to controls or animals injected with less fibrous materials. The use of doses of equal mass for both studies makes it difficult to compare potency among samples, as each sample could have vastly different fiber number and total surface area. Although these studies clearly show the carcinogenic potential of LAA fibers, intrapleural injections bypass the clearance and dissolution of fibers from the lung after inhalation exposures.

[9]Assuming Smith et al. (1979) used LAA.

Stanton et al. (1981) also examined tremolite and describe a series of studies on various forms of asbestos. Fibers embedded in hardened gelatin were placed against the lung pleura. As an intrapleural exposure, results might not be comparable to inhalation exposures because the dynamics of fiber deposition and pulmonary clearance mechanisms are not accounted for in the study design. Studies using two tremolite asbestos samples from the same lot were described as being in the optimal size range (>8 μm long and <0.25 μm in diameter) for carcinogenesis; the fibers were distinctly smaller in diameter than the tremolite fibers used by Smith et al. (1979). Exposure to each of the two tremolite samples led to mesotheliomas in 21 and 22 of 28 rats exposed. The Stanton et al. (1981) study also used talc, which did not lead to mesothelioma production. This talc was found to be the same as that used by Smith et al. (1979) and later by Wylie et al. (1993). Wylie et al. (1993) stated that, although the two tremolites were consistent by size with commercial amphibole asbestos, the talc used contained fibers that were much thinner and shorter, which is not typical of prismatic tremolite fibers.

Wagner et al. (1982) examined three types of tremolite (California talc, Greenland, and Korea) using SPF Sprague-Dawley (n = 48) and Wistar (n = 32) rats, then followed up with a range of in vitro tests using the same fiber samples. Rats were injected intrapleurally (20 mg tremolite) at 8−10 weeks of age and allowed to live out their lives. Median survival times after injections were 644 days (California talc), 549 days (Greenland tremolite), and 557 days (Korean tremolite). Positive controls had a decreased survival time due to an infection, which limits the interpretation of these data. Also, this study was performed separately using different rat strains for the three tremolite samples. The authors state that, although the decreased control survival time and use of different rat strains limit the usefulness of the study for quantitative analysis, the results can be described qualitatively. Of the three tremolites, only the Korean tremolite showed carcinogenic activity producing mesothelioma (14/47 rats, 30%). Analysis of the fiber characteristics showed the Korean sample had fibers that were longer than 8 μm and a diameter of less than 1.5 μm. The California talc and Greenland tremolite had little to no fibers in this size range (see Table D-7). Follow-up in vitro assays in the sample publication (Wagner et al., 1982) confirmed the in vivo results, with the exposure to Korean tremolite resulting in increased LDH and β-glucuronidase (BGL) release, cytotoxicity, and giant-cell stimulation.

Table D-7. Fiber characteristics of three tremolite samples analyzed by in vivo and in vitro methods (TEM measurements)

Sample	Location	Fiber type	Length µm	Diameter µm	No. of nonfibrous particles ($\times 10^4$)	Total no. of fibers ($\times 10^4$)	No. of fibers >8 µm long ($\times 10^3$) <1.5 µm diameter
A	California	Flake-like material	<6	<0.8	6.9	5.1	1.7
B	Greenland	Medium-sized fibrous material	<3	<1.2	20.7	4.8	0
C	Korea	Fine-fiber material	>8	<1.5	3.3	15.5	56.1

TEM = transmission electron microscopy.

Source: Wagner et al. (1982).

Davis et al. (1991) examined six tremolites with differing morphologies through intraperitoneal injections with male SPF Wistar rats. Four of the tremolites were from Jamestown, California; Korea; Wales; and Italy; and two were from Scotland (Carr Brae and Shinness). Of these, the three from California, Korea, and Wales were asbestiform, and the other three were fiber bundles or prismatic (see Table D-8). Rats were exposed (n = 33 or 36) with one intraperitoneal injection with samples that were 10 mg/2 mL-sterile PBS. Animals were allowed to live out their full life spans or until signs of debility or tumor formation developed. Although exposure was performed based on sample weight, each sample was analyzed to determine the number of expected fibers per milligram and, therefore, per exposure. These samples also were characterized further by counting fibers versus particles. Data were collected for all fibers (aspect ratio >3:1) and particles (aspect ratio <3:1) of total fibers. A fiber was defined as any component ≥8-µm long and <0.25 µm in diameter as measured by SEM (i.e., Stanton fibers).

Table D-8. Fiber characteristics in a 10-mg dose (as numbers of fibers)

Sample	No. of animals	No. of mesotheliomas	No. of fibers in 1 mg of injected dust ($\times 10^5$)	No. of fibers ≥8 µm long, <0.25 µm diameter[a] ($\times 10^5$)	No. of particles in 1 mg injected dust ($\times 10^5$)	Morphology
California	36	36	13,430	121	18,375	Asbestiform
Wales	36	35	2,104	8	4,292	Asbestiform
Korea	33	32	7,791	48	13,435	Asbestiform
Italy	36	24	1,293	1	20,137	Fiber bundles
Carr Brae	33	4	899	0	9,490	Fiber bundles
Shinness	36	2	383	0	5,901	Prismatic

[a]Stanton fibers.

Source: Davis et al. (1991).

The authors' overall conclusions were that all materials studied could cause mesothelioma by this method of exposure, and the number of Stanton fibers was not sufficient to explain the differences in response. Mesothelioma incidence was not correlated to Stanton fibers, total particles, or mass of dust. The best predictor of mesothelioma incidence was total fibers (see Table D-8). Although three samples were considered asbestiform (California, Wales [Swansea], Korea), all samples had <1% of counted fibers defined as Stanton fibers. The highest mesothelioma incidence was observed for the California sample, which contained the most Stanton fibers (121 fibers per mg dust). The tremolite from Wales, resulted in 97% mesothelioma incidence yet contained only eight Stanton fibers per milligram (more than 90% less than in the California sample). In contrast, the Italy tremolite, although containing only 0.08% Stanton fibers, resulted in 67% mesothelioma incidence. Little is known, however, about the characteristics of particles or fibers <5 µm long. This study highlights two issues associated with all fiber studies: the limits of analytical techniques and the variability in response based on the metric used to measure exposure. This study also supports the premise that asbestos samples containing fibers that are not long and thin can be carcinogenic.

The Roller et al. (1996) study was designed to provide data on the dose-response of various fiber types in relation to their fiber dimensions (as measured by SEM). Fibers were defined in this study as having an aspect ratio of greater than 5:1 for all lengths and widths. Female Wistar rats (n = 40) were given either one intraperitoneal injection of 3.3 mg or 15 mg of tremolite. Rats were examined for tumors in the abdominal cavity following a lifetime (up to 30 months) of observation. This paper described the fiber dimensions in depth (see Table D-9), while limited discussion focused on the exposure results. This table shows the characteristics of the fibers sorted first by aspect ratio and diameter, and the fiber size distribution binned by the

length and diameter for those fibers with a length >5 µm. Results were described in this study in a table as "positive rats" being those with histologically confirmed mesothelioma or macroscopically supposed mesothelioma. No information was provided on how these determinations were made. Exposure to 3.3 mg and 15 mg tremolite resulted in 9 mesotheliomas in 29 animals (64 weeks postexposure) and 30 mesotheliomas in 37 animals (42 weeks postexposure), respectively. This study demonstrates that intraperitoneal injection of tremolite led to mesothelioma in Wistar rats. Analysis of other tissues was not described.

Table D-9. Characteristics of tremolite fibers intraperitoneally injected into Wistar rats

Fiber number per ng dust and mass fraction (%)												
Aspect ratio (L/D) >5/1; D <2 µm (Roller et al., 1996 study)							**Aspect ratio (L/D) <3/1; D <3 µm (WHO, 1985 as reported in Roller et al., 1996)**					
Length:	>5 µm		>10 µm		>20 µm		Diameter:	>5 µm		>10 µm		>20 µm	
	No.	% Mass	No.	% Mass	No.	% Mass		No.	% Mass	No.	% Mass	No.	% Mass
	17.4	32	6.9	27	1.9	18		18.4	43	7.0	35	2.0	26

Fiber-size distribution for aspect ratio (L/D) >3/1 (all lengths, all diameters; SEM)								
% Total fibers L >5 µm	Length (µm)				Diameter (µm)			
	10% <	50% <	90% <	99% <	10% <	50% <	90% <	99% <
22%	0.8	2.4	9.2	29.4	0.14	0.27	0.67	1.49

SEM = scanning transmission microscopy.

Source: Roller et al. (1996).

D.2.3. Oral

McConnell et al. (1983) describe part of a National Toxicology Program study (NTP, 1990a, b, 1988, 1985) that was conducted to evaluate the toxicity and carcinogenicity of ingestion of several minerals. This study examined chrysotile and amosite in both hamsters and rats, and crocidolite and tremolite only in rats. This chronic bioassay was designed to encompass the lifetime of the animal, including exposure of the dams from which the test animals were derived. Although the study examined chrysotile, amosite, crocidolite, and tremolite, for the purposes of this assessment, the focus is on the results from exposure to tremolite. The tremolite (Gouverneur Talc Co., Gouverneur, NY) used was not fibrous. Instead, the material was crystalline, as this form was a common contaminant in talc at the time of these studies (McConnell et al., 1983) (see Table D-10). Citing the Stanton et al. (1981) paper, McConnell et al. (1983) stated that crystalline tremolite can become fibrous upon grinding. Tremolite was

incorporated by 1% weight into NIH-31 feed and given to 250 male and female F344 rats from birth until death (118 male and female controls).

Table D-10. Fiber characteristics and distribution of tremolite fibers analyzed in feed studies in F344 rats

Characteristic	Length interval[a]			
	<3 µm	≥3 µm, <5 µm	≥5 µm, <10 µm	≥10 µm
Mean width	0.77	1.78	2.87	5.22
Tremolite particles	120	61	17	49
% of Tremolite particles	19.4	9.85	3	8

[a]Average groups, more detailed in primary paper.

Source: McConnell et al. (1983).

No significant tumor induction was observed in the animals with oral exposure to tremolite. Although nonneoplastic lesions were observed in many of the aging rats, these were mostly in the stomach and occurred in both controls and exposed animals. The lesions included chronic inflammation, ulceration, and necrosis of the stomach (McConnell et al., 1983). McConnell et al. (1983) suggested that nonfibrous tremolite could account for the lack of toxicity following exposure in this group of animals. Also, oral studies of asbestos generally show decreased toxicity and carcinogenicity as compared to inhalation and implantation/injection studies.

D.3. MECHANISTIC DATA AND OTHER STUDIES IN SUPPORT OF THE MODE OF ACTION

D.3.1. In Vitro Studies—LAA

Hamilton et al. (2004) examined the potential for fibers, including LAA, to modify the function of antigen-presenting cells (APC). Analysis was performed at 24 hours with two forms of asbestos (crocidolite [25 or 50 µg/mL] and LAA obtained from Site No. 30, Libby, MT [25 or 50 µg/mL]) and ultrafine particulate matter ($PM_{2.5}$ [particulate matter 2.5 microns in diameter or less] [50 or 100 µg/mL]). Limited information is provided by Hamilton et al. (2004) on fiber characteristics. Samples from Site No. 30, however, are described as predominantly richterite and winchite by Meeker et al. (2003). Primary human alveolar macrophages were incubated for 24 hours with LAA (25 or 50 µg/mL), crocidolite (25 or 50 µg/mL), or ultrafine particulate matter (50 or 100 µg/mL). Following incubation, cells were isolated from remaining particles and nonviable cells, after which 0.25 × 106 macrophages were cocultured with autologous lymphocytes (1×10^6 cells) in an 11-day APC assay. This assay analyzes the antigen-presenting

function of the pretreated macrophages by stimulating the lymphocytes using tetanus toxoid as the antigen. The supernatant was assayed for cytokines on Day 11, and Hamilton et al. (2004) found that pretreatment with either asbestos or $PM_{2.5}$ significantly upregulated both Th1 and Th2 cytokines (interferon gamma [IFNγ]; interleukin-4 [IL-4]; and interleukin-13 [IL-13]) ($p < 0.05$). Therefore, preexposure to either fibers or particles increased APC function, as reflected in increased cytokine release after tetanus challenge. No significant differences, however, were discernable between asbestos and $PM_{2.5}$ pretreatment. The authors speculated that the variability in response among samples assayed—presumably due to the use of primary cells—obscures statistical significance. This study supports a role for fibers and $PM_{2.5}$ in potentiating immune response, although the specific role may be unclear as many agents can activate macrophages prior to antigen challenge.

Recent studies (Blake et al., 2008; Blake et al., 2007) compared the response of murine macrophages (primary and cell line RAW264.7) to LAA fibers and crocidolite asbestos fibers. The LAA fibers (7.21 ± 7.01 μm long, 0.61 ± 1.22 μm in diameter) used in these studies were obtained from the U.S. Geological Survey and were chemically representative of the Libby, MT, mine (Meeker et al., 2003). The crocidolite fibers (4.59 ± 4.22 μm long, 0.16 ± 0.09 μm in diameter) used in these studies were provided by Research Triangle Institute, NC, and the noncytotoxic control fiber (wollastonite, 4.46 ± 5.53 μm long, 0.75 ± 1.02 μm in diameter) was provided by NYCO Minerals, NY. Cells were exposed for 24 hours to fiber samples measured by relative mass (5 $\mu g/cm^2$), after which the cells were analyzed by transmission electron microscopy (TEM) to measure internalization. The results of the first study (Blake et al., 2007) indicate that LAA fibers can both attach to the plasma membrane and be internalized by macrophages, similar to the crocidolite fibers. These internalized fibers were primarily less than 2 μm long and were found localized in the cytoplasm, in cytoplasmic vacuoles, and near the nucleus following 3-hour exposure at a concentration of 62.5 $\mu g/cm^2$. This same concentration was selected for the remaining studies because it did not decrease cell viability for the LAA (92%). Cell viability was decreased for crocidolite (62%), however, at this concentration. As a result, the remaining assays would be expected to have decreased viability following exposure to crocidolite, which may impact the levels of various responses. For example, the ROS measurement would increase with increased cell number; therefore, some of the quantitative results would be difficult to compare among fiber types unless normalized to cell number.

Oxidative stress was measured by the induction of ROS and the reduction in GSH levels. These two measurements generally complement each other, as GSH is used to maintain intracellular redox balance in cells in response to increased ROS levels. Both LAA and crocidolite fiber internalization generated a significant increase ($p < 0.05$) in intracellular ROS as quantified by the oxidation of 2,7-dichlorodihydrofluorescein to dichlorofluorescein with hourly readings on a fluorescent plate reader. LAA exposure significantly increased ROS in a dose-dependent manner (6.25, 32.5, and 62.5 $\mu g/cm^2$) as early as 1 hour postexposure at the

highest dose ($p < 0.05$) as compared to a no-treatment group. Only the highest concentration of crocidolite was tested. The lower concentrations of LAA were not compared to crocidolite and wollastonite, but a comparison of the highest exposure concentrations (62.5 μg/cm^2) of LAA, crocidolite, and wollastonite revealed greater ROS production following LAA exposure (1 hour, $p < 0.05$). Blake et al. (2007) stated that similar results were seen in the primary cell line but did not report the data. To differentiate the type of ROS produced, dehydroergosterol fluorescence intensity levels were used, revealing that superoxide anion was significantly increased following exposure to LAA as compared to controls. This observation was further confirmed with the use of a free radical scavenger (PEG-SOD [polyethylene glycol-superoxide dismutase]) specific to superoxide anion. This coexposure of LAA and PEG-SOD led to a significant decrease in ROS as compared to cells exposed only to LAA ($p < 0.05$). Total intracellular superoxide dismutase (SOD) activity was also measured following exposure to LAA and showed a decrease in activity at 3 hours postexposure as compared to controls ($p < 0.05$). Crocidolite appears to increase intracellular SOD activity at 24 hours postexposure. These three assays demonstrate that LAA exposure leads to increased superoxide anion in macrophages, most likely by suppressing activity of intracellular SOD.

GSH levels were found to be decreased in response to LAA and crocidolite exposure in the macrophage cell line as compared to unexposed cells ($p < 0.05$). The decreased GSH levels were more prominent following crocidolite exposure as compared to LAA. Crocidolite exposure has been shown in other studies to lead to increased hydrogen peroxide but not superoxide anion (Kamp and Weitzman, 1999; Kamp et al., 1992). The increased hydrogen peroxide from crocidolite exposure can then lead to increased hydroxyl radical production (through interactions with endogenous iron), and potentially, deoxyribonucleic acid (DNA) adduct formation. DNA adduct formation (8-hydroxy-2'deoxyguanosine [8-OHdG]), 8-oxoguanine-DNA-glycosylase 1 (Ogg1) levels, and DNA damage (comet assay) also were measured. A significant increase in DNA damage in exposed macrophages, as measured by increases in both 8-OHdG formation and expression of Ogg1, a DNA repair enzyme that excises 8-OHdG from DNA following oxidative stress, was observed following exposure to crocidolite but not LAA. Increased superoxide anion following LAA exposure does not appear to yield oxidative damage similar to crocidolite. These results suggest a chemical-specific response to each type of amphibole that yields varied cellular responses. Therefore, the mechanism of action following response to LAA might be different than that of crocidolite, also an amphibole fiber.

To determine if the ROS production was related to fiber number for both LAA and crocidolite, cell-fiber interactions and fiber internalization were measured following exposure to equal concentrations of crocidolite, LAA, and wollastonite (62.5 μg/cm^2, 3 hours). With phase contrast light microscopy, the number of cells interacting with one or more fibers was counted (100 cells counted for each treatment). All murine macrophages bound or internalized at least one fiber from the LAA sample (mean ± SD, 4.38 ± 1.06 internalized) or the crocidolite sample

(3.28 ± 1.58 internalized) but not the wollastonite sample (Blake et al., 2007). No significant differences were observed in the responses to LAA or crocidolite samples, suggesting that the differences in measured ROS were not related to cell number. Fiber sizes varied between the two samples, with the crocidolite sample containing a more homogeneous mixture of long fibers (exact size not given), while the LAA sample contained a mixture of sizes and widths. These characteristics were not analyzed to determine what, if any, role they might play in the varied response.

The second study by Blake et al. (2008) reports the effects of in vitro exposure to LAA on apoptosis by exploring autoimmune response following asbestos exposure. Although LAA was not directly used in the autoimmune studies, the autoantibody (SSA/Ro52) is a known marker of apoptosis, and the in vitro studies included treatment with LAA. RAW264.7 cells exposed to LAA induced apoptosis over 72 hours, as measured by induction of poly (ADP-ribose) polymerase cleavage and increased Annexin V staining. Redistribution of SSA/Ro52 in apoptotic blebs was demonstrated in LAA-exposed RAW264.7 cells but not in the unexposed controls and wollastonite-exposed RAW264.7 murine macrophages, further confirming apoptosis following LAA exposure.

Rasmussen and Pfau (2012) studied the role of B1a B-lymphocytes in the development of autoantibody production following asbestos exposure. CH12.LX B-lymphocytes, a murine B1 lymphocyte cell line, were cultured with 35 μg/cm^2 of LAA or 1 μg/mL of lipopolysaccharide (LPS; positive control) for 48 hours. Asbestos exposure did not affect proliferation or antibody production. CH12.LX B-lymphocytes cultured for 24 hours in RAW medium treated with 35 μg/cm^2 LAA reduced CH12.LX proliferation and increased IgG1, IgG3, and IgA production when normalized to cell number. The authors identified that IL-6 and TNF-α were both elevated in the medium of asbestos-treated RAW macrophages. Treating CH12.LX B-lymphocytes with recombinant IL-6 or TNF-α at similar concentrations as in the asbestos-treated macrophage medium resulted in reduced CH12.LX proliferation. Interestingly, only the IL-6-treated CH12.LX cells had increased IgG and IgA production. However, both high and low concentrations of IL-6 increased IgG and IgA secretion, indicating that some other mechanism is present in the asbestos-treated RAW medium that regulates CH12.LX antibody production. These data suggest a potential mechanism for asbestos-induced autoantibody production in LAA-exposed residents.

Li et al. (2012) exposed THP-1 cells (macrophage cell line) to LAA[10] and chrysotile (0, 20, 40 μg/mL for 24 hours) to measure inflammatory response. This study measured cell death, caspase activation and release of IL-1β to determine if each fiber type activated the Nod-like receptor protein 3 (NLRP3) inflammasome. Results demonstrated that while both fiber types

[10] LAA, or Libby "Six-Mix" was used for this study. Fiber characteristics are described from previous studies. LAA mean fiber length = 7.21μm; mean surface area = 5 m^2/g.

appeared to activate NLRP3, chrysotile led to a greater effect as measured by cell death, activation of caspase-1, and release of IL-1β. However, results demonstrated that both fibers also led to increased ROS production compared to the same mass dose of chrysotile as measured by increases in expression of antioxidant enzymes, protein oxidation, and nitration and lipid peroxides. In order to further study these differences in biological response to these two fibers, BEAS-2B cells (bronchial epithelium cells) were exposed to supernatant from the THP-1 cells. Both activated the MAPK cascade, increased ERK and MAP3K8 phosphorylation, and increased AP-1 binding and IL-6 release. These results were attenuated with the addition of an IL-1β antagonist (IL-1 Ra). This study demonstrated that although exposure to both fibers led to the same biological responses, the level of response was variable. Although not studied, the authors suggest that differences in fiber length and surface area may play a role in this differential inflammatory response.

Serve et al. (2013) examined a possible role of autoimmunity in fibrosis by an in vitro examination of potential mechanisms of mesothelial cell autoantibodies (MCAA) leading to collagen deposition, a precursor to fibrosis. Nonmalignant, transformed human mesothelial cells (MeT-5A) were exposed to serum samples from LAA-exposed populations. These samples were identified as MCAA-positive or MCAA-negative and were pooled prior to exposure. MCAA was found to be present and induced collagen deposition but not mesothelial cell differentiation. The increase in collagen deposition observed was not through increased collagen synthesis but SPARC-related collagen processing and associated with specific matrix metalloproteinases (MMPs). This study demonstrated that MCAA binding leads to increased collagen deposition by altering MMP expression.

Duncan et al. (2014) examined the in vitro determinants of asbestos fiber toxicity, comparing two samples each of LAA (LA2000, LA2007) and amosite asbestos (UICC, RTI). Primary human airway epithelial cells (HAEC) were exposed for 24 hours to 2.64, 13.2, or 26.4 μg/cm^2 LAA and amosite asbestos, with each asbestos sample having been analyzed for fiber size distribution, surface area, and surface-conjugated iron (see Table D-11). The asbestos samples had similar characteristics, except RTI amosite, which consisted of longer fibers. Fiber toxicity was measured by cytotoxicity (LDH assay), levels of ROS production, as well as IL-8 mRNA levels as a measure of relative proinflammatory responses. Cytotoxicity levels were similar among all four samples at the highest dose, but statistically significant compared to no-treatment control. Results on an equal-mass basis demonstrated a statistically significant increase in *IL-8*, *IL-6*, *cyclooxygenase-2 (COX-2)*, and *TNF* mRNA levels for all four amphiboles at the two highest doses. The greatest increase in *IL-8* mRNA levels followed exposure to the RTI amosite sample, while response levels observed among the UICC amosite and both LAA samples were not statistically significant. Therefore, *IL-8* was used to further analyze dose metric for this response. Surface iron concentrations and surface reactivity were quantified with respect to hydroxyl radical production to assess the effect of these properties on

IL-8 mRNA expression. Surface iron concentrations were similar for the two LAA samples and for the two amosite samples, but the amosite samples had significantly greater surface iron as compared to the LAA samples. UICC amosite had slightly greater iron compared with RTI amosite. A strong correlation was observed between fiber dose metrics of length and external surface area. When these metrics were used in place of equal-mass dose, the differential *IL-8* mRNA expression following exposure to these four samples was eliminated.

Table D-11. Characterization of amphibole samples (Duncan et al., 2014)

	LA2000	LA2007	RTI amosite	UICC amosite
Particle count				
n (total particles)	561	510	588	525
n (total EMP)[a]	450	250	292	178
Particle number/mg				
Total particles × 10^7/mg	98.2	103	9.15	94.2
EMP × 10^7/mg	78.7	50.5	4.5	31.9
Particle size distribution				
Total particle mean length (µm)	3.7 ± 0.2	2.3 ± 0.2	6.4 ± 0.6	2.1 ± 0.3
Total particle mean width (µm)	0.36 ± 0.02	0.36 ± 0.01	0.44 ± 0.01	0.43 ± 0.01
Total particle mean aspect ratio	12.8 ± 0.6	8.4 ± 0.7	16.9 ± 1.6	5.6 ± 0.6
EMP mean length (µm)	4.4 ± 0.2	3.8 ± 0.3	12.1 ± 1.2	4.3 ± 0.5
EMP mean width (µm)	0.30 ± 0.01	0.29 ± 0.02	0.37 ± 0.01	0.27 ± 0.01
EMP mean aspect ratio	15.5 ± 0.6	15.1 ± 1.2	32.4 ± 3.0	13. 0 ± 1.0
Surface area				
Total surface area by GA (m^2/g)[b]	5.3	7.4	3.1	4.8
EMP surface area by TEM (m^2/g)[c]	1.1	2.6	2.8	1.5

[a]Elongated mineral particle (EMP) defined as having an aspect ratio >3:1.
[b]Measured by Kr gas adsorption (GA) and BET analysis.
[c]Measured by TEM and calculated by using the equation $SA = (L \times W + W \times T)/(L \times W \times T \times p)$.

The role of ROS in chromosomal damage from asbestos was examined in a recent study of LAA and Union for International Cancer Control (UICC) crocidolite in XRCC1-deficient human lung epithelial H460 cells (Pietruska et al., 2010). XRCC1 is involved in the repair mechanisms for oxidative DNA damage, particularly single-strand breaks. This study examined the effect of XRCC1 deficiency (induced in cells by shRNA knockdown) following exposure to genotoxic (crocidolite and LAA) and nongenotoxic compounds (wollastonite, titanium dioxide) on micronucleus formation. Cells were exposed to chemicals with known oxidants hydrogen peroxide (0−60 µM) or bleomycin (0−10 µg/mL), for 1 and 3 hours, or the nonoxidant paclitaxel

(0−5 nM, 24 hours) to confirm the clonogenic survival of the knockout cells, and as positive and negative controls. Fiber-size distribution for crocidolite and LAA is shown in Table D-12. Micronuclei induction was measured following treatment of cells by controls as described above, and by 5 µg/cm^2 fibers or titanium dioxide (TiO_2) particles for 24 hours. Following treatment, cells were fixed, permeabilized, and blocked before being exposed to anticentromere antibodies, and micronuclei were counted and scored as centromere negative arising from DNA breaks (clastogenic) or centromere positive arising from chromosomal loss (aneugenic). Spontaneous micronuclei induction was increased in XRCC1-deficient cells as compared to controls. Wollastonite and titanium dioxide did not induce micronuclei in either cell type. Crocidolite and LAA-induced dose-dependent increases in micronuclei formation in both cell types, including an increase in the proportion of micronuclei in XRCC1-deficient cells (see Table D-13). LAA exposure led to a decreased amount of micronuclei as compared to crocidolite. Specifically in relation to clastogenic versus aneugenic micronuclei, crocidolite exposure led to mainly clastogenic micronuclei, while LAA exposure led to a mixture of aneugenic and clastogenic micronuclei. Nuclear bud formation was also observed but only with exposure to crocidolite and bleomycin. Western blot analysis was performed to analyze protein expression related to DNA damage repair (XRCC1) and cell cycle progression (p53, p21) (data not shown in publication). The differences observed between crocidolite and LAA are most likely related to their physicochemical differences. However, these results support a genotoxic effect of exposure to both crocidolite and LAA.

Table D-12. Size distribution of UICC crocidolite and LAA used in Pietruska et al. (2010)[a]

Length (µm)	% fibers in size range	
	Crocidolite	LAA
0.1−1.0	46.4	12.6
1.1−5.0	44.8	38.5
5.1−8.0	3.8	23.1
8.1−10.0	0.9	10.4
10.1−20.0	2.4	11.6
≥20.1	1.7	3.6

[a]Distribution by diameter also given in original manuscript.

Source: Adapted from Supplemental Material of Pietruska et al. (2010).

Table D-13. Percent clastogenic micronuclei following exposure to LAA or crocidolite

	H460 cells	XRCC1-deficient
LAA (5 μg/cm^2)	71.5 ± 3.4%	86.0 ± 1.2%[a]
Crocidolite (5 μg/cm^2)	57.2 ± 2.2%	65.1 ± 2.2%[a]

[a]$p < 0.05$ as compared to control cells.

Source: Pietruska et al. (2010).

Mechanisms of oxidative stress following exposure to LAA were also studied in human mesothelial cells (Hillegass et al., 2010). Gene-expression changes were measured with Affymetrix U133A microarrays (analysis with GeneSifter) following exposure to 15×10^6 μm^2/cm^2 LAA[11] as compared to the nonpathogenic control (75×10^6 μm^2/cm^2 glass beads) in the human mesothelial cell line LP9/TERT-1 for 8 and 24 hours. Gene expression of only one gene (manganese superoxide dismutase [*MnSOD*; *SOD2*]) was altered following exposure to LAA for 8 hours, while 111 genes had an altered gene expression following exposure to LAA for 24 hours (altered by at least twofold as compared to controls).

The gene for *MnSOD; SOD2* was observed to be significantly upregulated at both time points ($p < 0.05$) as compared to the nonpathogenic control. This gene was confirmed in normal human pleural mesothelial cells (*HKNM-2*) by quantitative RT-PCR at 24 hours following exposure to the nontoxic dose of LAA. Upregulation of three genes from this and previous studies by these authors was confirmed by quantitative RT-PCR (*SOD2*, *ATF*, and *IL-8*) in HKNM-2 cells exposed to both LAA and crocidolite asbestos. Gene ontology of these results demonstrated alterations related to signal transduction, immune response, apoptosis, cellular proliferation, extracellular matrix, cell adhesion and motility, and ROS processing. Follow-up studies at both the nontoxic dose (15×10^6 μm^2/cm^2) and the toxic dose (75×10^6 μm^2/cm^2) exposure levels in LP9/TERT-1 cells examined SOD protein and activity, ROS production, and GSH levels. At 24 hours, *SOD2* protein levels were increased following exposure to the toxic dose of LAA ($p < 0.05$) but not at 8 hours. Cells exposed to all doses of LAA and crocidolite asbestos had increased copper-zinc superoxide dismutase (Cu/ZnSOD; SOD1) protein at 24 hours ($p < 0.05$) but not at 8 hours. Although total SOD activity remained unchanged, a dose-related *SOD2* activity was observed following exposure to both doses of LAA for 24 hours, but this appeared to be minimal and was not statistically significant (activities at 8 hours were not examined). Oxidative stress was measured by dichlorodihydrofluorescein diacetate

[11]LAA samples for this study were characterized by analysis of chemical composition and mean surface area (Meeker et al., 2003). Doses were measured in surface area and described based on viability assays with fiber samples as either nontoxic (15×10^6 μm^2/cm^2) or toxic (75×10^6 μm^2/cm^2).

fluorescence staining detected by flow cytometry and was observed to be both dose- and time-dependent in cells exposed to LAA and was increased following exposure to the toxic dose of LAA (statistical analysis not possible). Oxidative stress was further supported by analysis of gene expression of heme oxygenase 1 (HO-1) following exposure to LAA in both LP9/TERT-1 and HKNM-2 cells for 8 and 24 hours. HO-1 was significantly increased following exposure to the toxic dose of LAA in both cell lines (*p*-value not given). GSH levels were transiently depleted following 2−8 hours exposure to 75×10^6 $\mu m^2/cm^2$ levels of LAA, with a gradual recovery up to 48 hours in LP9/TERT-1 cells (HKNM-2 not analyzed). Exposure to crocidolite asbestos at the toxic dose led to a significant GSH decrease at all-time points up to 24 hours ($p < 0.05$). These studies demonstrate that LAA exposure leads to increases in oxidative stress as measured by ROS production, gene expression, protein and functional changes in oxidative stress proteins (SOD), and GSH-level alterations in human mesothelial cells.

Pfau et al. (2012) conducted a study to determine the effect of LAA exposure on the amino acid transport system x^-_c which is one of the pathways murine macrophages detect and respond during stressful conditions. RAW 264.7 murine macrophages were cultured in the presence of LAA for 24 hours and then compared to the control substances silica, LPS, and wollastanite. System x^-_c was increased in LAA-treated cells but not in silica or wollastanite controls. ROS production increased system x^-_c activity. Furthermore, inhibition of system x^-_c increased ROS production and reduced viability in LAA-treated cells but not silica-treated cells. Altogether, these data suggest that system x^-_c may play a role in macrophage survival and inflammation following LAA exposure.

The relative toxicity of LAA was measured by gene-expression changes of *IL-8*, *COX-2*, and heme oxygenase (*HO*)-*1*, as well as other stress-responsive genes, as compared to amosite (Research Triangle Institute, NC) in primary HAEC in vitro. Comparisons were made with both fractionated (aerodynamic diameter ≤2.5 µm) and unfractionated fiber samples (Duncan et al., 2010). Crocidolite fibers (UICC) were also included in some portions of this study for comparison. Fractionation was performed using the water elutriation method (Webber et al., 2008) and characterized as described in Lowers and Bern (2009). Primary HAECs were exposed to 0, 2.64, 13.2, and 26.4 $\mu g/cm^2$ of crocidolite, amosite, AM2.5 (fractionated), LAA, or LA2.5 (fractionated) for 2 and 24 hours in cell culture. Confocal microscopy was used to determine fiber content in cells exposed for 4 and 24 hours to 26.4 $\mu g/cm^2$ AM2.5 or LA2.5 only. At 4 hours postexposure, fibers were mainly localized on the periphery of the cell with some fibers internalized. By 24 hours postexposure, most fibers appeared to be internalized and localized by the nucleus. Cytotoxicity was determined by measurement of LDH from the maximum dose (26.4 $\mu g/cm^2$) of both, fractionated and unfractionated, amosite and LAA samples, with less than 10% LDH present following exposure to all four samples. Cytotoxicity was also determined for just the fractionated samples of amosite and LAA by measuring intracellular calcein fluorescence emitted by live cells and showed 95% and 99% viability for AM2.5 and LA2.5, respectively.

These results support a limited cytotoxicity of both amosite and LAA under these concentrations and time frames.

Gene-expression changes in specific inflammatory markers (*IL-8, COX-2, HO-1*) were analyzed by quantitative RT-PCR for amosite, AM2.5, LAA, LA2.5, and CRO at both 2 and 24 hours postexposure (all doses). Minimal increases in gene expression of *IL-8, COX-2*, or *HO-1* were observed at 2 hours postexposure to all five fiber types; at 24 hours postexposure, however, a dose response was observed following exposure to all fiber types. The smaller size fractions resulted in differences in magnitude of gene-expression changes between AM2.5 and LA2.5, with AM2.5 leading to greater induction of *IL-8* and *COX-2* as compared to LA2.5. HO-1 levels were comparable between the two samples (see Table D-14). Gene expression of transforming growth factor *(TGF)-B1* was also quantified but only following exposure to AM2.5 and LA2.5 (all doses; data not shown in publication). Levels of IL-8 protein were also measured following 24 hours exposure to AM2.5 and LA2.5 (all doses) and were statistically significant at the two highest exposures (13.2 and 26.4 µg/cm^2). Gene-expression changes were also examined for 84 genes involved in cellular stress and toxicity using a 96-well RT-PCR array format following 24 hours exposure to 13.2 µg/cm^2 amosite, LAA, AM2.5, or LA2.5 or to 26.4 µg/cm^2 LA2.5 only. The results show a proinflammatory gene-expression response. Gene-expression profiles were similar between amosite and LAA, but differences were observed between AM2.5 and LA2.5.

Table D-14. Gene-expression changes following exposure to 26.4 µg/cm^2 amphibole asbestos for 24 hours[a]

Genes for specific inflammatory markers	Amosite (AM)	Amosite, fractionated (AM2.5)	LAA	LAA, fractionated (LA2.5)
IL-8	50 ± 7.5	120 ± 25	46 ± 8.3	37 ± 7.8
COX-2	5.4 ± 0.5	16 ± 2.8	9.0 ± 1.7	1.6 ± 0.3
HO-1	2.9 ± 0.2	4.5 ± 0.3	2.5 ± 0.2	5.1 ± 0.6

[a]All results in fold change ± standard deviation as compared to untreated control cells.

Source: Duncan et al. (2010).

To determine if surface iron on the fibers played a role in the inflammatory response, Duncan et al. (2010) also examined surface iron concentrations by two methodologies: inductively coupled plasma optical emission spectroscopy and citrate-bicarbonate-dithionite. Both assays determined AM2.5 appeared to have surface iron as measured by thiobarbituric acid-reactive product formation following exposure to amosite, AM2.5, LAA, and LA2.5. Both amosite samples were found to generate the greatest amount of hydroxyl radicals compared to

the two LAA samples, with the fractionated AM2.5 and LA2.5 exhibiting small increases in ROS produced compared to the unfractionated samples.

D.3.2. In Vitro Studies—Tremolite

In general, all fibrous tremolite samples were shown to be carcinogenic, with those containing more of the longer, thinner fibers (>10 μm length, <1 μm diameter) being more potent carcinogens. Most studies described here used weight as the measurement of fibers for exposure, with the doses ranging from 0 to 40 mg/animal. One set of studies did expose animals with fibers measured by number (100 fibers/cm^3) (Bernstein et al., 2006; Bernstein et al., 2005).

D.3.2.1. *Cytotoxicity*

Wagner et al. (1982) examined the in vitro cytotoxicity of three forms of tremolite (see Table D-7) used in their in vivo studies. LDH and BGL were measured in the medium following incubation of unactivated primary murine macrophages to 50, 100, and 150 μg/mL of each sample for 18 hours. Cytotoxicity of Chinese hamster lung fibroblasts V79-4 was measured by methylene blue staining (fiber concentrations not given). Giant-cell formation in A549 human basal alveolar epithelial cell cultures was measured, using 100 and 200 μg/mL of each sample for 5 days. Crocidolite fibers were used as the positive control.

In all three assay systems, the Korean tremolite produced results similar to the positive control: increased toxicity of primary murine macrophages, increased cytoxicity of Chinese hamster ovary (CHO) cells, and increased formation of giant cells from the A549 cell line. The tremolite sample from Greenland (Sample B) did result in increased toxicity over controls, although to a lesser degree (statistics are not given). The authors speculated that the iron content in Sample B might have contributed to these results. Although differential toxicity of these samples was noted on a mass basis, data were not normalized for fiber content or size. The inference is that differential results are due, at least in part, to differential fiber counts.

In a study to further elucidate the role of ROS following exposure to asbestos, Suzuki and Hei (1996) examined the role of heme oxygenase (HO) in response to asbestos. HO is induced in response to oxidative stress and functions to degrade heme; it might, therefore, prevent iron-mediated hydroxyl radical production. All fibers tested led to an increase in HO, although chrysotile (UICC) and crocidolite (UICC) led to a greater increase than tremolite (Metsovo, Greece) and erionite (Rome, Oregon). No statistics, however, are described for these results. This study focused on responses to 20 and 40 μg/mL of chrysotile and then used doses that yielded 0.5 and 0.3 relative survival fractions for all other fibers (crocidolite, 20 and 40 μg/mL; tremolite, 150 and 300 μg/mL; erionite, 200 and 400 μg/mL). Fibers were not characterized in this paper. When normalized by survival fraction, the inductions of HO above the control were 3.89-, 3.86-, 2.75-, and 2.78-fold above background levels for chrysotile, crocidolite, tremolite,

and erionite, respectively. Limited information is provided on the results of tremolite exposures beyond an increase in HO following an 8-hour exposure. This increased HO following exposure to tremolite demonstrates a response similar to that observed for crocidolite and chrysotile in this study. Crocidolite is further analyzed with exposures to the antioxidants superoxide dismutase and catalase, leading to a dose-dependent decrease in HO induction, which supports the role of HO in oxidative stress.

Wylie et al. (1997) examined the mineralogical features associated with cytotoxic and proliferative effects of asbestos in hamster tracheal epithelial (HTE) cells and rat pleural mesothelial (RPM) cells with a colony-forming efficiency assay. HTE cells are used because they give rise to tracheobronchial carcinoma, while RPM cells give rise to mesothelioma. Cells were exposed to fibers by weight, number, and surface area (see Table D-15).

Table D-15. Fiber characteristics of five fibers examined in vitro for cytotoxic (HTE cells) and proliferative effects (RPM cells)

Sample	Description (% of sample)	Surface area (mm^2/g)	Fibers/µg	Fibers ≥5 µm/µg
FD14	Talc (37), tremolite (35), serpentine (15), other (<2), unknown (12)	6.2 ± 0.2	2.5×10^3	0.8×10^3
SI57	Talc (60), tremolite (12), unknown (21), other (4), anthophyllite (3), quartz (1)	4.9 ± 0.2	1.1×10^4	4.8×10^3
CPS183	Talc (50), quartz (12), unknown (28), tremolite (4), other (4), anthophyllite (3)	4.9 ± 0.4	1.1×10^4	9.2×10^3
NIEHS crocidolite	Riebeckite (100)	10.3 ± 1.3	5.3×10^5	3.8×10^5
NIEHS chrysotile	Chrysotile (100)	25.4 ± 0.5	5.3×10^4	3.4×10^4

NIEHS = National Institute of Environmental Health Sciences.

Source: Wylie et al. (1997).

Colony-forming efficiency assay results are expressed as the number of colonies in exposed cultures divided by the control colonies multiplied by 100. Increases in colony numbers indicate increased cell proliferation or survival in response to the exposure. Decreases in colony numbers indicate toxicity or growth inhibition in response to the exposure. The results of the analysis with fiber exposure by mass ($\mu g/cm^2$) show elevated colonies in HTE cells following exposures to both asbestos fibers ($p < 0.05$) at the lowest concentrations, while significant decreases are observed for both asbestos fibers at the higher concentrations (0.5 $\mu g/cm^2$, $p < 0.05$) (Wylie et al., 1997).

No proliferation was observed for either chrysotile or crocidolite asbestos fibers in RPM cells, but cytotoxicity was observed at concentrations >0.05 $\mu g/cm^2$ ($p < 0.05$). All talc samples

were less cytotoxic in both cell types. Comparing results of these samples when exposure is measured by fiber number, the same number of crocidolite asbestos fibers >5-μm long leads to proliferation in HTE cells, but proliferation did not occur for FD14 fibers. The other two talc samples showed both insignificant cytotoxicity (SI57) and significant cytotoxicity (CPS183, $p < 0.05$). Therefore, when measured by fiber number, the results show differential responses for the fibers analyzed, suggesting the mineralogy of the fibers is more important in determining the biological response to fibers. In the RPM cells, however, similar responses were seen for all fibers analyzed, except for the slight cytotoxicity of FD14 at 2.6 fibers/cm^2. This suggests that fiber number does play a role in biological response in this cell type.

The results of these samples in both cell lines demonstrated that the cellular responses seemed unrelated to the surface area, which demonstrates the impact of the dose metric on data. Analyzing the data for cytotoxicity and proliferation based on the exposure measurement demonstrated differences in response depending solely on how the fibers were measured (e.g., by mass, number, or surface area). These results show variability in interpreting the same assay based on the defined unit of exposure. Most early studies used mass as the measurement for exposure, which can impact how the results are interpreted. When possible, further analysis of fiber number and surface area might help elucidate the role of these metrics, particularly for in vivo studies.

D.3.2.2. *Genotoxicity*

Athanasiou et al. (1992) performed a series of experiments to measure genotoxicity following exposure to tremolite, including the Ames mutagenicity assay, micronuclei induction, chromosomal aberrations, and gap-junction intercellular communication. Although a useful test system for mutagenicity screening for many agents, the Ames assay is not the most effective test to detect mutations induced by mineral fibers. Mineral fibers can cause mutation through generation of ROS or direct disruption of the spindle apparatus during chromatid segregation. Fibers do not induce ROS in the Ames system, however, and the *Salmonella typhimurium* strains do not endocytose the fibers. Only one study was found in the published literature that used the Ames assay to measure mutagenicity of tremolite. Metsovo tremolite asbestos has been shown to be the causative agent of endemic pleural calcification and an increased level of malignant pleural mesothelioma (see Section 4.1). To measure the mutagenicity of Metsovo tremolite, *S. typhimurium* strains (TA98, TA100, and TA102) were exposed to 0−500 μg/plate of asbestos (Athanasiou et al., 1992). This assay demonstrated that, like most asbestos fiber types tested in earlier studies, Metsovo tremolite did not yield a significant increase in revertants in the Ames assay, including in the TA102 Salmonella strain, which is generally sensitive to oxidative damage. Although these strains can detect ROS mutations, they would not be able to produce ROS from fibers alone or through necessary signaling pathways, and they do not endocytose

fibers. Thus, negative results in the Ames assay do not inform the genotoxicity of Metsovo tremolite.

Furthermore, this study demonstrated the clastogenic effects of tremolite, including chromosomal aberrations and micronuclei induction. Tremolite exposure (0−3.0 μg/cm^2) in Syrian golden hamster embryo (SHE) cells resulted in a statistically significant increase in chromosomal aberrations ($p < 0.02$) when all treatment groups were combined and then compared to controls; however, no clear dose-response relationship was evident (Athanasiou et al., 1992). Tremolite exposure in SHE cells did lead to a dose-dependent increase in chromosome aberrations that was statistically significant at the highest doses tested (1.0−3.0 μg/cm^2) ($p < 0.01$) (see Table D-16).

Table D-16. Micronuclei induction (BPNi cells) and chromosomal aberrations (SHE cells) following exposure to tremolite for 24 hours

Asbestos dose (μg/cm^2)	Micronuclei incidence/1,000 cells	Chromosomal aberrations (including chromatid gaps, breaks, isochromatid breaks, and chromosome type)
0	17	3
0.5	31[a]	4
1.0	70[b]	12[c]
2.0	205[b]	9[a]
3.0	Not tested	13[c]

[a]Significantly different from control ($p < 0.05$).
[b]Significantly different from control ($p < 0.01$).
[c]Significantly different from control ($p < 0.02$).

Source: Athanasiou et al. (1992).

Micronuclei induction was measured in BPNi cells after 24-hour exposure to 0−2.0 μg/cm^2 tremolite. A statistically significant dose-dependent increase in levels of micronuclei was demonstrated following tremolite exposure at concentrations as low as 0.5 μg/cm^2 ($p < 0.01$). Literatures searches did not find tremolite tested for clastogenicity in other cell types, but the results of this study suggest interference with the spindle apparatus by these fibers. No analysis was performed to determine whether fiber interference of the spindle apparatus could be observed, which would have supported these results.

To determine whether tremolite has some tumor promoter characteristics, Athanasiou et al. (1992) further examined intercellular communication following exposure to 0−4.0 μg/cm^2 tremolite in both Chinese hamster lung fibroblasts (V79) and SHE BPNi cells, which are sensitive to transformation. Inhibition of gap-junctional intercellular communication has been

proposed to detect tumor-promoting activity of carcinogens (Trosko et al., 1982). No effect on gap-junction intercellular communication following tremolite exposure was observed.

Okayasu et al. (1999) analyzed the mutagenicity of Metsovo tremolite, erionite, and the man-made ceramic (RCF-1) fiber. Whether this tremolite is the same as that used in previous studies from this group is unclear. Tremolite from Metsovo, Greece, used in this study was characterized as 2.4 ± 3.1 μm long and 0.175 ± 0.13 μm in diameter (arithmetic mean) with the number of fibers per microgram of sample equal to 1.05×10^5. Human-hamster hybrid A(L) cells contain a full set of hamster chromosomes and a single copy of human chromosome 11. Mutagenesis of the CD59 locus on chromosome 11 is quantifiable by antibody complement-mediated cytotoxicity assay. The authors state that this is a highly sensitive mutagenicity assay, and previous studies have demonstrated mutagenicity of both crocidolite and chrysotile (Hei et al., 1992). The cytotoxicity analysis for mutagenicity was performed by exposing 1×10^5 A(L) cells to a range of concentrations of fibers as measured by weight (0−400 μg/mL or 0−80 μg/cm^2) for 24 hours at 37°C. CD59 mutant induction showed a dose-dependent increase in mutation induction for erionite and tremolite, but RCF-1 did not.

D.4. SUMMARY

In vitro studies have been conducted with LAA from the Zonolite Mountain mine. These studies demonstrated an effect of LAA on inflammation and immune function (Duncan et al., 2010; Blake et al., 2008; Blake et al., 2007; Hamilton et al., 2004), oxidative stress (Hillegass et al., 2010), and genotoxicity (Pietruska et al., 2010). These results suggest that LAA may act through similar mechanisms as other forms of asbestos, but data gaps still remain to determine specific mechanisms involved in LAA-induced disease.

Studies that examined cellular response to tremolite also found that fiber characteristics (length and width) play a role in determining ROS production, toxicity, and mutagenicity (Okayasu et al., 1999; Wagner et al., 1982). As with the in vivo studies, the definition of fibers and the methods of fiber measurement vary among studies.

D.5. REFERENCES

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APPENDIX E. EVALUATION OF EXPOSURE-RESPONSE DATA FOR RADIOGRAPHIC CHANGES IN WORKERS FROM THE MARYSVILLE, OH COHORT COMBINING DATA FROM THE 1980 AND 2002−2005 HEALTH EXAMINATIONS

E.1. EXPOSURE DATA

The U.S. Environmental Protection Agency (EPA) collaborated with a research team at the University of Cincinnati (UC) to update the exposure reconstruction for use in the job-exposure matrix (JEM) for all workers in the Marysville, OH cohort, taking into account additional industrial hygiene data that were not available for previous studies conducted in this cohort. As discussed in detail in Appendix F, exposure estimates for each worker in the O.M. Scott Marysville, OH plant were developed based on available industrial hygiene phase contrast microscopy (PCM) data from the plant. Figure E-1 shows the average exposure concentrations of fibers in air (PCM fibers/cc) of each department from 1957 to 2000, indicating the time periods when industrial hygiene data for fiber concentration in air were not available (1957−1971) and were available (1972 and after).

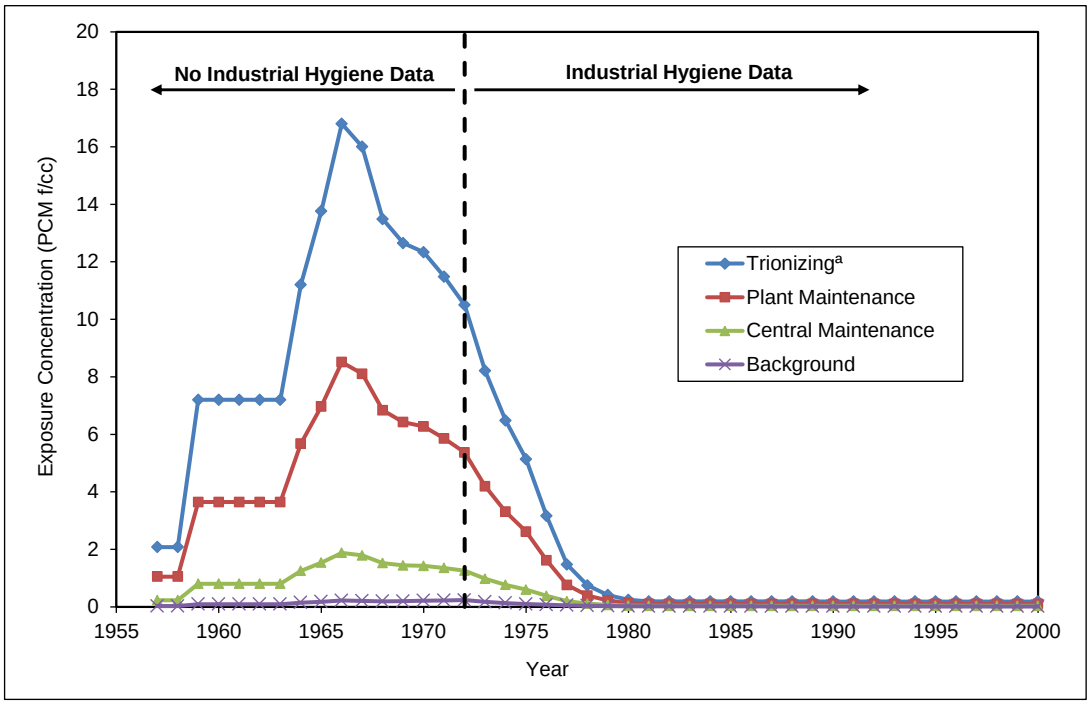


Figure E-1. Exposure concentrations in Marysville, OH facility.

[a]Trionizing is a term used in the Marysville, OH facility and includes unloading of railcars containing vermiculite ore (track), using conveyers to move the vermiculite ore into the expander furnaces, separation of the expanded vermiculite from sand, blending lawn-care chemicals, and drying and packaging of the final product. As no unexpanded ore was used in the pilot plant, research, polyform, office, packaging, or warehouse, jobs in these categories were assigned as the background exposure. Workers assigned to plant maintenance activities spent 50% of their time in trionizing and 50% of their time in areas assigned as plant background. Workers assigned to central maintenance spent 10% of their time in trionizing areas and 90% of their time in areas assigned as plant background. Central maintenance jobs were eliminated in 1982 and contracted out (see Appendix F).

In brief, the starting point for the JEM was the estimated concentration of fibers in air (fibers/cc) of each department from 1957−2000. The details are presented in Appendix F. Using available data on the date of hire and the departments in which each person worked and taking into account extensive overtime for some workers in some seasons, the cumulative exposure (CE; fibers/cc-yr)[12] for each worker for each season for each year since the date of hire was estimated. The final CE metric (fibers/cc-yr) was obtained by adding the seasonal exposure value for each worker for the total duration of employment for that worker. Each worker's CE was then adjusted to a cumulative human equivalent exposure concentration (CHEEC; fibers/cc-yr) to represent exposure 24 hours/day and 365 days/year (assuming that any exposure off site was zero) for the full duration of employment. Note: Although Appendix F uses the

[12]Although the units of cumulative exposure are generally written as fibers/cc-year in the epidemiologic literature, it actually means fibers/cc times years of exposure.

term CHEEC, the more conventional term, CE, is used in this appendix to refer to cumulative exposure adjusted to an equivalent human exposure adjusted to 24 hours/day and 365 days/year.

Mean exposure concentration (C, fibers/cc) was calculated by dividing the CE value (fibers/cc-yrs) by the duration of exposure (years), where exposure duration was calculated as the sum of the days worked by each worker (accounting for time away from work) divided by 365.25 days/year. Residence-time-weighted exposure (RTW, fibers/cc-yrs^2) was calculated as follows:

$$RTW = \sum [CE(s) \cdot t(s)]/365.25 \qquad \text{(E-1)}$$

where:

$CE(s)$ = cumulative exposure (fibers/cc-yrs) occurring in season "s"

$t(s)$ = number of days between the midpoint of season "s" and the date of x-ray

This RTW exposure metric includes consideration of time since first exposure (TSFE) in that it more heavily weights exposures in the past.

E.2. DATA SETS FOR MODELING

The primary analysis in Section 5.2.3 of this assessment models data for Marysville workers evaluated in 2002−2005 and hired in 1972 or later without previous exposure to asbestos (Rohs et al., 2008). The cohort is defined as the Rohs subcohort for this appendix. This data set was chosen for the primary analysis because it was considered to have the highest quality information as the job exposure matrix is directly supported by the industrial hygiene data and the radiographs were evaluated by the same readers using the same evaluation guidelines. The primary analysis estimates the effect of TSFE (years) using the larger subset of workers evaluated in 2002−2005, regardless of hire date and without previous exposure to asbestos (Rohs et al., 2008). This cohort is defined as the Rohs cohort for this appendix.

The complementary analysis in this appendix combines the radiographic evaluations for all workers who participated in the Lockey et al. (1984) study and the follow-up study by Rohs et al. (2008) and without previous exposure to asbestos. This cohort is defined as the combined cohort for this appendix. This strategy was adopted as it provided the maximum range in TSFE to inform the dependence of adverse health outcomes on TSFE. Outcome assessments (i.e., chest x-rays) were performed at two different time points, 1980 and 2002−2005, by different readers.

The summary statistics for the three cohorts are presented in Table 5-3 of the main document.

Radiographs were evaluated by two B Readers with a consensus evaluation by a third reader in the case of disagreement in the original study by Lockey et al. (1984). In the follow-up by Rohs et al. (2008), a radiographic reading was considered positive "when the median

classification from the three independent B Readings was consistent with pleural and/or interstitial changes" (see p. 631). Lockey et al. (1984) used modified International Labour Organization (ILO) 1971 standards; Rohs et al. (2008) used ILO 2000 standards. The ILO 1971 standards did not provide separate diagnostic categories for localized pleural thickening (LPT) and diffuse pleural thickening (DPT). The ILO 1971 standards included diagnostic categories for pleural plaques and for other pleural thickening (PT). See Table 3 in Lockey et al. (1984) for the summary of the original x-ray results.

The full data set used to model the exposure-response relationship for the adverse health outcome obtained was as follows. The radiographic data from Lockey et al. (1984) (n = 513) and Rohs et al. (2008) (n = 280), were combined for a total of 793 x-ray evaluations (this includes repeated x-rays on the same individual). X-rays obtained from workers who reported exposure to asbestos at other locations were excluded from consideration (n = 793 − 105 = 688 x-ray evaluations).

For workers who were x-rayed in both Lockey et al. (1984) and Rohs et al. (2008), on of the observations was excluded (as described below) so that no repeat x-ray observation for any individual worker in the data set was used for modeling. For workers who were negative for radiographic changes in Lockey et al. (1984) and did not participate in Rohs et al. (2008), the Lockey et al. (1984) data were retained. For workers who were negative for radiographic changes in Lockey et al. (1984) and participated in Rohs et al. (2008), the Rohs et al. (2008) data were retained. For workers who were positive for radiographic changes in Lockey et al. (1984) and also in Rohs et al. (2008), the 1984 study data were retained. Two workers were positive in 1984 and negative in 2008. In accord with recommendations from the UC research group (Lockey, 2013), the 2008 study data were retained for these two workers. The different results in these two readings could be the result of a temporary cause (localized acute inflammation, fat tissue, or pleural effusion that resolved), reader variability, or changed ILO criteria for pleural abnormalities and do not imply that the pleural abnormality is reversible. This procedure for assembling the data set for the full cohort resulted in
n = 688 x-rays − 252 duplicates = 436 x-rays, representing 436 individual workers. Two workers from Lockey et al. (1984) were excluded because their hire date and the x-ray date were the same (n = 436 − 2 = 434). For each worker, the estimated CE corresponded to the date of the x-ray retained for analysis. That is, if the 1980 x-ray was used, the individual's CE estimate covered the period from start of work through the x-ray date in 1980. If the 2002−2005 x-ray was used, CE covered the period from start of work through the date of job stop or 2000, whichever occurred earlier. The facility stopped using any vermiculite in its products in 2000.

All of the data used for modeling (x-ray diagnosis and exposure reconstruction) are available in Health and Environmental Research Online. All of the modeling was done with the individual exposure and health outcome data.

E.3. STATISTICAL ANALYSIS OF THE COMBINED COHORT

E.3.1. Endpoints Modeled

The x-ray changes identified in the 1980 study (Lockey et al., 1984) and the 2002−2005 study (Rohs et al., 2008) included the following:

- LPT (2002−2005 and as pleural plaques in 1980)
- PT (1980 only)
- DPT (2002−2005 only)
- Small interstitial opacities (1980 and 2002−2005)

Lockey et al. (1984) used modified 1971 ILO classification and reported costophrenic angle obliteration (CAO) only, pleural plaques, and pleural thickening. There were no workers with CAO in the latter two categories. Workers with CAO only were not included as someone with an adverse health outcome attributed to exposure to fibers. A total of 10 workers had pleural abnormalities attributed to exposure to Libby Amphibole asbestos (LAA) fibers. In this assessment, EPA excluded one worker with pleural abnormalities because of previous exposure to asbestos. One worker with plaques and one worker with pleural thickening, but no plaques, had no abnormalities in their 2002−2005 radiographs. The more recent results are used for these two workers. Among the remaining seven workers with pleural abnormalities in 1980, five workers were diagnosed with pleural thickening and pleural plaque and two workers were diagnosed with pleural thickening but no plaque. To be consistent with EPA's understanding of how classification was done in Rohs et al. (2008), the two workers with pleural thickening and no plaque were included in the LPT category. For the modeling of the combined cohort, these endpoints can be grouped into three categories, as follows:

- LPT (includes LPT and PT, but not DPT; 70 cases)
- Any pleural thickening (APT) (includes LPT, PT, and 3 cases of DPT without LPT or PT; 73 cases)
- Any radiographic change (ARC) (includes APT and 3 cases of small interstitial opacities without any pleural thickening; 76 cases)

Of these three alternative endpoints, APT is identified as the preferred metric of outcome because it is more inclusive and eliminates the uncertainty regarding the type of pleural thickening observed in the 1980 study (Lockey et al., 1984) using the 1971 ILO guidance. However, for completeness, modeling was also performed for LPT and ARC and these results are also presented.

E.3.2. Investigation of Explanatory Variables and Potential Confounders

The explanatory variables (other than CE) investigated included those related to time (hire year, TSFE, exposure duration, and age at x-ray) and those not related to time (other covariates including gender, smoking status, and body mass index [BMI]).

Regression models were used to determine whether each covariate (time-related or other covariates) would meet the definition of a confounder—that is, whether it is associated with the exposure in the study population, is associated with the outcome, and is not intermediate between exposure and outcome (i.e., does not lie on the causal pathway). The association with time-related variables was assessed using a univariate linear regression model. For that model, the outcome was the natural log-transformed exposure metric (CE, mean exposure, or RTW exposure) and the predictor was the covariate of interest. The association with outcome was assessed using a univariate logistic model, where the outcome was APT and the predictor was the covariate of interest. The results are summarized in Table E-1.

Table E-1. Evaluation of association between covariates and exposure, and between covariates and occurrence of any pleural thickening (APT).[a] Cells display beta coefficient (standard error), *p*-value for predictor[b].

	Association with cumulative exposure	Association with mean exposure	Association with RTW exposure	Association with APT
Time-related				
Hire yr	**−0.1873 (0.0109), <0.0001**	**−0.1040 (0.0095), <0.0001**	**−0.2556 (0.0149), <0.0001**	**−0.0970 (0.0184), <0.0001**
TSFE	**0.0719 (0.0070), <0.0001**	**0.0156 (0.0057), 0.0060**	**0.1456 (0.0075), <0.0001**	**0.1119 (0.0153), <0.0001**
Exposure duration	**0.1072 (0.0073), <0.0001**	**0.0309 (0.0066), <0.0001**	**0.1784 (0.0087), <0.0001**	**0.0988 (0.0145), <0.0001**
Age at x-ray	**0.0713 (0.0060), <0.0001**	**0.0266 (0.0051), <0.0001**	**0.1294 (0.0070), <0.0001**	**0.0737 (0.0113), <0.0001**
Other covariates				
Male gender	**2.0119 (0.3849), <0.0001**	**1.2180 (0.2949), <0.0001**	**2.6587 (0.5255), <0.0001**	1.8754 (1.0247), 0.0672
Ever smoker[c]	**0.5500 (0.2109), 0.0094**	**0.3232 (0.1592), 0.0430**	**0.6811 (0.2893), 0.0190**	0.2219 (0.2761), 0.4216
Current	−0.0212 (0.2548), 0.9336	0.1610 (0.1952), 0.4101	−0.3559 (0.3448), 0.3026	**−1.1280 (0.4763), 0.0179**
Former	**0.9622 (0.2334), <0.0001**	**0.4402 (0.1787), 0.0142**	**1.4293 (0.3158), <0.0001**	**0.7464 (0.2887), 0.0097**
Smoking pack-yrs	**0.01703 (0.00532) 0.0015**	**0.00739 (0.00406) 0.0695**	**0.02696 (0.00722) 0.0002**	0.00624 (0.00635) 0.3259
BMI (evaluated in 2002−2005 only)[c]	−0.0289 (0.0204), 0.1570	−0.0196 (0.0172), 0.2564	−0.0306 (0.0219), 0.1644	−0.0256 (0.0262), 0.3288

[a]Association with exposure assessed using a linear regression model, where the outcome is natural log-transformed exposure and the predictor is the covariate of interest. Association with outcome assessed using a logistic model, where the outcome is APT status and the predictor is the covariate of interest. Based on $n = 434$ individuals (73 cases of any PT and 361 without PT).
[b]Bold entries indicate statistically significant associations.
[c]Data on smoking status were missing for five individuals in the full cohort. Data on BMI were unavailable for 216 individuals in the combined cohort.

Based on the statistical significance of the beta coefficients, each of the four time-related variables (hire year, TSFE, exposure duration, and age at x-ray) was, as expected, strongly associated with measures of fiber exposure (mean, cumulative, and RTW exposure). These four time-related variables were also highly correlated with each other, with correlation coefficients ranging from absolute magnitudes of 0.51 (between hire year and TSFE) to 0.85 (between duration and TSFE); this high correlation raises concerns about collinearity which can cause instability in regression models if highly correlated variables are included together. There is no indication from the general literature on asbestos or durable mineral fibers that age is a risk

factor for pleural thickening in the absence of exposure. There is considerable support from the general asbestos literature that TSFE is often the most influential explanatory variable when analyzing the exposure-response relationship for asbestos fibers (Paris et al., 2009; Paris et al., 2008; Jakobsson et al., 1995; Ehrlich et al., 1992; Järvholm, 1992). Consequently, among the time-related variables, only TSFE was considered further as a separate predictor variable in exposure-response modeling, noting that both CE and RTW CE include exposure duration within the exposure metric. The correlation between TSFE and exposure was also high for certain metrics, with correlation coefficients of 0.23 and 0.36 for TSFE and CE, and TSFE and RTW exposure, respectively ($p < 0.0001$ for both). However, the correlation between TSFE and mean exposure was not significant (correlation coefficient of 0.07 [$p = 0.1334$]). In evaluating results of models containing TSFE and either cumulative or RTW exposure, the potential for collinearity and resultant model instability was considered.

The other covariates investigated included gender, smoking status, and BMI. Although gender was associated with each of the LAA exposure variables (see Table E-1), it was not associated with the outcome and thus not considered to be a potential confounder (or effect modifier). The analysis based on gender is limited by the small number of females included in the full cohort ($n = 31$), but there is no indication from the general literature on asbestos that males and females have a different probability of developing pleural thickening following exposure to asbestos.

The analysis of smoking status (current, former, or never smoker) appears contradictory in that current smoker status appears to have an inverse relationship with the risk of APT, relative to never smokers. However, on further investigation, it was evident that current smokers had much lower TSFE compared to former smokers (medians of 13.7 and 31.6 years, respectively), and were also on average younger than former smokers (median age at x-ray of 46 years compared to 56 years). The apparent discrepancy of smokers seeming to have lower risk of APT than nonsmokers could be due, therefore, to the increased risk from longer TSFE among former smokers, rather than a protective effect among current smokers. In addition, the analyses based on ever-smoker status or on pack-years did not indicate potential confounding (see Table E-1). This is consistent with the conclusion of the ATS (2004) that smoking does not affect the presentation of asbestos-related pleural fibrosis. Consequently, smoking status was not included in further analyses.

BMI was investigated as a potential confounder because fat pads along the chest wall can sometimes be misdiagnosed as pleural thickening in conventional x-rays. Thus, there might be a positive relation between BMI and pleural thickening. The analysis of BMI as a confounder is limited because data on BMI were not collected in the 1980 study (Lockey et al., 1984). Using the available data, the analysis showed that BMI was not a potential confounder as it was not associated with either exposure or outcome (see Table E-1). Accordingly, BMI was not included in further analyses.

CE is commonly used in modeling of some asbestos outcomes. What is known about the distribution and retention of inhaled fibers is summarized in Section 3. For example, lung cancer exposure-response for asbestos is usually modeled with CE. However, for pleural effects from exposure to chrysotile asbestos, a mean exposure metric in a model that included TSFE was also proposed (Paris et al., 2008). Therefore, for this assessment several exposure metrics were investigated in the modeling, including mean exposure (fibers/cc), CE (fibers/cc-yr), and RTW CE (fibers/cc-yrs^2).

The importance of TSFE to date of x-ray is clearly illustrated by comparing the results of Lockey et al. (1984) with the results of Rohs et al. (2008). These two studies were conducted in the same worker population (with some loss to follow-up) 24 years apart. In the initial study (Lockey et al., 1984), only 2% of the individuals showed pleural changes; in the follow-up study (Rohs et al., 2008), 28% of the individuals showed pleural changes. There was very little additional exposure to fibers after 1980. This result is consistent with findings in other occupational cohorts exposed to various forms of asbestos fibers that TSFE is a significant explanatory variable for pleural thickening, even in the absence of continued exposure (Paris et al., 2009; Paris et al., 2008; Jakobsson et al., 1995; Ehrlich et al., 1992; Järvholm, 1992). An important point of clarification is that TSFE is not the same as time to the first appearance of the adverse health outcome. The pleural thickening or small interstitial opacities could have formed at any time between the start of exposure and the time the endpoint was observed in the x-rays (e.g., for a worker who was negative for APT in 1980 but positive in 2004, the APT could have occurred anytime between 1980 and 2004, as only two x-ray events are available).

It has been suggested that pleural abnormalities increase in extent (Sichletidis et al., 2006) and that the prevalence increases as a function of TSFE (Lilis et al., 1991). The fibers persist in the respiratory tract and pleural tissue for a long time and can continue to damage the tissue even in the absence of continued exposure. An alternative explanation is that the fibrosis is already initiated by the exposure, but additional time is needed for the lesion to progress in size to be visible on the x-ray. There are no data available to distinguish these possibilities in the Marysville cohorts. Therefore, models that include TSFE as an explanatory variable and allow for the prevalence of APT to increase with longer follow-up even in the absence of continued exposure were given some preference in this analysis.

E.3.3. Model Forms and Exposure Metrics

A range of model forms were investigated to determine which was most appropriate for use in characterizing the exposure-response relationship to derive the point of departure (POD). These models forms are summarized in Table E-2.

Table E-2. Model forms considered in developing the point of departure (POD)

Category	Name	Code	Equation
Univariate *X* = C, CE, RTW	Log-Logistic	UV LL	$p(x) = bkg + \frac{1 - bkg}{1 + \exp[-a - b \times \ln(x)]}$
	Dichotomous Hill a) Estimated plateau b) Fixed plateau	UV DH UV DH FP	$p(x) = bkg + \frac{Plateau - bkg}{1 + \exp[-a - b \times \ln(x)]}$
Bivariate *X* = C, CE *T* = time from first exposure	Bivariate log-logistic	BV LL	$p(x,T) = bkg + \frac{1 - bkg}{1 + \exp[-a - b \times \ln(x) - c \times T]}$
	Bivariate Dichotomous Hill a) Estimated plateau b) Fixed plateau	BV DH BV DH FP	$p(x,T) = bkg + \frac{Plateau - bkg}{1 + \exp[-a - b \times \ln(x) - c \times T]}$
	Cumulative normal Dichotomous Hill	CN DH	$p(x,T) = bkg + \frac{Plateau(T) - bkg}{1 + \exp[-a - b \times \ln(x)]}$ $Plateau(T) = bkg + (1 - bkg) \times \Phi(T\|m,s)$
	Cumulative normal Michaelis-Menten	CN MM	$p(x,T) = bkg + \frac{Plateau(T) - bkg}{1 + \exp[-a - \ln(x)]}$ $Plateau(T) = bkg + (1 - bkg) \times \Phi(T\|m,s)$

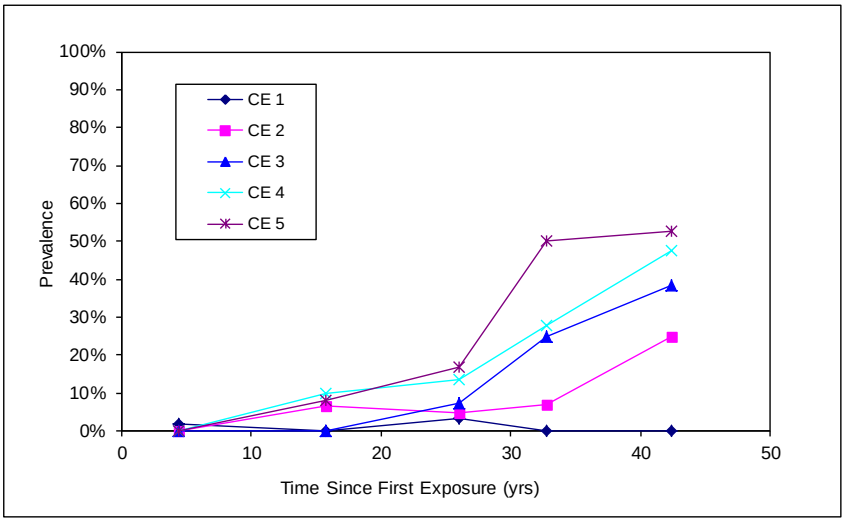
The background prevalence (*bkg*) of the health effect of interest was treated as an estimated parameter for all models. The exposure metrics tested included mean exposure concentration, CE, and RTW exposure. Univariate models that were tested included log-logistic (UV LL) and Dichotomous Hill with estimated (UV DH) or fixed plateau (UV DH FP).

Bivariate models that were tested included log-logistic (BV LL) and Dichotomous Hill with estimated (BV DH) or fixed plateau (BV DH FP) with the same exposure metrics as noted above and with TSFE incorporated as an additional explanatory variable in the exponential term. This is the more conventional way of incorporating an additional explanatory variable in a logistic model.

As an additional approach, modified versions of the Dichotomous Hill and Michaelis-Menten models were evaluated with the exposure metrics of mean and CE and with the *plateau* term modeled as a function dependent on TSFE. These model forms were tested because a plot of the shape of the prevalence curve (based on APT) as a function of TSFE at fixed CE shows that that the curve begins low and then rises in a nonlinear fashion (see Figure E-2 panel A), and that the "plateau" at high CE tends to increase as TSFE increases (see Figure E-2 panel B). This behavior suggests that expressing the plateau as a function with an S-shape could be suitable. Several S-shaped curves were tested, including the cumulative

normal, cumulative gamma, and cumulative Weibull. Based on Akaike Information Criterion (AIC), there was no significant difference in performance for any of these functions; therefore, the cumulative normal function was chosen because of its familiarity and ease of use. The resulting models are referred to as the cumulative normal Dichotomous Hill (CN DH) or the cumulative normal Michaelis-Menten (CN MM). The effect of increasing TSFE in these model forms is to increase the plateau (maximum prevalence at high exposure) and also to increase the slope of the response (the increase in prevalence per unit increase in exposure). However, these model forms do not allow TSFE to function as a separate predictor of prevalence alongside with the exposure metric as in the BV LL and BV DH models. It is acknowledged that this is a less conventional way of incorporating an additional explanatory variable in a logistic model. However, these model forms based on the cumulative normal function are included so that the results with this data set can be judged along with the results of other models.

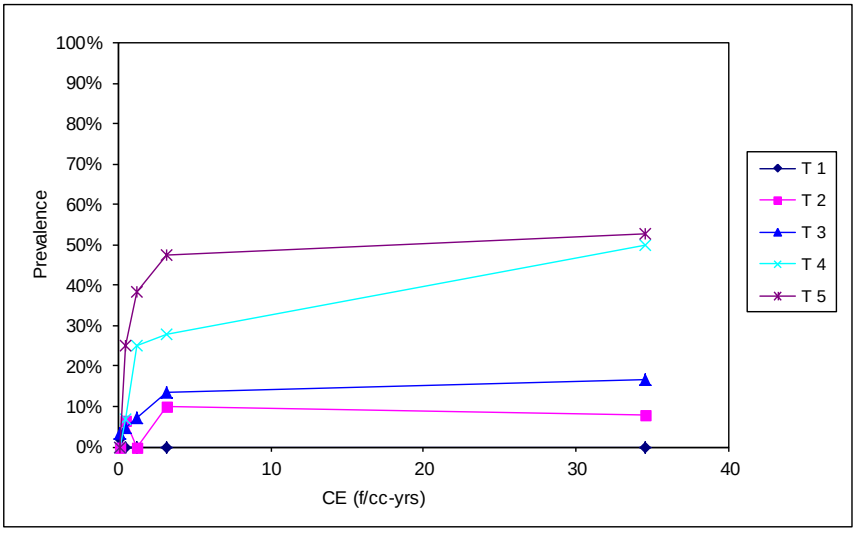
Panel A: Prevalence vs. time since first exposure stratified by cumulative exposure.



CE Bins

Bin Number	Bin Lower Bound	Bin Upper Bound	Mean Value	No. of Workers	No. of Cases	Prev
CE 1	0.00	0.23	0.09	87	2	2.3%
CE 2	0.23	0.91	0.53	87	5	5.7%
CE 3	0.91	1.73	1.20	86	16	18.6%
CE 4	1.73	7.20	3.22	87	19	21.8%
CE 5	7.20	100.00	34.50	87	31	35.6%

Panel B: Prevalence vs. cumulative exposure stratified by time since first exposure



TSFE Bins

Bin Number	Bin Lower Bound	Bin Upper Bound	Mean Value	No. of Workers	No. of Cases	Prev
T 1	0.0	9.8	4.4	87	1	1.1%
T 2	9.8	23.4	15.7	80	5	6.3%
T 3	23.4	29.8	26.0	93	7	7.5%
T 4	29.8	36.3	32.7	87	20	23.0%
T 5	36.3	100.0	42.4	87	40	46.0%

Figure E-2. Observed dependence of any pleural thickening (APT) prevalence on cumulative exposure (CE) and time since first exposure (TSFE).

E.3.4. Benchmark Response

As discussed in Section 5.2.2.4, a benchmark response (BMR) of 10% extra risk is used in this assessment. For the modeling of the full cohort a BMR of 10% extra risk is also used for all endpoints (LPT, APT, or ARC). The vast majority of cases in the combined cohort are classified as LPT. Using the same BMR across all endpoints also permits easier comparison of the results.

E.3.5. Modeling Results

The modeling results are summarized in Table E-3 through E-5, below. For models that include TSFE as an independent explanatory variable, the results are shown for two alternative values: TSFE = 70 years and TSFE = 25 years. These two values were selected because 25 years is the median value of TSFE for the combined cohort, and consequently using the values for TSFE = 25 years does not require extrapolation outside the observed range of the data. Results were derived for TSFE = 70 years because the ultimate objective of this effort is to derive a reference concentration (RfC) that is applicable to an individual exposed for 70 years.

Table E-3. Modeling results for localized pleural thickening (LPT) in the combined cohort of Marysville workers evaluated in 1980 or in 2002−2005

Model	Exp. metric	*bkg*	*a*	*b*	*c*	*m*	*s*	Plateau[a]	H-L *p*	AIC	BMD (70)	BMDL (70)	BMC (70)	BMCL (70)	BMD (25)	BMDL (25)	BMC (25)	BMCL (25)
UV LL	C	0.000	−0.921	0.338	--	--	--	1.000	0.030	370.49	2.3×10^{-2}	5.9×10^{-3}	2.3×10^{-2}	5.9×10^{-3}				
	CE	0.014	−2.127	0.466	--	--	--	1.000	0.175	350.35	8.6×10^{-1}	2.6×10^{-1}	1.2×10^{-2}	3.7×10^{-3}				
	rtwCE	0.014	−3.780	0.534	--	--	--	1.000	0.383	328.39	1.9×10^{1}	8.7×10^{0}	7.9×10^{-3}	3.5×10^{-3}				
UV DH FP	C	0.000	−0.675	0.357	--	--	--	0.850	0.031	370.35	2.3×10^{-2}	6.3×10^{-3}	2.3×10^{-2}	6.3×10^{-3}				
	CE	0.016	−1.960	0.502	--	--	--	0.850	0.189	350.04	9.0×10^{-1}	2.8×10^{-1}	1.3×10^{-2}	3.9×10^{-3}				
	rtwCE	0.014	−3.731	0.578	--	--	--	0.850	0.445	327.92	2.0×10^{1}	9.1×10^{0}	8.0×10^{-3}	3.7×10^{-3}				
UV DH	C	0.007	2.388	0.903	--	--	--	0.309	0.048	370.64	3.2×10^{-2}	1.2×10^{-2}	3.2×10^{-2}	1.2×10^{-2}				
	CE	0.025	−0.767	1.992	--	--	--	0.325	0.526	346.33	1.0×10^{0}	6.7×10^{-1}	1.5×10^{-2}	9.6×10^{-3}				
	rtwCE	0.020	−7.107	2.033	--	--	--	0.371	0.895	324.73	2.1×10^{1}	1.4×10^{1}	8.4×10^{-3}	5.6×10^{-3}				
BV LL	C, TSFE	0.008	−4.377	0.338	0.112	--	--	1.000	0.169	301.80	5.4×10^{-8}	$<1 \times 10^{-12}$	5.4×10^{-8}	$<1 \times 10^{-12}$	1.6×10^{-1}	5.0×10^{-2}	1.6×10^{-1}	5.0×10^{-2}
	CE, TSFE	0.010	−5.190	0.348	0.103	--	--	1.000	0.012	300.97	5.2×10^{-6}	1.8×10^{-11}	7.5×10^{-8}	2.5×10^{-13}	3.3×10^{0}	1.0×10^{0}	1.3×10^{-1}	4.2×10^{-2}
BV DH FP	C, TSFE	0.009	−4.434	0.403	0.125	--	--	0.850	0.220	300.71	1.5×10^{-7}	1.2×10^{-12}	1.5×10^{-7}	1.2×10^{-12}	1.7×10^{-1}	6.1×10^{-2}	1.7×10^{-1}	6.1×10^{-2}
	CE, TSFE	0.012	−5.382	0.409	0.114	--	--	0.850	0.002	299.98	1.2×10^{-5}	1.4×10^{-10}	1.7×10^{-7}	2.0×10^{-12}	3.5×10^{0}	1.2×10^{0}	1.4×10^{-1}	4.9×10^{-2}
BV DH	C, TSFE	0.015	−5.151	0.667	0.190	--	--	0.559	0.643	301.05	5.1×10^{-7}	3.9×10^{-11}	5.1×10^{-7}	3.9×10^{-11}	1.9×10^{-1}	8.4×10^{-2}	1.9×10^{-1}	8.4×10^{-2}
	CE, TSFE	0.016	−6.387	0.615	0.160	--	--	0.586	0.062	300.78	3.2×10^{-5}	1.4×10^{-9}	4.6×10^{-7}	2.0×10^{-11}	3.8×10^{0}	1.6×10^{0}	1.5×10^{-1}	6.3×10^{-2}
CN MM	C, TSFE	0.011	3.151	1.000	--	38.47	13.24	0.991	0.200	299.42	4.8×10^{-3}	2.1×10^{-3}	4.8×10^{-3}	2.1×10^{-3}	7.8×10^{-2}	3.2×10^{-2}	7.8×10^{-2}	3.2×10^{-2}
	CE, TSFE	0.015	−0.273	1.000	--	38.27	14.00	0.988	0.540	298.22	1.5×10^{-1}	6.3×10^{-2}	2.1×10^{-3}	9.0×10^{-4}	1.8×10^{0}	8.2×10^{-1}	7.3×10^{-2}	3.3×10^{-2}

Table E-3. Modeling results for localized pleural thickening (LPT) in the combined cohort of Marysville workers evaluated in 1980 or in 2002−2005 (continued)

Model	Exp. metric	*bkg*	*a*	*b*	*c*	*m*	*s*	Plateau[a]	H-L *p*	AIC	BMD (70)	BMDL (70)	BMC (70)	BMCL (70)	BMD (25)	BMDL (25)	BMC (25)	BMCL (25)
CN DH	C, TSFE	0.017	11.05	3.26	--	41.02	13.88	0.982	0.435	299.83	1.7×10^{-2}	2.0×10^{-3}	1.7×10^{-2}	2.0×10^{-3}	3.7×10^{-2}	2.4×10^{-2}	3.7×10^{-2}	2.4×10^{-2}
	CE, TSFE	0.018	−0.233	1.592	--	39.59	14.58	0.981	0.158	299.49	3.0×10^{-1}	2.8×10^{-2}	4.2×10^{-3}	4.0×10^{-4}	1.6×10^{0}	8.8×10^{-1}	6.5×10^{-2}	3.5×10^{-2}

Grey Cells = Although a maximum likelihood solution was obtained at TSFE = 25, a value for lower limit of the benchmark concentration (BMCL) could not be derived. Consequently, the model was derived for TSFE = 28, where a value for BMCL could be estimated. The median value for TSFE in the Rohs cohort is 28 yrs.

[a]For CN models, the plateau term shown is for TSFE = 70 yrs.

Exp = exposure; H-L *p* = Hosmer-Lemeshow *p*-value; BMC = benchmark concentration; BMD = benchmark dose; BMDL = lower limit of the benchmark dose.

a, b, c m and s are model fitting parameters

Table E-4. Modeling results for any pleural thickening (APT) in the combined cohort of Marysville workers evaluated in 1980 or in 2002−2005

Model	Exp. metric	*bkg*	*a*	*b*	*c*	*m*	*s*	Plateau[a]	H-L *p*	AIC	BMD (70)	BMDL (70)	BMC (70)	BMCL (70)	BMD (25)	BMDL (25)	BMC (25)	BMCL (25)
UV LL	C	0.000	−0.846	0.350	--	--	--	1.000	0.061	378.25	2.1×10^{-2}	5.7×10^{-3}	2.1×10^{-2}	5.7×10^{-3}				
	CE	0.013	−2.062	0.469	--	--	--	1.000	0.193	357.63	7.5×10^{-1}	2.3×10^{-1}	1.1×10^{-2}	3.3×10^{-3}				
	rtwCE	0.013	−3.760	0.545	--	--	--	1.000	0.355	333.67	1.8×10^{1}	8.1×10^{0}	7.2×10^{-3}	3.3×10^{-3}				
UV DH FP	C	0.000	−0.592	0.372	--	--	--	0.850	0.063	378.06	2.2×10^{-2}	6.2×10^{-3}	2.2×10^{-2}	6.2×10^{-3}				
	CE	0.015	−1.896	0.509	--	--	--	0.850	0.210	357.23	8.0×10^{-1}	2.5×10^{-1}	1.1×10^{-2}	3.6×10^{-3}				
	rtwCE	0.013	−3.732	0.596	--	--	--	0.850	0.425	333.03	1.8×10^{1}	8.6×10^{0}	7.3×10^{-3}	3.5×10^{-3}				
UV DH	C	0.011	2.673	1.000	--	--	--	0.318	0.091	377.95	3.3×10^{-2}	1.2×10^{-2}	3.3×10^{-2}	1.2×10^{-2}				
	CE	0.025	−0.760	2.198	--	--	--	0.335	0.611	352.14	9.9×10^{-1}	6.67×10^{-1}	1.4×10^{-2}	9.5×10^{-3}				
	rtwCE	0.020	−7.567	2.161	--	--	--	0.389	0.936	328.53	2.1×10^{1}	1.38×10^{1}	8.4×10^{-3}	5.6×10^{-3}				
BV LL	C, TSFE	0.008	−4.422	0.360	0.116	--	--	1.000	0.238	303.30	7.1×10^{-8}	$<1 \times 10^{-12}$	7.1×10^{-8}	$<1 \times 10^{-12}$	1.5×10^{-1}	5.0×10^{-2}	1.5×10^{-1}	5.0×10^{-2}
	CE, TSFE	0.010	−5.263	0.356	0.107	--	--	1.000	0.022	303.38	4.0×10^{-6}	2.16×10^{-11}	5.7×10^{-8}	$<1 \times 10^{-12}$	3.0×10^{0}	9.6×10^{-1}	1.2×10^{-1}	3.8×10^{-2}
BV DH FP	C, TSFE	0.010	−4.546	0.443	0.133	--	--	0.850	0.455	301.68	2.2×10^{-7}	1.0×10^{-11}	2.2×10^{-7}	1.0×10^{-11}	1.7×10^{-1}	6.3×10^{-2}	1.7×10^{-1}	6.3×10^{-2}
	CE, TSFE	0.012	−5.549	0.431	0.121	--	--	0.850	0.006	301.94	1.1×10^{-5}	2.7×10^{-10}	1.6×10^{-7}	3.8×10^{-12}	3.3×10^{0}	1.1×10^{0}	1.3×10^{-1}	4.2×10^{-2}
BV DH	C, TSFE	0.015	−5.393	0.707	0.199	--	--	0.588	0.724	301.62	6.0×10^{-7}	1.4×10^{-10}	6.0×10^{-7}	1.4×10^{-10}	1.9×10^{-1}	8.7×10^{-2}	1.9×10^{-1}	8.7×10^{-2}
	CE, TSFE	0.018	−7.165	0.709	0.186	--	--	0.577	0.068	302.08	3.0×10^{-5}	3.3×10^{-9}	4.3×10^{-7}	4.7×10^{-11}	4.0×10^{0}	1.7×10^{0}	1.6×10^{-1}	6.7×10^{-2}
CN MM	C, TSFE	0.011	3.134	1.000	--	37.53	12.64	0.995	0.232	300.86	4.9×10^{-3}	2.2×10^{-3}	4.9×10^{-3}	2.2×10^{-3}	7.2×10^{-2}	3.1×10^{-2}	7.2×10^{-2}	3.1×10^{-2}
	CE, TSFE	0.015	−0.243	1.000	--	37.48	13.42	0.992	0.665	300.27	1.4×10^{-1}	6.4×10^{-2}	2.0×10^{-3}	9.1×10^{-4}	1.7×10^{0}	7.6×10^{-1}	6.7×10^{-2}	3.1×10^{-2}
CN DH	C, TSFE	0.017	11.172	3.326	--	39.89	13.20	0.989	0.534	300.53	1.8×10^{-2}	3.6×10^{-3}	1.8×10^{-2}	3.6×10^{-3}	5.0×10^{-2}	3.2×10^{-2}	5.0×10^{-2}	3.2×10^{-2}
	CE, TSFE	0.018	−0.222	1.778	--	38.89	14.05	0.987	0.243	301.04	3.3×10^{-1}	5.3×10^{-2}	4.7×10^{-3}	7.5×10^{-4}	1.5×10^{0}	8.6×10^{-1}	6.0×10^{-2}	3.4×10^{-2}

[a]For CN models, the plateau term shown is for TSFE = 70 yrs.

Table E-5. Modeling results for any radiographic change (ARC) in the combined cohort of Marysville workers evaluated in 1980 or in 2002−2005

Model	Exp. metric	*bkg*	*a*	*b*	*c*	*m*	*s*	Plateau[a]	H-L *p*	AIC	BMD (70)	BMDL (70)	BMC (70)	BMCL (70)	BMD (25)	BMDL (25)	BMC (25)	BMCL (25)
UV LL	C	0.000	−0.732	0.383	--	--	--	1.000	0.055	382.856	2.2×10^{-2}	7.1×10^{-3}	2.2×10^{-2}	7.1×10^{-3}				
	CE	0.015	−2.075	0.510	--	--	--	1.000	0.238	360.193	7.9×10^{-1}	2.6×10^{-1}	1.1×10^{-2}	3.7×10^{-3}				
	rtwCE	0.013	−3.859	0.580	--	--	--	1.000	0.374	334.455	1.8×10^{1}	8.4×10^{0}	7.1×10^{-3}	3.4×10^{-3}				
UV DH FP	C	0.000	−0.469	0.408	--	--	--	0.850	0.057	382.701	2.3×10^{-2}	7.6×10^{-3}	2.3×10^{-2}	7.6×10^{-3}				
	CE	0.016	−1.904	0.553	--	--	--	0.850	0.262	359.875	8.2×10^{-1}	2.8×10^{-1}	1.2×10^{-2}	4.1×10^{-3}				
	rtwCE	0.000	−0.469	0.408	--	--	--	0.850	0.057	382.701	2.3×10^{-2}	7.6×10^{-3}	9.2×10^{-6}	3.1×10^{-6}				
UV DH	C	0.000	1.754	0.776	--	--	--	0.384	0.073	383.619	2.7×10^{-2}	1.0×10^{-2}	2.7×10^{-2}	1.0×10^{-2}				
	CE	0.025	−0.849	2.139	--	--	--	0.358	0.570	356.772	9.9×10^{-1}	6.6×10^{-1}	1.4×10^{-2}	9.4×10^{-3}				
	rtwCE	0.020	−7.244	2.022	--	--	--	0.420	0.882	331.410	2.1×10^{1}	1.4×10^{1}	8.4×10^{-3}	5.6×10^{-3}				
BV LL	C, TSFE	0.008	−4.303	0.416	0.118	--	--	1.000	0.237	304.545	3.6×10^{-7}	1.0×10^{-10}	3.6×10^{-7}	1.0×10^{-10}	1.3×10^{-1}	5.0×10^{-2}	1.3×10^{-1}	5.0×10^{-2}
	CE, TSFE	0.011	−5.263	0.410	0.107	--	--	1.000	0.006	304.776	2.1×10^{-5}	4.1×10^{-9}	3.0×10^{-7}	5.9×10^{-11}	2.6×10^{0}	9.6×10^{-1}	1.0×10^{-1}	3.9×10^{-2}
BV DH FP	C, TSFE	0.010	−4.443	0.507	0.136	--	--	0.850	0.379	302.957	8.2×10^{-7}	6.1×10^{-10}	8.2×10^{-7}	6.1×10^{-10}	1.5×10^{-1}	6.3×10^{-2}	1.5×10^{-1}	6.3×10^{-2}
	CE, TSFE	0.012	−5.593	0.495	0.122	--	--	0.850	0.092	303.329	4.4×10^{-5}	2.1×10^{-8}	6.3×10^{-7}	3.0×10^{-10}	2.9×10^{0}	1.2×10^{0}	1.2×10^{-1}	4.7×10^{-2}
BV DH	C, TSFE	0.016	−5.300	0.774	0.202	--	--	0.610	0.869	303.397	1.4×10^{-6}	2.6×10^{-9}	1.4×10^{-6}	2.6×10^{-9}	1.7×10^{-1}	8.3×10^{-2}	1.7×10^{-1}	8.3×10^{-2}
	CE, TSFE	0.018	−7.299	0.787	0.189	--	--	0.594	0.439	303.896	7.3×10^{-5}	8.3×10^{-8}	1.0×10^{-6}	1.2×10^{-9}	3.6×10^{0}	1.6×10^{0}	1.4×10^{-1}	6.4×10^{-2}
CN MM	C, TSFE	0.011	3.012	1.000	--	36.23	12.29	0.997	0.289	303.611	5.5×10^{-3}	2.6×10^{-3}	5.5×10^{-3}	2.6×10^{-3}	6.1×10^{-2}	3.0×10^{-2}	6.1×10^{-2}	3.0×10^{-2}
	CE, TSFE	0.015	−0.356	1.000	--	36.13	13.10	0.995	0.346	303.006	1.6×10^{-1}	7.6×10^{-2}	2.3×10^{-3}	1.1×10^{-3}	1.5×10^{0}	7.3×10^{-1}	5.8×10^{-2}	2.9×10^{-2}
CN DH	C, TSFE	0.016	9.507	2.883	--	38.64	12.89	0.993	0.202	303.621	1.7×10^{-2}	3.4×10^{-3}	1.7×10^{-2}	3.4×10^{-3}	4.9×10^{-2}	3.3×10^{-2}	4.9×10^{-2}	3.3×10^{-2}
	CE, TSFE	0.018	−0.326	1.751	--	37.71	13.82	0.990	0.443	303.906	3.5×10^{-1}	5.4×10^{-2}	4.9×10^{-3}	7.7×10^{-4}	1.4×10^{0}	8.3×10^{-1}	5.5×10^{-2}	3.3×10^{-2}

[a]For CN models, the plateau term shown is for TSFE = 70 yrs

The units in the benchmark dose (BMD) and lower limit of the BMD (BMDL) columns are those of the exposure metric used in the model. When the exposure metric was based on CE, the benchmark concentration (BMC) and lower limit of the BMC (BMCL) values were calculated by dividing the BMD and BMDL by the value of TSFE. When the exposure metric was RTW, the BMC and BMCL were calculated by dividing the integral of TSFE from 0 to 70 years ($=70^2/2$). The units of the BMC and BMCL are fibers/cc.

E.3.6. Considerations for Identification of the Preferred Model(s) for the Combined Cohort

The following factors were considered in evaluating the model results in order to identify models that might provide a sound basis for selection of a POD and derivation of an RfC.

- All models with an unacceptable Hosmer-Lemeshow (H-L) goodness-of-fit statistic ($p < 0.10$) were eliminated. This is in accord with the approach usually followed in BMD modeling (U.S. EPA, 2012).

- Models with lower AIC values were generally preferred over models with higher AIC values. Fits of models with AIC values that were within 2 units of each other were considered to be approximately equivalent (U.S. EPA, 2012; Burnham and Anderson, 2002).

- Models with a relatively low fitted plateau (the maximum prevalence at high exposure and long TSFE) were given lower priority. This factor was considered because the prevalence of an adverse health outcome in individuals exposed to asbestos fibers is expected to approach some relatively high value (e.g., 80−100%) in situations with high exposure and long follow-up time (Winters et al., 2012; Järvholm, 1992; Lilis et al., 1991).

- Model results with a wide interval between the BMC and BMCL were given low priority because the wide interval indicates an uncertain value for BMCL.

- Models that had a good visual agreement between observed and predicted responses, especially in the region of the BMR, were preferred over models with poor agreement. This is implemented by inspection of graphs of the predicted response from the model with the observed data, stratified into bins. This is a subjective evaluation and depends in part on how the observed data are binned.

E.3.7. Selection of the Preferred Models for the Combined Cohort

The model results presented in Tables E-3 to E-5 were reviewed with respect to the factors described above. In general, findings were similar for all three endpoints, with the following main conclusions:

- All univariate models (UV LL, UV DH, and UV DH FP) based on the three exposure metrics (mean, cumulative, and RTW exposure) performed relatively poorly, as

indicated by high AIC values greater than 25 units larger than the best fitting models within each endpoint (see Tables E-3 to E-5) and/or H-L *p*-values below 0.1. Consequently, this class of models was not retained for further consideration in the derivation of the POD.

- Bivariate Dichotomous Hill models based on C or CE and TSFE were not considered as the fitted plateau term was considerably lower than 85%.

- Bivariate models based on TSFE and C or CE where TSFE acts on the slope term directly (BV LL and BV DH FP) generally yielded results with favorable AIC values. However, models based on TSFE and CE had H-L *p*-values below 0.1 and were not considered further. Models based on TSFE and C had adequate H-L *p*-values ($p > 0.1$) and had relatively narrow intervals between the BMC and the BMCL when TSFE = 25 years (the median value for the combined cohort). In contrast, these same models yielded results with extremely wide intervals between the BMC and the BMCL when extrapolated to TSFE = 70 years. These results indicate the potential for considerable model uncertainty when extrapolating beyond the range of the observed data. Consequently, this class of models was retained for further consideration in the derivation of the POD only for TSFE = 25 years. Because the results at TSFE = 25 years are quite similar for the BV LL and BV DH FP models, only the BV DH FP models were assessed further. This is consistent with the modeling presented in Section 5 of the main document.

- Bivariate models, where the TSFE term acts on the plateau term (CN MM and CN DH) with either mean or CE, demonstrated adequate goodness of fit with H-L *p*-values > 0.1, and had low AIC values, a plateau term that approaches 1.0 at high TSFE, and relatively narrow intervals between the BMC and the BMCL (BMC/BMCL ratios of approximately 2 at TSFE = 25 years and approximately 6 at TSFE = 70 years). Consequently, this class of models where the TSFE variable acts on the plateau term (CN DH and CN MM) was also retained for further consideration in the derivation of the POD.

Based upon these considerations, five models were identified for further consideration including the BV DH FP (C, TSFE)[13], CN DH (C or CE, TSFE) and the CN MM (C or CE, TSFE). Each of these models demonstrated adequate goodness of fit, and incorporates both exposure and TSFE as predictors of the prevalence of pleural thickening, and have comparable AIC values (usually within 2 units of each other).

Between the CN models (CN DH and CN MM) where the plateau term is a function of TSFE, there was no clear and consistent statistical basis (i.e., goodness of fit or relative fit) for distinguishing between C and CE as the preferred exposure metric. However, it should be noted that there is not a large difference in the BMCL regardless of whether C or CE is used as the exposure metric. The model using CE was used in this analysis of the combined cohort because CE is commonly used in exposure-response modeling for asbestos. In addition, there was a

[13]This notation indicates the model form and the explanatory variable in parentheses.

statistically significant association between duration of exposure and prevalence of APT in the univariate analysis (see Table E-1). Finally, duration of exposure was not included as a separate predictor because CE includes duration of exposure. A relationship between CE and the adverse health effects could reflect a cumulative increase in internal dose for the fiber or could reflect accumulating tissue damage.

Likewise, between the two CN models, there was little statistical basis for distinguishing between the MM models and the DH models, and both yielded similar BMCL values. The CN DH model was selected as being more flexible compared to the CN MM model because it treats the shape term for the exposure metric as a fitting parameter as opposed to assigning the shape term to 1 as in the CN MM model. Thus, the two models given highest priority for deriving a POD for the combined cohort were the CN DH model with CE (for TSFE = 25 or TSFE = 70 years) and the BV DH FP model with C (for TSFE = 25 years). Results from these two model forms are presented in the remainder of this appendix.

In order to compare observed APT prevalence in the combined cohort (73 cases in 434 workers) to that predicted by the CN DH model using CE and TSFE as explanatory variables, it is necessary to group the workers into bins according to TSFE and CE. The CE bins were formed by dividing the cohort into four groups of approximately equal size, as shown in Table E-6.

Table E-6. Cumulative exposure (CE) bins

CE bin	Bin lower bound	Bin upper bound	Number of workers in bin
1	0.00	0.34	109
2	0.34	1.13	108
3	1.13	3.74	108
4	3.74	96.91	109

The TSFE bins were formed by dividing the cohort into three groups of similar size, as shown in Table E-7.

Table E-7. Time since first exposure (TSFE) bins

TSFE bin	Bin lower bound	Bin upper bound	Number of workers in bin
1	0	20.0	141
2	20.0	30.0	125
3	30.0	50.0	168

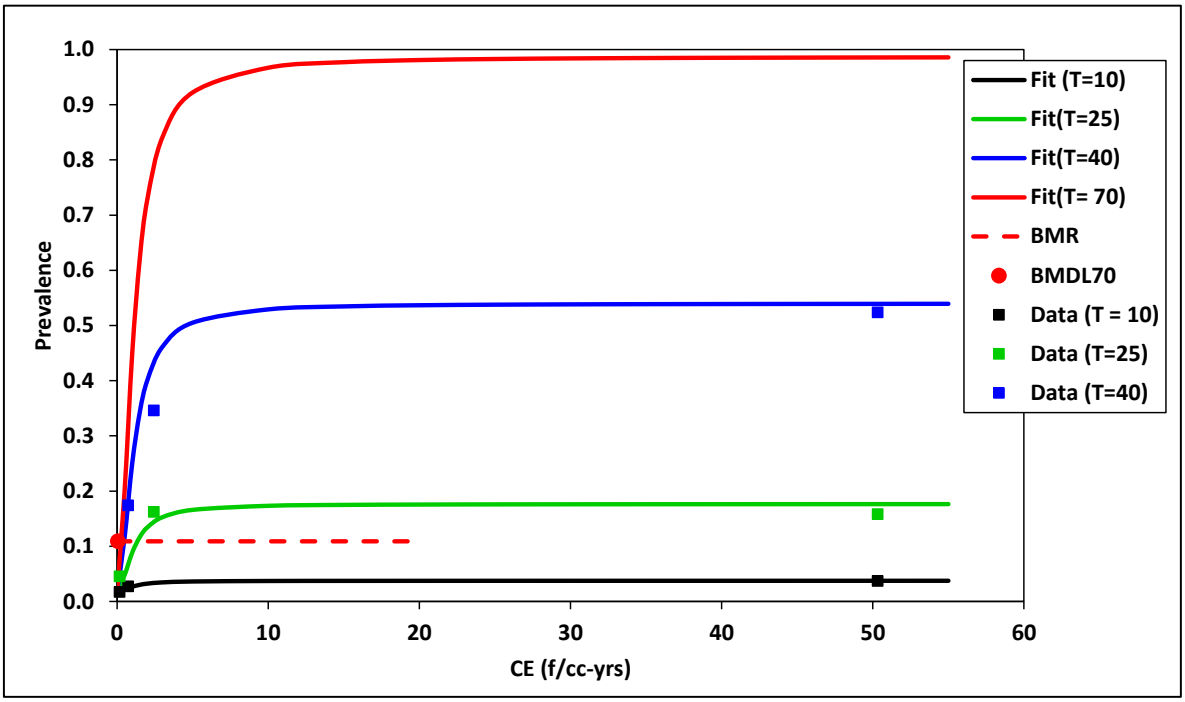
Using these binning rules yielded the prevalence of APT for each bin is shown in Table E-8.

Table E-8. Prevalence of any pleural thickening (APT) stratified into bins

TSFE bin midpoint	Cumulative exposure bin midpoint (fibers/cc-yr)			
	0.17	**0.73**	**2.43**	**50.33**
10	1/58= 0.02	1/37 = 0.03	0/19 = 0	1/27 = 0.04
25	2/44= 0.05	0/25 = 0	6/37 = 0.16	3/19 = 0.16
40	0/7 = 0	8/46 = 0.17	18/52 = 0.35	33/63 = 0.52

Figure E-3 shows the agreement between observed APT prevalence (shown as data points) and predicted prevalence (shown as smooth lines) for the CN DH (CE, TSFE) model. Panel A compares observed to predicted as a function of CE, stratified by average TSFE. The red line represents the model predictions for TSFE = 70 years. Note that there are no workers with this long a length of follow-up, so there are no observations to compare to the model predictions for this curve. Panel B compares the observed and predicted prevalence as a function of TSFE, stratified by CE. As illustrated, the agreement between observed and predicted prevalence is relatively good in both dimensions. These graphs help illustrate the key feature of the CN DH model, which is that the maximum prevalence at high CE is low for short TSFE, and increases towards 1.0 only as TSFE increases towards 70 (see Panel A). Likewise, Panel B shows that for TSFE of 70, prevalence is predicted to be low at low CE values, and prevalence approaching the maximum does not occur until CE values reach relatively high levels (in the range of 50 fibers/cc-yrs). Also note, even though TSFE does not act directly on the slope of the exposure-response curve, because the plateau increases as TSFE increases (see Panel A), the initial slope also increases as TSFE increases.

Panel A: Observed vs. predicted as a function of cumulative exposure (CE)



Panel B: Observed vs. predicted as a function of time from first exposure (TSFE)

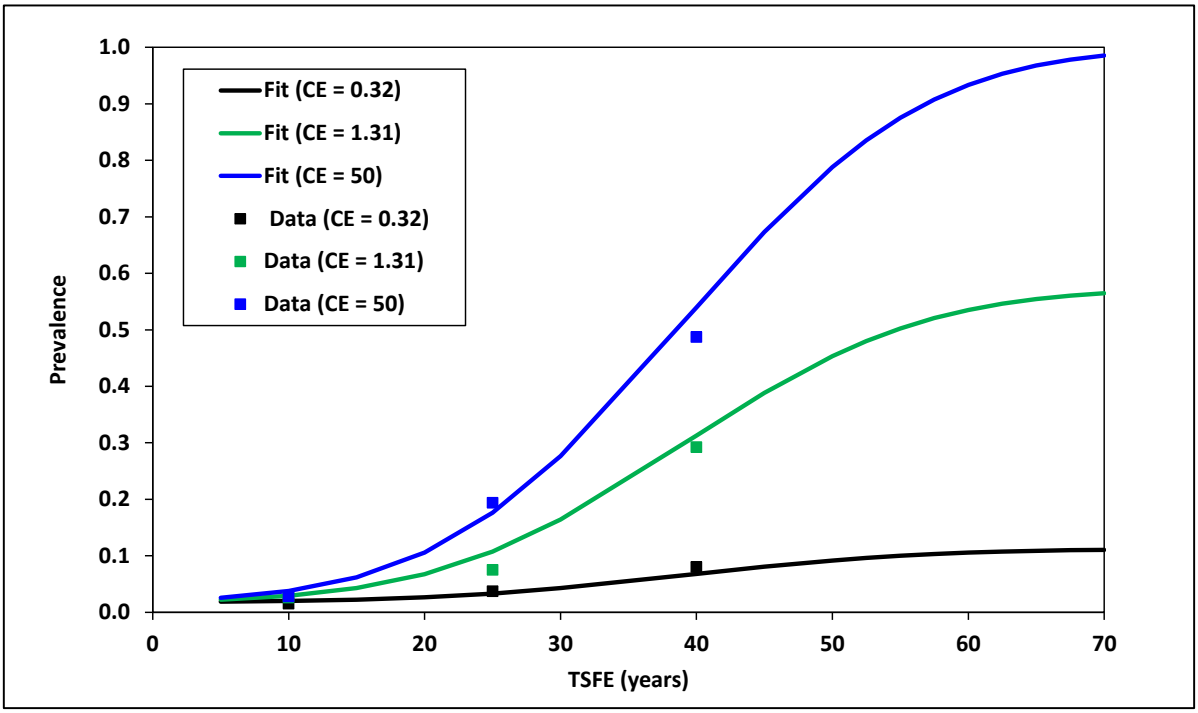
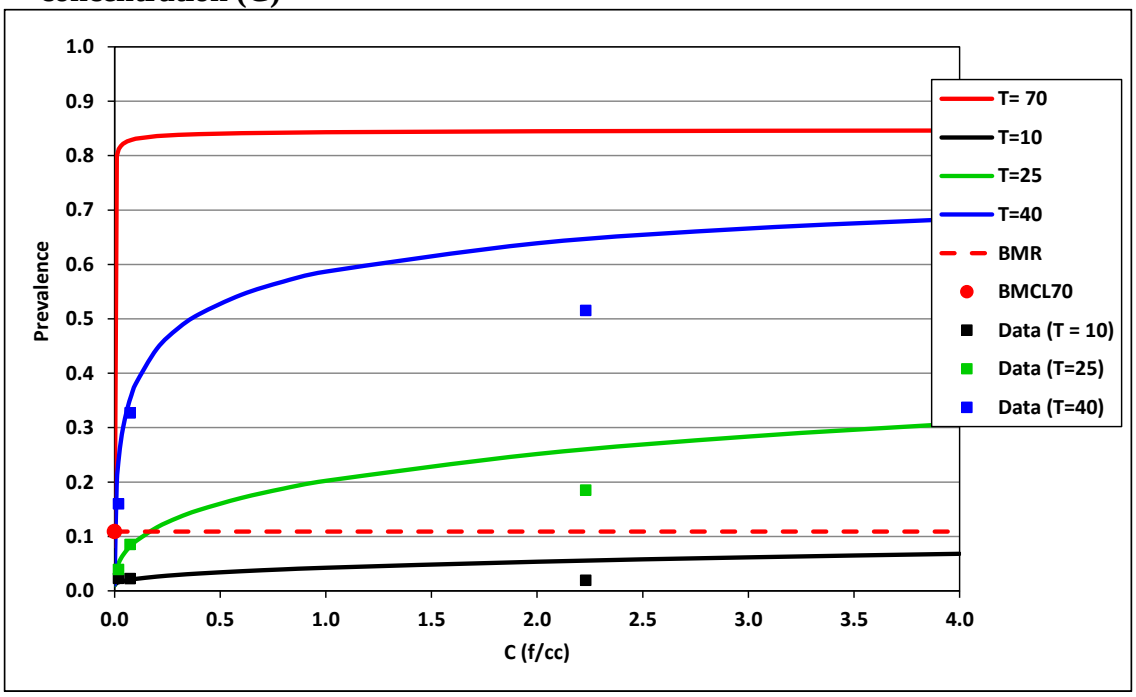


Figure E-3. Graphical display of predicted vs. observed any pleural thickening (APT) prevalence for cumulative normal Dichotomous Hill (CN DH) model fit to the combined cohort.

1

Figure E-4 shows analogous graphs for the BV DH FP (C, TSFE) model. Binning was performed as above, except that workers were stratified by C rather than CE. As illustrated in Panel A, for this model the dependence of prevalence on C as a function of TSFE (see Panel A) is generally similar in shape to that for the CN DH model (see Figure E-3 Panel A), although in this case, the plateau value of 0.85 would ultimately be reached for high values of C for all values of TSFE. As shown in Panel B, extrapolating from the model to TSFE = 70 predicts that prevalence will approach or exceed 0.8 for any exposure concentration C of 0.02 fiber/cc or higher.

Panel A: Observed vs. predicted as a function of mean exposure concentration (C)



Panel B: Observed vs. predicted as a function of time from first exposure (TSFE)

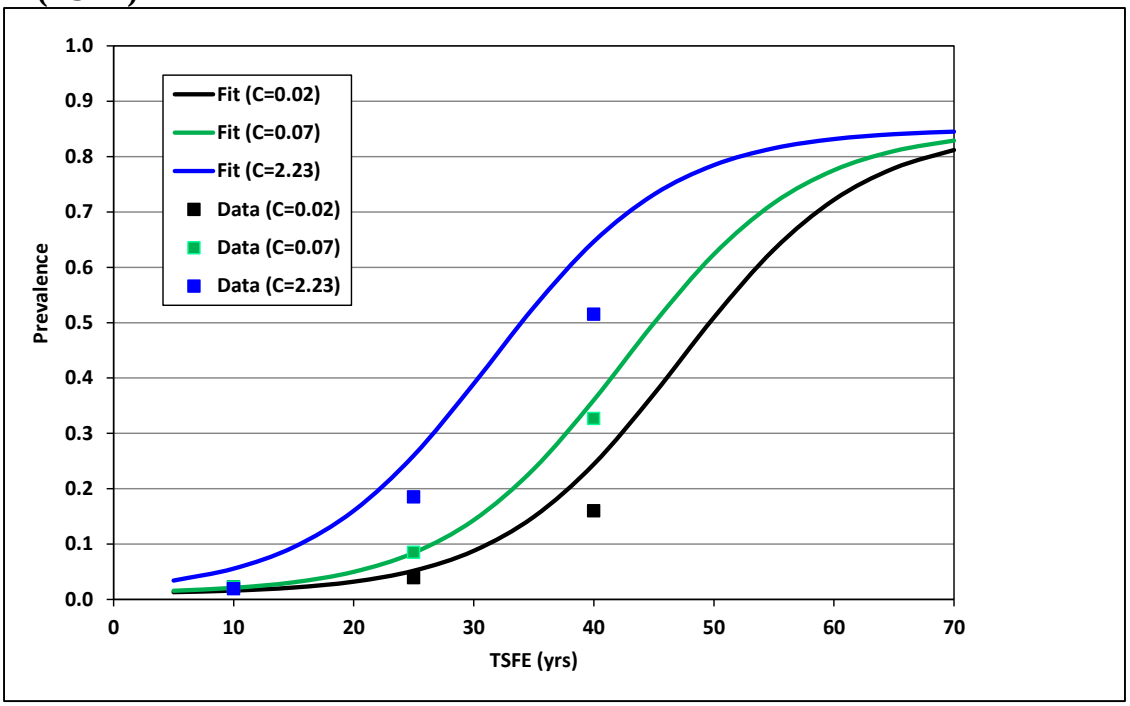


Figure E-4. Graphical display of predicted vs. observed any pleural thickening (APT) prevalence for the Bivariate Dichotomous Hill model with fixed plateau (BV DH FP) with exposure parameters of mean exposure concentration (C) and time since first exposure (TSFE) fit to the combined cohort.

Based on a visual inspection of the agreement between observed and predicted prevalence (compare Figure E-3 with Figure E-4, for TSFE = 10, 25, and 40 years), the CN DH (CE, TSFE) and the BV DH FP (C, TSFE) show adequate fits between the observed and predicted response in the region of the BMR. Consequently, results for both models are presented in the remainder of this appendix.

E.4. MODELING OF THE ROHS SUBCOHORT INFORMED BY MODELING OF THE COMBINED COHORT

In the primary analysis described in Section 5.2.2.5, it was determined that the data from the Rohs subcohort were not sufficient to provide a reliable estimate of the dependence on TSFE in the BV DH FP model, so the effect of TSFE was estimated in a two-step procedure where the dependence on TSFE was first determined from a fit of the BV DH FP model to a larger cohort of the Marysville workers without restriction based on hiring date (n = 252, the Rohs cohort), and then carrying the estimated effect of TSFE (the c parameter) over to the group of 119 workers hired in 1972 or later as evaluated in 2002−2005. Table E-9 summarizes the results of applying this same strategy based on the CN DH model.

- Row 1 shows the results of an attempt to fit the CN DH model to the Rohs subcohort using the values for m and s (the parameters which characterize the dependence of the plateau on TSFE) derived from a fit of the combined cohort to the CN DH model. As shown, a solution was found for the BMD at a value of TSFE = 70 years; however, the corresponding BMDL could not be estimated for TSFE = 70 years. At TSFE = 25 years both the BMD and BMDL were estimated.

- Row 2 shows the same approach, except that the background term was assigned a fixed value of 0.03 rather than being treated as a fitting parameter. As shown, this reduction in parameter number allowed estimation of the BMDL and BMCL at both TSFE = 25 and 70 years.

- Row 3 is very similar to the approach presented in Section 5.2.2.5.2, fitting the BV DH FP model to the Rohs subcohort using a two-step procedure. The only difference is that the value of the c parameter shown in Table E-9 is based on a fit of the BV DH FP model to the combined cohort (n = 434) rather than the Rohs cohort (n = 252) used in the primary analysis.

Table E-9. Modeling results for any pleural thickening (APT), applying parameters derived from modeling in the combined cohort of Marysville workers evaluated in 1980 or in 2002−2005, to the subcohort of Marysville workers evaluated in 2002−2005 and hired in 1972 or later

Model	Exposure metrics	*bkg*	*a*	*b*	*c*	M	*s*	Plateau[a]	H-L *p*	AIC	BMD (70)	BMDL (70)	BMC (70)	BMCL (70)	BMD (25)	BMDL (25)	BMC (25)	BMCL (25)
CN DH	CE, TSFE	0.063	−92.662	78.27	--	38.89	14.05	0.987	0.122	75.65	3.2×10^{0}	--[b]	4.5×10^{-2}	--[b]	3.3×10^{0}	8.8×10^{-1}	1.3×10^{-1}	3.5×10^{-2}
CN DH	CE, TSFE	0.030	−0.986	1.890	--	38.89	14.05	0.987	0.602	75.85	5.3×10^{-1}	5.9×10^{-2}	7.6×10^{-3}	8.4×10^{-4}	2.2×10^{0}	8.7×10^{-1}	8.7×10^{-2}	3.5×10^{-2}
BV DH FP	C, TSFE	0.038	−2.760	1.272	0.133	--		0.850	0.718	75.55	--	--	1.2×10^{-3}	3.4×10^{-7}	--	--	1.3×10^{-1}	5.5×10^{-2}

Grey cells indicate fixed parameter values.
[a]Value for Plateau in CN DH model is for TSFE = 70 yrs.
[b]Fit is unstable; value could not be estimated.

Figure E-5 compares the dependence of the BMC and BMCL values on TSFE for the CN DH model fit to the combined cohort (n = 434, red lines) to that for the BV DH FP model fit to the Rohs subcohort (n = 119, blue lines) using the two-step approach described above. As shown, the two models yield generally similar values for BMC and BMCL values at 25 years and for BMC values at 70 years. However, BMCL values are widely divergent at 70 years.

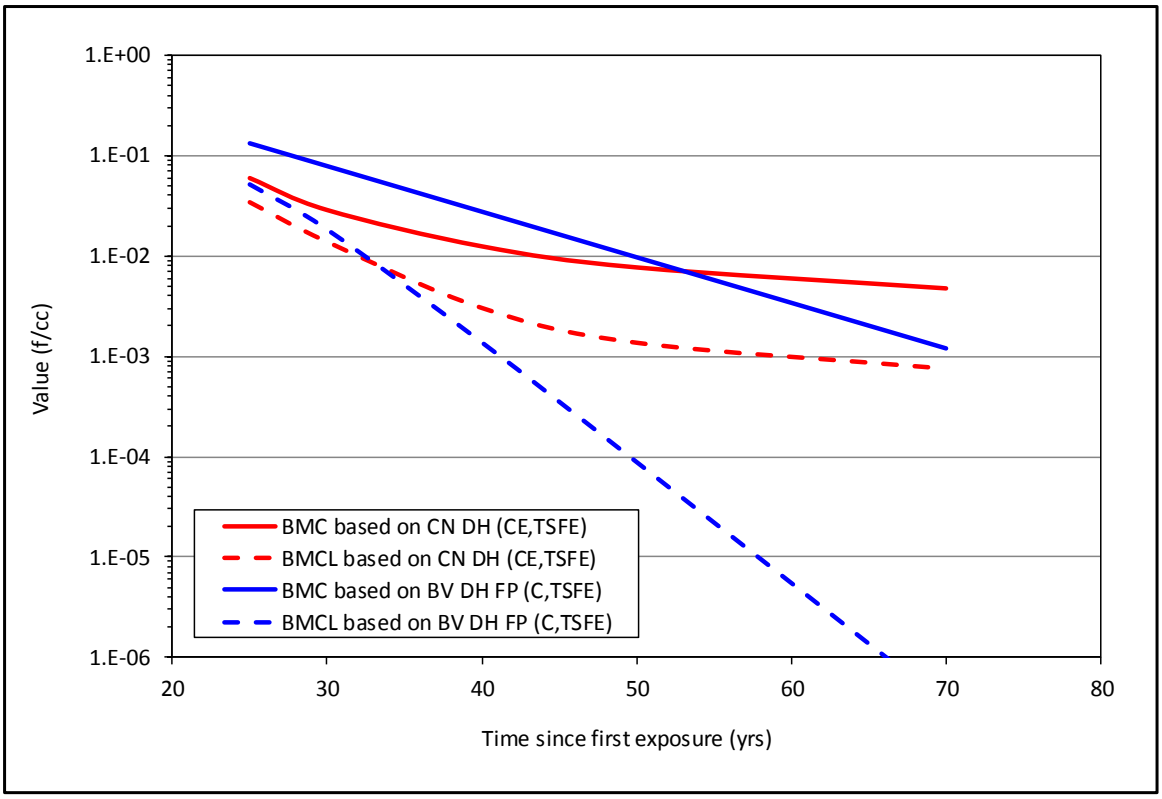


Figure E-5. Benchmark concentration (BMC) and lower limit of benchmark concentration (BMCL) values as a function of time since first exposure (TSFE) for two models: the cumulative normal Dichotomous Hill (CN DH) model using cumulative exposure and TSFE fit to the combined cohort, and the Bivariate Dichotomous Hill Fixed Plateau (BVF DH FP) model using mean exposure concentration (C) and TSFE fit to the Rohs subcohort using a two-step procedure.

E.5. SELECTION OF A POINT OF DEPARTURE (POD) TO DERIVE AN RFC FROM THE COMBINED COHORT AND THE ROHS SUBCOHORT

As discussed in Section E.3, EPA evaluated the combined cohort by fitting 19 different combinations of models and exposure metrics to each of 3 different endpoints, and calculated BMCL values for each of 2 different values of TSFE (25 and 70 years). Based on a consideration of the H-L goodness-of-fit statistic, the AIC values, the magnitude of the difference between BMC and BMCL values, and a consideration of visual agreement between

observed and predicted prevalence values, three different combinations of model and exposure metrics were identified as being preferred as candidates for selection of the POD:

- BV DH FP (C, TSFE = 25 years)
- CN DH (CE,TSFE = 25 and 70 years)

Recognizing that results were generally similar across all three endpoints (APT, LPT, and ARC), the results based on APT were identified as being preferred. For the CN DH (CE, TSFE) model, values from both TSFE = 25 and TSFE = 70 were judged to be potentially useful, and were retained. For the BV DH FP (C, TSFE) model, results at TSFE = 70 were judged to be unreliable due to the wide difference between BMC and BMCL, and only the results from TSFE = 25 were retained.

As discussed in Section E.4, EPA also evaluated the Rohs subcohort by fitting the CN DH model to the APT data, using a two-step fitting procedure where the coefficient of the TSFE term was first determined by fitting the combined cohort, and then retaining that coefficient as a constant when the model was fit to the subcohort. Similar to the combined cohort, BMCL values at both TSFE = 25 and TSFE = 70 were judged to be credible, and were retained.

Based on this approach, the BMCL values listed in Table E-10 were identified as plausible PODs for derivation of the RfC.

Table E-10. Benchmark concentration (BMC) and lower limit on benchmark concentration (BMCL) values for several alternative strategies

TSFE	Cohort	Model (parameters)	BMC (f/cc)	BMCL (f/cc)
25 yrs	Combined cohort	CN DH (CE, TSFE)	6.0×10^{-2}	3.4×10^{-2}
	Combined cohort	BV DH FP (C, TSFE)	1.5×10^{-1}	6.3×10^{-2}
	Rohs subcohort	CN DH (CE, TSFE)	8.7×10^{-2}	3.5×10^{-2}
70 yrs	Combined cohort	CN DH (CE, TSFE)	4.7×10^{-3}	7.5×10^{-4}
	Rohs subcohort[a]	CN DH (CE, TSFE)	7.6×10^{-3}	8.4×10^{-4}

[a]Background fixed at 0.03, see Table E-9.

E.6. DERIVATION OF AN RFC FROM THE COMBINED COHORT AND THE ROHS SUBCOHORT

Following EPA practices and guidance (U.S. EPA, 2002, 1994) as discussed in Section 5.2.3, a composite uncertainty factor (UF) of 300 is used when deriving the RfC from the POD calculated at the median TSFE (25 years). This includes an uncertainty factor of 10 to account for intraspecies variability ($UF_H = 10$), a factor of three to account for database

uncertainty (UF_D = 3) and an extra factor of 10 to account for the lack of information on people at risk for a full lifetime. When using the POD based on the BMCL calculated at TSFE = 70 years, the additional adjustment factor of 10 is not necessary and a composite UF of 30 is used (UF_H = 10 and UF_D = 3). The calculations of the RfC for the combined cohort and the Rohs subcohort using both options are shown in Table E-11. The RfCs are rounded to one significant digit.

Table E-11. Alternative reference concentration (RfC) values

Cohort	Starting from	Mode (parameters)	Calculation
Combined cohort	TSFE = 25 yrs	CN DH (CE,TSFE)	RfC = $(3.4 \times 10^{-2})/300 = 1 \times 10^{-4}$ fibers/cc
Combined cohort	TSFE = 25 yrs	BV DH FP (C, TSFE)	RfC = $(6.3 \times 10^{-2})/300 = 2 \times 10^{-4}$ fibers/cc
Rohs subcohort	TSFE = 25 yrs	CN DH (CE,TSFE)	RfC = $(3.5 \times 10^{-2})/300 = 1 \times 10^{-4}$ fibers/cc
Combined cohort	TSFE = 70 yrs	CN DH (CE,TSFE)	RfC = $(7.5 \times 10^{-4})/30 = 3 \times 10^{-5}$ fibers/cc
Rohs subcohort	TSFE = 70 yrs	CN DH (CE,TSFE)	RfC = $(8.4 \times 10^{-4})/30 = 3 \times 10^{-5}$ fibers/cc

For comparison, the above values all fall within approximately threefold when compared to the primary RfC derived in Section 5 of 9×10^{-5} fibers/cc.

E.7. SENSITIVITY ANALYSIS

EPA conducted a sensitivity analysis regarding choices of several alternative cohorts, alternative endpoints, alternative exposure metrics, and alternative model fitting strategies. The alternative cohorts included the combined cohort and the Rohs cohort.

The alternative endpoints included LPT, APT, or ARC including the total number of individuals at risk for APT in the combined cohort (434 individuals) and the individuals with APT and with exclusion of the 3 individuals with interstitial opacities only (431 individuals).

The alternative exposure metrics included the total CE for each worker and the CE with lags of 5, 10, and 15 years. For the combined cohort using the CN DH model, there was no variation in the POD as a function of lag time (these results are not presented). Another alternative CE metric was constructed by setting all exposure to zero after 1980. This was done because the Marysville facility discontinued use of Libby ore in 1980. Thus, exposure after 1980 included fibers from South Carolina ore, Virginia ore, Palabora ore, and perhaps residual fibers from Libby ore remaining in the facility.

The results of the sensitivity analysis are summarized in Table E-12. For those results with a narrow range in the interval between the BMC and the BMCL, this analysis shows a fairly consistent POD ($BMCL_{10}$ at TSFE of both 25 and 70 years).

Table E-12. Summary of sensitivity analysis using the cumulative normal Dichotomous Hill (CN DH) model using cumulative exposure (CE) and time since first exposure (TSFE) as explanatory variables

Cohort	Endpoint	BMCL (f/cc)	
		TSFE = 25	TSFE = 70
Combined cohort (434)	LPT (70)	3.5×10^{-2}	4.0×10^{-4}[a]
	APT (73)	3.4×10^{-2}	7.5×10^{-4}
	ARC (76)	3.3×10^{-2}	7.7×10^{-4}
Combined cohort, less those with interstitial opacity only (431)	APT (73)	3.4×10^{-2}	7.1×10^{-4}
Combined cohort, exposure after 1980 = 0 (434)	APT (73)	1.2×10^{-2}	3.8×10^{-6}[a]
Rohs cohort (252)	LPT (66)	2.4×10^{-2}	6.1×10^{-4}
	APT (69)	2.4×10^{-2}	1.0×10^{-3}
	ARC (71)	2.5×10^{-2}	1.1×10^{-3}

[a]Result is considered less reliable because of wide interval between the BMC and the BMCL (BMC:BMCL ratio >10 and >200, respectively).

To further evaluate the performance of the exposure-response modeling, the CN DH and the BV DH FP models were used to calculate the number of APT cases that would be predicted in the three cohorts using both the CN DH and BV DH FP models. The results are summarized in Table E-13.

Table E-13. Observed and predicted numbers of any pleural thickening (APT) when modeling in various subsets of the Marysville workers

Cohort	Hire date	X-ray date		*N*	APT cases	APT cases predicted			
						CN DH (CE, TSFE)		BV DH FP (C, TSFE)	
		1980	2002–2005		Observed	One step	Two step[a]	One step	Two step[b]
Combined cohort	Any	x	x	434	73	72.6		73.7	
Rohs subcohort	≥1972		x	119	13	12.9	10.8	12.9	12.9
Rohs cohort	Any		x	252	66	68.8	68.7	69.5	70.0

[a]$m = 38.89$, $s = 14.055$.
[b]$c = 0.1333$.

E.8. REFERENCES

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APPENDIX F.
WORKER OCCUPATIONAL EXPOSURE RECONSTRUCTION FOR THE MARYSVILLE COHORT

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F.1. INTRODUCTION

This appendix presents the data and methods used to reconstruct fiber exposure levels for workers at the O.M. Scott facility in Maysville, Ohio. It builds on the previous work of Dr. James Lockey and coworkers who investigated possible effects of exposures to dust containing Libby Amphibole asbestos (LAA) at the Marysville plant (Rohs et al., 2008; Lockey et al., 1984).

The data used in the original exposure reconstruction, and as reported in the published manuscripts, were based on the exposure measurements available at that time (Lockey et al., 1984). The current exposure reconstruction is based on approximately three times as many measurements as utilized in 1980 (899 vs. 325). These exposure measurements were obtained by the U.S. Environmental Protection Agency (EPA), from O.M. Scott, and through trial documents from the United States of America versus W.R. Grace et al., as well as the archived data used in the 1980 exposure reconstruction.

F.2. DESCRIPTION OF THE EXPOSURE SETTING

Beginning in 1957 and continuing until 2000, the plant in Marysville manufactured a number of lawn care products including fertilizers and pesticides that were bound to a vermiculite carrier as a delivery vehicle. This is of potential concern because some types of vermiculite ore contain asbestos fibers, and processing the vermiculite ore in the workplace could have led to release of asbestos fibers to air and inhalation exposure of workers.

F.2.1. Vermiculite Ore Sources

Initially (1957−1958), vermiculite ore was obtained only from Enoree, South Carolina. Beginning in 1959, vermiculite ores from both Libby, Montana and Enoree were used. At first, Libby vermiculite ore was only about one-third of the total vermiculite used, but the fraction from Libby increased from 1964 to 1972, such that by 1972 Libby was the predominant source (>95%). Libby vermiculite ore continued as the predominant source until 1980, when its use was discontinued (Borton et al., 2012). Other sources of vermiculite ore used at the plant included Palabora, South Africa (first used in 1970) and Louisa County, Virginia (first used in 1979). In 2000, the company developed a new process and vermiculite usage ended.

This variation in vermiculite ore source is significant because different types of vermiculite ores have varying amounts and types of asbestos content (see Appendix C). Of the vermiculite ores used at the Marysville facility, the highest asbestos fiber content is observed for LAA in Libby vermiculite ore, with lower levels of actinolite and anthophyllite in South Carolina vermiculite ore, and very low levels of actinolite, tremolite, and chrysotile in South African vermiculite ore and tremolite in Virginia vermiculite ores. Consequently, depending on the time frame when workers were employed in the Marysville facility, workers may have been exposed to a mixture of fiber types. Because fiber concentrations in air were measured using

phase contrast microscopy, which does not distinguish fiber types, exposure metrics derived from the measurements include all airborne fibers in the work area.

F.2.2. Qualitative Information Sources

Information on workplace activities and processes involving vermiculite was obtained from multiple sources. First, O.M. Scott provided report that included information about the plant, including maps of the plant layout prior to 1980. Second, archived files from Lockey et al. (1984) were identified. Third, as a result of the recent W.R. Grace trial, additional material relevant to the O.M. Scott plant was discovered. The Department of Justice (DOJ) was contacted for the release of these data. Seven 4-inch binders were available for review and every page (approximately 3,150 pages) was reviewed to identify information relevant to the current project. Aspects of particular interest included the manufacturing process, usage and source of raw materials, engineering and design changes in the plant, work practices, and exposure assessment methodology. Approval was received from the DOJ to use the relevant data for this project. Written reports, letters, memos, and notes contained background information on plant operations. A total of 1,489 pages were read for potentially useful and pertinent information and abstracted into a data file. From these records, the following information was obtained:

- Plant layout, including changes over time. This allowed the association of the descriptions used on air sampling data forms/reports with jobs or departments within the plant. A limited number of aerial images were available to identify major structures.

- Process descriptions, including workers per shift, workers per department, sources of raw materials, and raw material volume in number of railroad cars received, tonnage of railroad cars from Libby and South Carolina, and tonnage of unexpanded vermiculite received.

- A list of job titles and tasks for each department.

Lastly, two focus group discussions were conducted with workers who had been employed at the plant in the 1957−1980 time frame (Borton et al., 2012). Gaps in understanding were filled with information gathered from the focus groups, specifically regarding:

- Plant layout and changes over time, including engineering controls,
- Historical pattern of job rotations within department from 1957 to 1980,
- Time spent in work locations at the plant site,
- Overtime associated with departments and season, and
- Use/nonuse of respirators.

F.2.3. Vermiculite Processing

Vermiculite was processed at the plant in the trionizing department. Trionizing is a term used in the Marysville, OH facility and includes all operations where bulk vermiculite ore was handled or processed. Raw vermiculite ore was delivered in railcars and unloaded outside into hoppers for storage before being fed into an expander furnace. After expansion, a cyclone separated the expanded vermiculite from other material before the vermiculite was dried, crushed, and sized by screening. The expanded vermiculite was mixed with additives to form the final product for lawn treatment (Lockey, 1985).

Because the potential for exposure to fibers released from vermiculite to air depended on the type of activity being performed, exposure measurements in the trionizing department were first assigned to each of the jobs, as follows:

- Track
- Blender
- Cleanup[14]
- Dryer
- Expander
- Feeder
- Mill
- Resin

The track job was further divided into track unload (exposures associated with the actual unloading of vermiculite from railcars) and track other (exposures that occurred while working in the railcar unloading area at times when unloading was not occurring).

F.2.4. Exposure Controls in the Trionizing Department

A number of exposure reduction efforts in the vermiculite expander operation have been documented from archived files from the original Lockey study, focus groups, and material released by the DOJ from the W.R. Grace trial. The first major engineering control was the installation of a central vacuum system in 1961. Dust collectors were installed and improved ventilation was initiated in 1968. Additional improvements, such as adding hoods and a bag house to remove dust from the stoner deck exhaust and enclosing vibrating conveyers, were implemented in 1970−1973. A more comprehensive and integrated approach to dust control took place approximately in 1975/1976−1980. A number of engineering controls and work

[14]Since the initial 1980 study, cleanup has been recognized as one of the tasks through which the indoor trionizing workers rotated. However, no industrial hygiene samples unique to cleanup were initially available and cleanup was previously given the mean value of the other industrial hygiene measurements (Lockey, 1985). The newly available measurements included samples specified as cleanup and these were assigned to the cleanup activity.

practices were added during these years. In 1976, a major construction change isolated track unloading activities from the production areas, reducing transfer of particulates into the plant during raw material transfer (OSHA, 1979). Additional engineering controls included the installation of more roof fans and dust collectors. Work practices emphasized vacuuming rather than dry sweeping and improved sealing of leaks in the vermiculite expanders. During this time period, routine weekly checks for leaks by maintenance personnel began. In 1980, wet scrubbers were added to clean the air from areas not served by the bag house.

F.2.5. Respiratory Protective Equipment and Clothing Change Considerations

Respirator usage was inadequate (OSHA, 1979). Respirators were used only sporadically due to heat in the production area and discomfort during use. Paper masks were preferred by workers and were often reused from day to day. There was no documentation of fit testing of the paper masks. Paper masks can provide some protection against the larger particles, but likely provided little reduction in respirable particles, particularly when reused. Therefore, no adjustment was made to lower the exposure estimates due to respirator use.

Per focus groups, workers were provided paid work time for required showers at the facility after each production shift beginning in 1961−1962. Work coveralls were laundered on-site after each work shift starting in approximately 1966. Street clothes were stored during the work shift in locker rooms separated from the production area (Borton et al., 2012). Consequently, off-site exposures to work-related fibers were not likely to have been significant.

F.2.6. Other Departments in the Facility

Workers in other departments in the plant where only expanded vermiculite or no vermiculite was used were defined as having "plant background" exposure. These included the following (Borton et al., 2012):

- Polyform.
- Office.
- Research lab.
- Pilot plant.
- Warehouse.
- Packaging.

The polyform process started in 1969 and was separate from any vermiculite operations (Borton et al., 2012). Other departments included central maintenance and plant maintenance. Workers in these departments spent part of their time in the trionizing area and part of their time in jobs in areas categorized as plant background. The central maintenance department became a contract service in 1983, and after this date most workers in central maintenance were not

employees of O.M. Scott. However, some O.M. Scott employees continued to work in central maintenance after 1983.

F.3. INDUSTRIAL HYGIENE DATA SOURCES

Three sources of industrial hygiene (IH) measurements of fiber concentrations in workplace air were identified: sampling reports from O.M. Scott that included measurements at the facility from 1972 to 1994, archived files from the Lockey et al. (1984) study, and the W.R. Grace trial discovery material.

F.3.1. Document Evaluation, Data Entry, Cleaning, Editing, and Standardization

Air sampling reports included quantitative measurement of airborne dust and fiber concentration associated with a department job. These records were computerized following an approved data entry scheme. Records were double entered and verified.

Two identical Microsoft Access databases were created for initial and duplicate entry of the quantitative data. Each individual performing data entry had a unique and separate database to avoid possible data entry confusion. A random 10% check of entered data was conducted throughout the data entry process to maintain quality of data, to address data entry questions and to resolve potential database issues. Data entry differences were below 5% throughout the entry process.

A final verification of data entry used SAS Version 9.2 PROC COMPARE to import the initial and duplicate Access tables. All discrepancies were addressed by reviewing the original document. The initial and duplicate Microsoft Access databases were archived. A copy of the initial database was converted to Microsoft Excel format for standardization and ease of analyses.

F.3.2. Process of Standardization

The standardization process included categorizing entered data into appropriate variable fields, spell checking, identifying duplicate record entry from duplicate documents, merging records for the same sample or measurement, evaluating data for completeness, and categorizing groups of data based on type of sample or measurement.

Data were reviewed and edited to ensure the information was entered into the appropriate data field. A frequency of the data fields using SAS 9.2 PROC FREQ identified spelling differences and patterns to ensure correct labeling of the data. Additional data variables were created depending on recognized need to distinguish important pieces of data.

A new variable called group ID was created to identify, track, and consolidate partial and/or complete duplicate data into one unique sample. Partial data were identified on a combination of sample date, sample record ID, sample result, volume, sampling time, and/or document patterns. A document pattern would include instances where only a group of sample

results were available in one document and another document(s) would match the exact sequence of sample results.

Data were further categorized based on the type of sample. Categories include dust samples, bulk samples, personal and area fiber samples, limit of detection (LOD) or quantification (LOQ) samples, off-site locations, and time-weighted average (TWA) samples. Some samples were collected with a direct-reading fibrous aerosol monitor, but these were not used because no calibration information was included in the records. Thus, only the fiber count data collected with a sampling pump were used. In addition, group IDs lacking a sample result, sample year, or department were excluded.

The natural logs of personal and area samples were evaluated by year and department. The ranges and means of the personal and area samples were approximately equal. When plotted by year and department, the data were seen to be in the same range, with the values overlapping. Therefore, personal and area sample data sets were merged and both were used for the development of the Exposure Matrix. Group IDs with only LOD or LOQ values were grouped by year and categorized as trionize or background. In order to assign an estimate for the LOD or LOQ, the median value of each group was divided by two and assigned to all samples in that group. Given the small number of LOD and LOQ samples (n = 35), it is unlikely any significant bias was introduced using this method. TWA values were not used when the individual measurements that comprised the TWA were already available.

Attempts in other studies to convert from total dust to fiber count have relied on similarities in equipment or process where side-by-side samples were collected. However, no side-by-side matched pairs of dust/fiber data were identified from this plant. Therefore, total dust measurements were not converted to fiber counts and were not used as part of the fiber exposure estimation.

F.4. OVERVIEW OF THE EXPOSURE DATA

F.4.1. Sampling and Analysis Methods

F.4.1.1. *Sampling*

Collection of IH air samples to determine worker exposure to fibers started in 1972. Samples were obtained by drawing air through a filter to capture airborne fibers. Initially, samples were collected either the industrial hygienist carrying the sampler and "following the worker" or by placing the sampler at a stationary location. Personal sampling began in 1976 by using a pump and filter cassette worn by the worker.

No corporate plan for air sampling was found in the available documents. Air sampling practices were discussed with the focus group participants who noted some instances of leaving sampling pumps in control rooms during high dust activities such as the use of compressed air to remove particulates from surface areas. This activity was not uniformly omitted from air sampling results; however, there was no documentation that high-exposure work was excluded

from the sampling efforts. In fact, in the early years, some activities recorded in the sampling record included reference to compressed air "blow down," one of the activities associated with potentially high exposures. Consequently, all sample results were considered representative of conditions during collection and were included in the data set.

F.4.1.2. *Analysis*

Air filter samples were analyzed by a microscopist using phase contrast microscopy (PCM) and the results were expressed as PCM fibers per cubic centimeters (f/cc) of air (Borton et al., 2012). Fiber counting followed the NIOSH P&CAM 239 and 7400 counting methods. In these methods, a countable fiber is defined as an elongated particle with a length greater than 5 µm, a diameter less than 3 µm, and an aspect ratio (length:diameter) of 3:1 or greater. This microscopic technique provides no information on the chemical or crystal structure of elongated particles; therefore, the PCM fiber counts represent all elongated particles fitting the counting criteria.

F.4.2. Summary Statistics

Table F-1 shows a total of 899 IH samples were available for this analysis. Most (81%) were collected in the trionizing departments where exposure to vermiculite and fibers tended to be highest, and 19% of the measurements came from other (background) locations in the plant.

Table F-1. Industrial hygiene fiber measurements by document source

Document source	Trionize	Background	Total (%)
DOJ	23	0	23 (2.6)
EPA	398	122	520 (57.8)
UC	135	45	180 (20.0)
MULTIPLE [a]	172	4	176 (19.6)
Total (%)	728 (81)	171 (19)	899 (100)

[a] Results listed in two or more sources with duplicates removed

Table F-2 shows the number of samples stratified by year and by job. As shown, the first fiber count measurements were available in 1972 and the last in 1994. The frequency of sample collection was not uniform over time, with the highest numbers of samples being collected in 1976 and 1978.

F.4.3. Data Review and Assessment

Figure F-1 provides a graphical display of the IH data from the trionizing department plotted as a function of time. Note that the concentration scales are not the same in all panels. Highest concentrations tended to occur during track unload, feeder, and expander jobs. Exposure levels in most trionizing jobs showed a general tendency to decrease over time as engineering controls improved and as Libby vermiculite use was discontinued.

Figure F-2 shows a graphical summary of data from nontrionizing (background) departments and jobs. In this case, there are no clear distinctions among departments or jobs, so the data are shown without stratification. One data point (a value of 4.03 fibers/cc that was identified as having been collected in the lab) was identified as an outlier because it was substantially higher than any other value in the background data set. This value is not considered to be representative of exposures in background jobs, and was excluded from all further evaluations. As indicated in the figure, although less dramatic than for the trionizing department, there is also an apparent tendency for background exposure levels to decrease over time.

Table F-2. Industrial hygiene fiber measurements by department and year

Category	Job	1972	1973	1975	1976	1977	1978	1979	1980	1981	1982	1983	1984	1985	1986	1987	1988	1993	1994	Total
Trionize (indoor jobs)	Blender					3	21			3										27
	Cleanup			1	15	6	26		5	1	1		1							56
	Dryer	1	1			2	2	2		3	6		2		10	7	10			46
	Expander	8	38	18	83	6	51	7	10	12	3	3	3	3	11	6	6	1	7	276
	Feeder				10	1	12			3	2						1		3	32
	Mill				1	2	22	13	1	3	3		5	2	7	7	4		7	77
	Resin						11	1	1	4	4		4			3				28
	Total indoor	9	39	19	109	20	145	23	17	29	19	3	15	5	28	23	21	1	17	542
Trionize (outdoor jobs)	Track other					6	23		4	6	2	3	6	1	18	10	9	2	12	102
	Track unload		1	1	6	27	15	3	2	3	3	2	6	8	6		1			84
	Total outdoor		1	1	6	33	38	3	6	9	5	5	12	9	24	10	10	2	12	186
Background	Cafeteria														1	1				2
	Central maint.												3			1				4
	Control	1				4	15			3	3				3		1			30
	Research Lab					1									2	1				4
	Office														2	2			1	5
	Packaging	2				5	28	2		3	3	3	2	3	6	4	5		9	75
	Plant maint.									3			6	2	6	1	6			24
	Polyform maint.						1									1				2
	Polyform			1																1
	Poly packaging						9													9
	Warehouse			1			1			3	1				3	2	4			15
	Total	3		2		10	54	2		12	7	3	11	5	23	13	16		10	171
All	Grand total	12	40	22	115	63	237	28	23	50	31	11	38	19	75	46	47	3	39	899

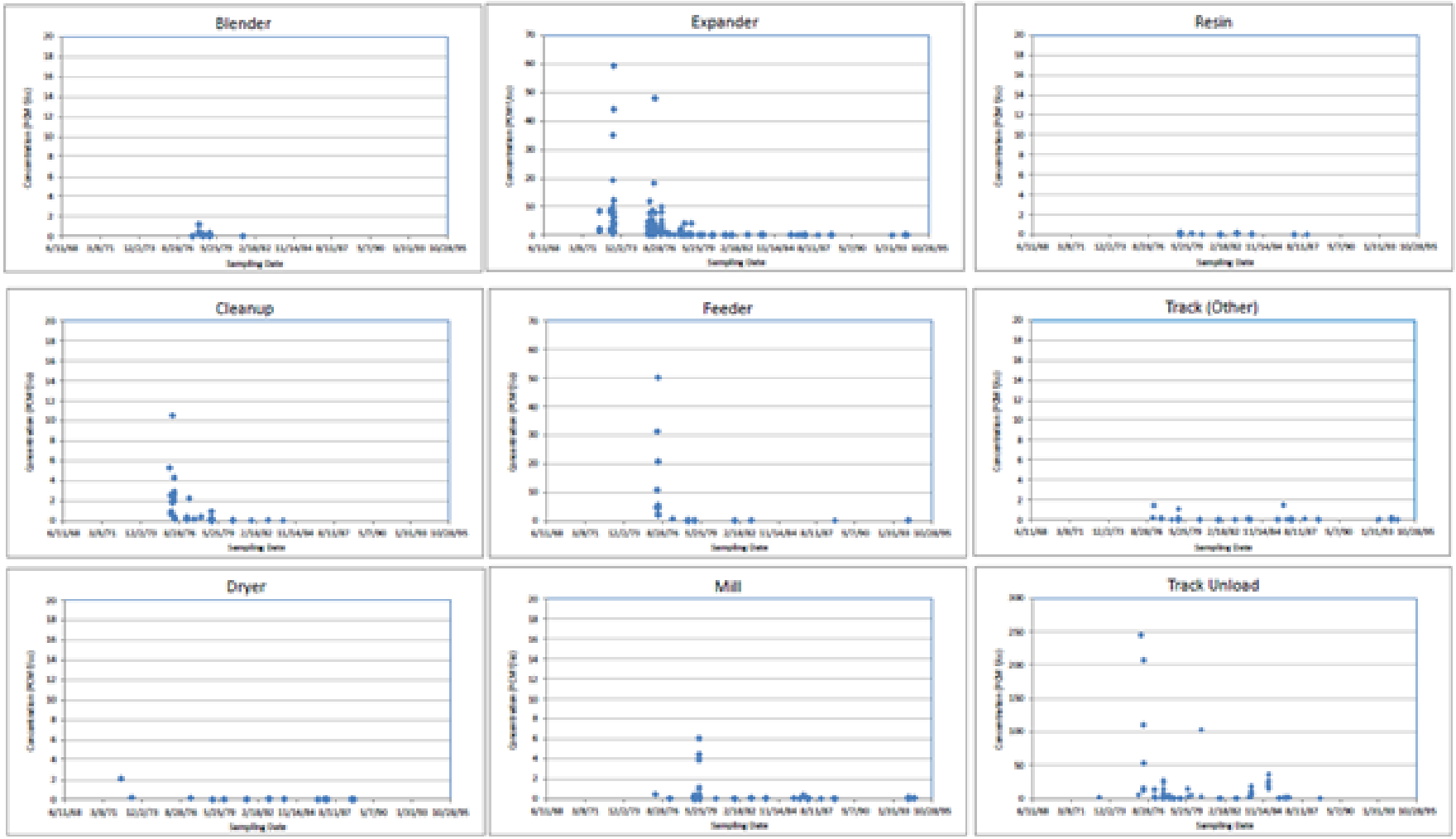


Figure F-1. Trionizing department data by year and job.

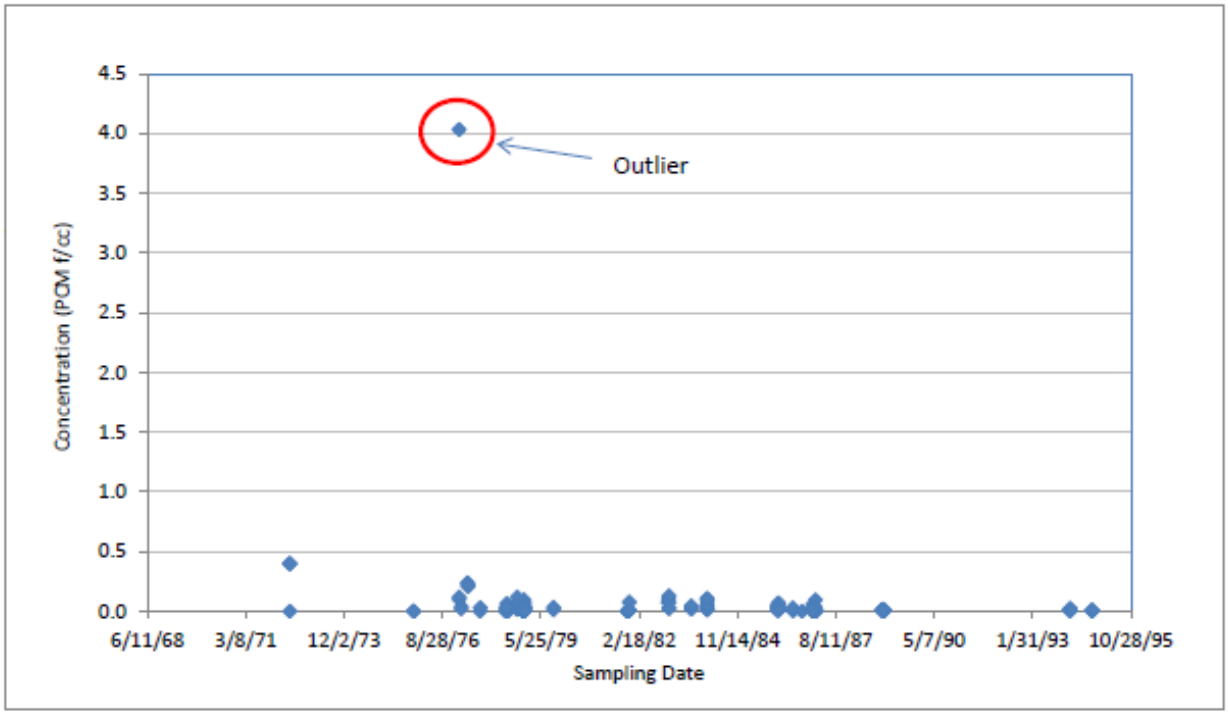


Figure F-2. Background data by year.

Note: Outlier is a data point collected from the research lab and is not considered representative of background exposure; it was excluded from evaluation.

Figure F-3 plots observed concentrations as a function of sampling duration (the length of time over which air was drawn through the filter). As seen, there is a clear tendency for samples with the highest concentrations to have the shortest sampling durations, especially for track unload and other trionizing jobs. This finding is expected because high concentrations of fibers in this work process generally occur when overall particulate levels are high. The PCM analytical method requires that the microscopist be able to visualize the fibers for counting, and this cannot occur if the overall loading of the filter obscures elongated particles. Therefore, sampling in high dust conditions must be for a short time interval (often 15 minutes or less) to prevent overloading of the filter. If overloading occurs, the sample is void, and marked "overloaded."

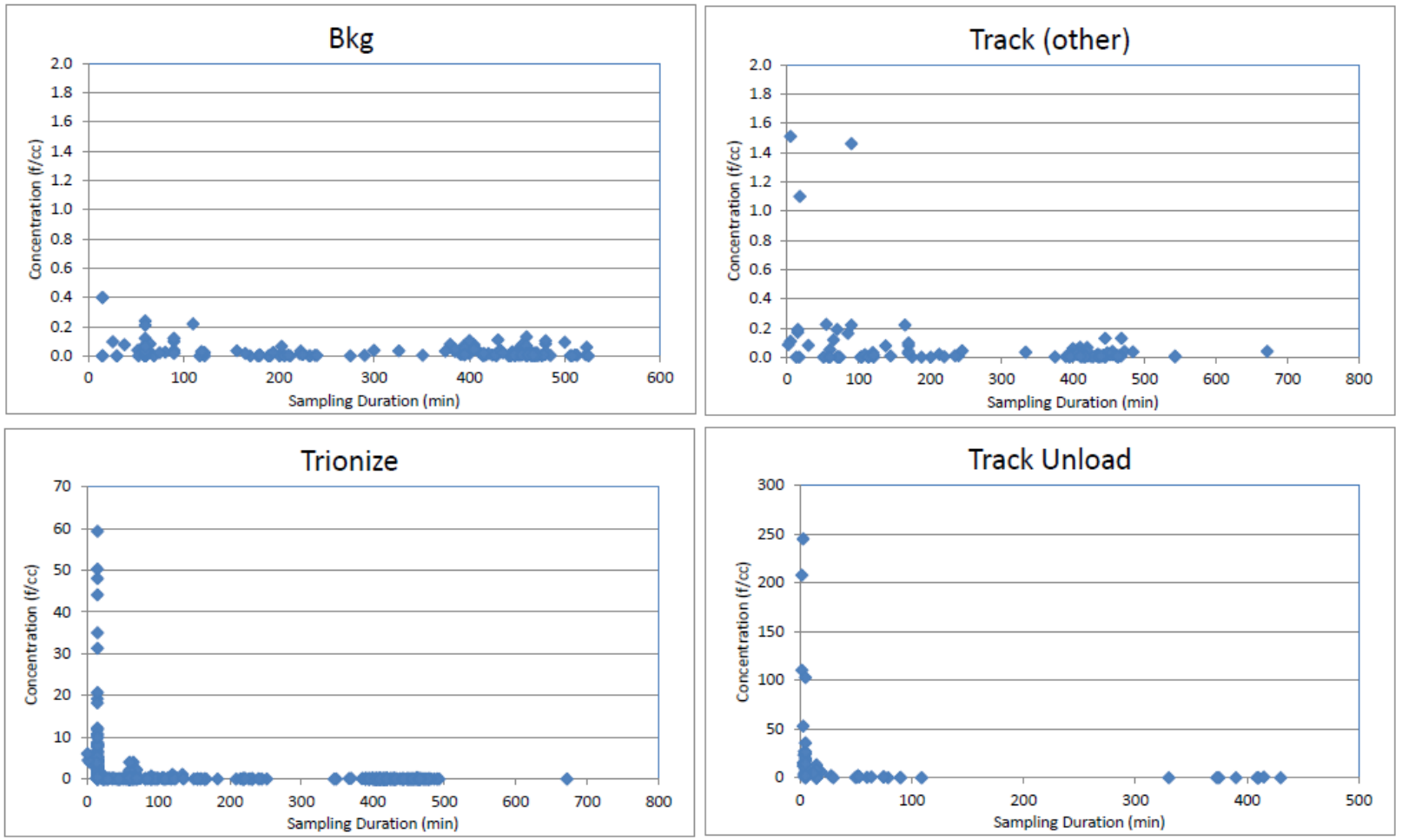


Figure F-3. Relation between sampling duration and measured concentration.

Short-duration samples may represent actual conditions in the workplace for a specific job overall or for a short-term operation in a job. In the first instance, the sample result represents the full duration of the job; in the second, the sample result would be time-weighted as part of a job. No information was available to indicate worker exposure duration was related to either sampling duration or exposure concentration. Consequently, all measurements were used without any adjustments based on sampling duration.

F.5. DEVELOPMENT OF THE JOB-EXPOSURE MATRIX

F.5.1. General Strategy

A job-exposure matrix (JEM) is a table that provides estimated exposure levels in air (fiber/cc) for workers in each job for each year. The exposure interval of interest for the Marysville worker cohort begins in 1957 when vermiculite was first used in the plant and extends to 2000 when vermiculite usage ended. Because measurements of fibers in the air are available only for the central portion (1972−1994) of the exposure interval of interest (1957−2000), the JEM was constructed in two steps:

Step 1: Industrial hygiene data collected between 1972 and 1994 were used to derive estimates of yearly average concentrations by job during this interval. Exposure levels in 1994 that were derived from industrial hygiene data were assumed to remain constant until 2000.

Step 2: Information available from plant records and worker focus groups was used to estimate concentrations from 1957 to 1971 by extrapolation from 1972 values.

Two alternative strategies were used to construct JEMs. The first strategy, implemented by UC, was based on the log-transformed data, and the exposure metric provided in the JEM was the geometric mean exposure concentration (Borton et al., 2012). This approach was used because the probability of response is expected to be a nonlinear function of exposure, and use of the log-transformed values helps minimize the effect of measurement error on the regression model (Seixas et al., 1988). The second approach, implemented by EPA working in consultation with UC, utilized the untransformed data, and the exposure metric provided in the JEM was the arithmetic mean exposure concentration. This approach was used because toxicity values derived by EPA are typically based on the long-term average exposure level rather than the geometric mean exposure level (U.S. EPA, 1994). The details of these two approaches are provided below.

F.5.2. Derivation of a Job-Exposure Matrix (JEM) Based on Log-Transformed Data

F.5.2.1. *Trionizing Department 1972−2000*

The trionizing department included jobs from the entry of vermiculite into the plant through final product. Jobs included track, screen/mill, feeder, dryer, expander, blender, resin, and cleanup. Workers rotated through the various jobs within the department. Overall rotation among jobs reported in the 1980 Lockey study (Lockey, 1985) was verified by focus groups.

As seen in Table F-2, the frequency of sample collection was sparse in many years, limiting the calculation of a mean exposure level for each indoor trionizing job for each year. This issue is particularly evident in the early years, as 147 of the 176 measurements in 1972−1976 are from the expander, with the remaining as follows: cleanup (16 measurements), feeder (10), dryer (2), mill (1), blender (0), and resin (0).

Plots of the log-transformed IH measurements over time were made for individual trionizing jobs. All samples that were below the level of detection (n = 35) were assigned one-half the median of the limit of detection or limit of quantitation for the corresponding department-year. Only the plot of expander data, representing 51% of all indoor trionizing measurements, spanned the time frame of interest. Plots for the six nonexpander jobs, at the dates available were generally consistent with the expander data plots. All of the indoor trionizing jobs were in the same building where engineering controls in one area would likely influence exposures both at the job where the control was implemented and also at nearby work locations. Moreover, workers reported equal time spent in the various indoor jobs. Therefore, in order to leverage the available data, it was determined that the exposure measurements for indoor trionizing jobs should be combined. The outdoor track job included two very different work activities: unloading railcars containing vermiculite (track unload) and general track work such as bringing in the railcars and monitoring discharge (track other). The two track job activities (unload and other) had a substantially larger range of sampling results and were treated separately.

In accordance with this strategy, the following steps were implemented to derive the geometric-mean-based JEM for the trionizing department from 1972 to 2000:

1. The data were log transformed.

2. A curve was drawn through the data set for all indoor trionizing jobs to estimate annual log-mean values. Figure F-4 illustrates this curve. As values for 1980−1994 were similar and near the level of detection, the log-mean value for all the samples was used and then extended until 2000. For all exposure values for the combined indoor trionizing jobs from 1973−1978, a smooth-fitted curve was drawn using Microsoft Excel to connect the log-mean values of "index years" (1973, 1976, and 1978) having a substantial number of exposure measurements (approximately 40 or more). This approach was chosen to assure that stable log-mean values were used to define the curve over this time period. The log-mean value for 1977 IH

measurements naturally fell on the curve between 1976 and 1978. Therefore, for the 1972−1979 time period, log-mean values for only 4 years (1972, 1974, 1975, 1979) were lacking. The line connecting 1976 backward through 1973 provided values for 1974 and 1975 and the continuation of this line provided the value for 1972. Connecting 1978 (index year) to 1980 provided the value for 1979. For each year, the annual geometric mean exposure estimate was determined by exponentiation of the log-mean value from the curve. The decline seen in exposures throughout the 1976−1978 time period is consistent with reports of implementing engineering controls such as dust collection, enclosing vibrating conveyors, adding ventilators, erecting a wall between the railroad track and the main building, and sealing leaks in the system.

3. The log-transformed measurement results for track unload and track other were plotted and a straight line produced to best fit the data points. The geometric mean exposure for each year was determined by exponentiation of the value on the line for that year.

4. For the trionizing department, it was estimated that 11% of work time was spent in track and 89% in all other jobs. This is consistent with the previous weights used in the 1980 Lockey study (Lockey, 1985) and confirmed by the focus groups.

5. The focus groups reported that when working track, track unload required about 25% of the time and track other comprised about 75% of the track job time. Therefore, a weighted average for exposure at track within the trionizing department was derived. This 25% time estimate for track unload is higher than previously reported (Lockey, 1985).

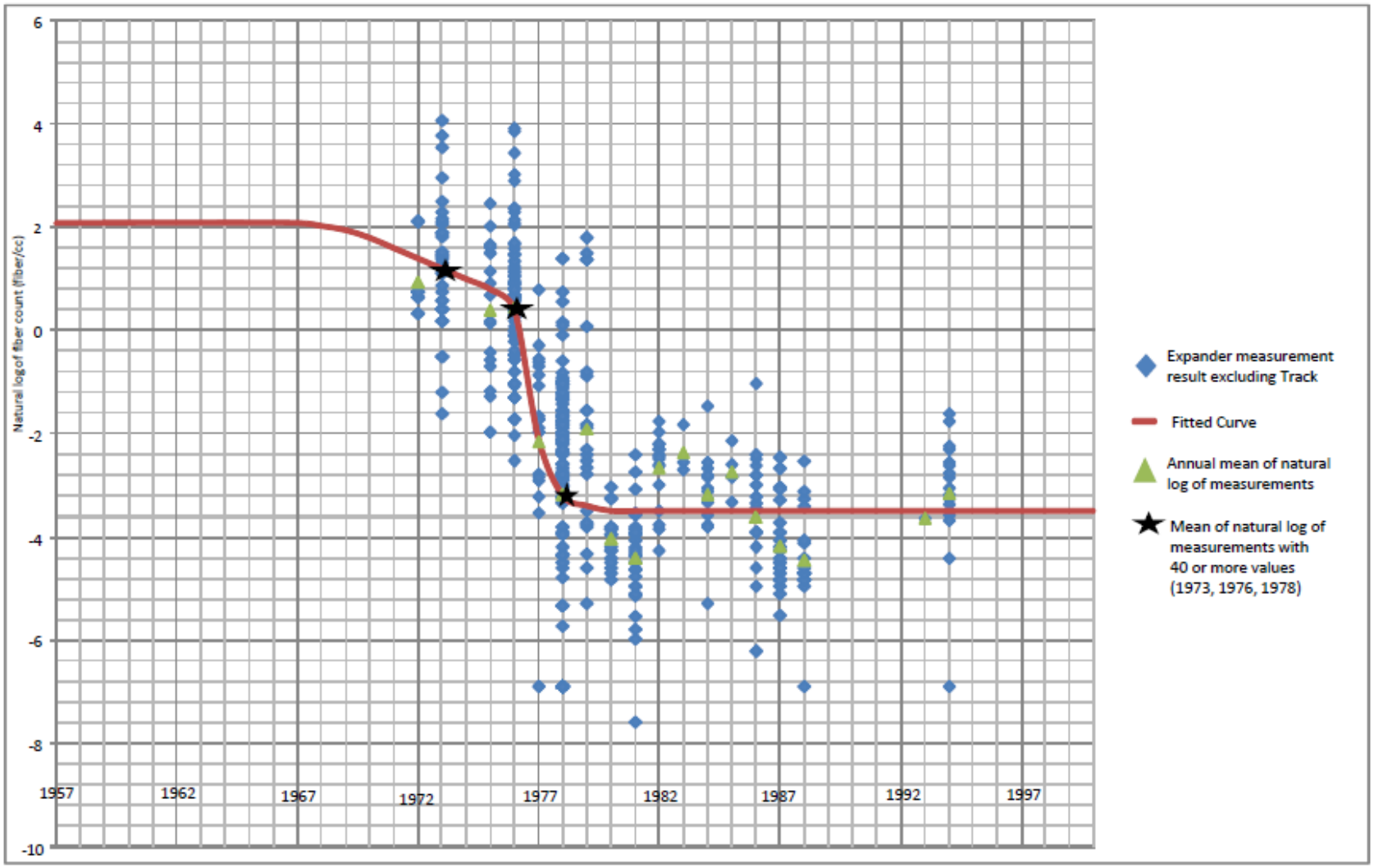


Figure F-4. Natural logarithm of all usable industrial hygiene measurements across all indoor jobs within the trionizing department, and the fitted line (red) used to represent the geometric mean.

F.5.2.2. ***Trionizing Department 1957−1971***

Estimation of exposure values in the trionizing department before 1972 (prior to exposure measurements) required consideration of two factors: (1) changes in dust levels over time due to the effects of dust control measures in the department and (2) changes in the vermiculite source material used.

F.5.2.2.1. ***Adjustment for changing indoor dust levels***. As noted above, a graphical display of IH concentration values for indoor trionizing jobs indicated that all samples generally followed the same pattern: higher in the early years of industrial hygiene sampling and declining gradually over time. Further, the focus groups reported that no single engineering change resulted in a dramatic reduction in the perception of dustiness in the plant. Thus, the workers' recollections supported the findings from the industrial hygiene data demonstrating a smooth decline in levels of exposure rather than a dramatic stepwise drop due to any one engineering change.

Focus group participants who had worked in the trionizing department before 1972 reported that dust exposures in indoor trionizing jobs were at least two times higher in the 1960s than in the 1970s. Therefore, the year 1972 was used as the start of the "gradual" retrospective increase in exposure back to 1967 as 1972 was the first year when industrial hygiene measurements were available, and the percentage of Libby vermiculite used was 93%. The year 1967 was selected because it was the year preceding engineering controls. Accordingly, a line was drawn to connect these two points (see Figure F-4). Before 1967, estimates for fiber exposure levels were extended backward in time, assuming no change in dust levels retrospectively from 1967.

In contrast to the indoor trionizing jobs, the track unload and track other jobs were outdoors and were likely unaffected by indoor plant engineering controls. Hence, estimates for fiber exposure levels for track duties were not adjusted for a time-dependent change in dust levels.

F.5.2.2.2. ***Adjustments for vermiculite raw material sources*.** Two primary sources of information were located regarding vermiculite ore sources in the 1957−1972 time frame:

- An archived UC document from the original site investigation with estimates of railroad car loads delivered to the plant per year. Documents indicate railroad cars from Libby were 100-ton cars and from South Carolina 70-ton cars.

- The Chamberlain memo (internal O.M. Scott memo) provides information regarding vermiculite ore sources for 1964−1972 in railroad car loads per year.

Per the UC document, 100% of the vermiculite ore estimated to be used from 1957−1959 was from South Carolina. Per the Chamberlain memo, it was best estimated that Libby vermiculite ore began arriving in 1960. Focus groups held by UC investigators with a cross-sectional representation of former O.M. Scott employees placed the first use of Libby vermiculite ore earlier, in 1958 or 1959. In the absence of definitive documentation, UC used its best professional judgment to assign the start date for the use of Libby vermiculite ore as 1959.

Documentation was found from the original 1980 UC documents indicating an estimated Libby tonnage contribution of 32% from 1959−1963. These percentages for 1959−1963 were adopted for use in this project. After adjusting for the difference in railcar sizes, the Chamberlain memo indicates that Libby tonnage usage increased from 57% in 1964 to 73% in 1965 to 92% in 1966. Table F-3 summarizes the distribution of unexpanded vermiculite sources received at the plant between 1957 and 1971.

Table F-3. Vermiculite tonnage by year and source

Year	% Tonnage Libby	% Tonnage SC	Comment
1957		100	No confirmation of Libby usage
1958		100	No confirmation of Libby usage
1959	32	68	Libby usage began per focus groups; Chamberlain memo[a] says 1960
1960	32	68	Chamberlain memo and 1980 UC document
1961	32	68	Chamberlain memo and 1980 UC document
1962	32	68	Chamberlain memo and 1980 UC document
1963	32	68	Chamberlain memo and 1980 UC document
1964	57	43	Chamberlain memo
1965	73	27	Chamberlain memo
1966	92	8	Chamberlain memo
1967	87	13	Chamberlain memo
1968	79	21	Chamberlain memo
1969	82	18	Chamberlain memo
1970	90	10	Chamberlain memo
1971	95	5	Chamberlain memo

[a]Internal O.M. Scott memo.

To develop the relationship of fiber levels between South Carolina and Libby vermiculite, IH samples associated with either 100% Libby or 100% South Carolina vermiculite were identified. Two jobs with the highest number of samples from the same year from each source were used to establish the relationship. The data are summarized in Table F-4, below.

Table F-4. Relative concentrations of fibers in Libby and South Carolina vermiculites

Data Set	Libby vermiculite		South Carolina vermiculite	
	Sample count	Mean (f/cc)	Sample count	Mean (f/cc)
1977 Track unload	13	7.85	11	0.82
1978 Expander	8	0.55	7	0.20
Count-weighted mean		5.07		0.58

The ratio of the count-weighted average of these samples is (5.07/0.58) is 8.7:1, and this ratio was used for estimating the proportion of Libby versus South Carolina fiber exposure levels from 1959 to 1971.

F.5.2.3. *Exposure Estimates for Nontrionizing Departments*

As noted above, departments using only expanded vermiculite or no vermiculite were defined as having "plant background" exposure. These included the departments of polyform, office, research, pilot plant, warehouse, and packaging. This decision was based on plots of available sampling data showing similar levels and qualitative reports documenting that no fibers were in the finished product.

Plant background exposure concentrations before 1972 were estimated using similar methodology as for the trionizing department. It was assumed that background levels were not affected by engineering control as in trionizing, but were influenced by the percentage of Libby vermiculite used. Therefore, for the years prior to 1972, the measured plant background rate in 1972 was adjusted only for the yearly percentage of Libby vermiculite used. The 2 years before Libby vermiculite usage, 1956 and 1957, were assigned concentration values equal to the level of detection (0.01 fiber/cc). This is in line with industrial hygiene measurements post Libby vermiculite usage through 1994.

Background exposure estimates derived as described above were applied to workers in polyform, office, research, pilot plant, warehouse, and packaging.

Because maintenance workers spent some time in the trionizing department as well as in background areas, the values for these workers were adjusted as follows:

- Plant Maintenance—although there were some differences of opinion in the focus groups regarding where plant maintenance spent their time, the consensus reached was to assign approximately 50% of time in trionizing and 50% in areas defined as plant background for their work in shop and other departments.

- Central Maintenance—according to the focus groups, these employees worked outside of trionizing for about 90% time (background) and within trionizing for about 10% time for installation of new equipment/parts. Around 1982−1983, the central

maintenance department was contracted to outside personnel, although some O.M. Scott workers continued to work in central maintenance.

F.5.2.4. *Results: Job-Exposure Matrix (JEM) Based on Geometric Mean Exposure Levels*

Table F-5 presents the JEM from 1957 to 2000 using the methodology detailed above. Exposure concentrations represent the geometric mean exposure level, by job and year.

Table F-5. Geometric mean-based job-exposure matrix (JEM) for Marysville workers

Year	Trionizing (all jobs)	Plant maintenance[a]	Central maintenance[b]	Background[c]
1957	0.801	0.406	0.089	0.010
1958	0.801	0.406	0.089	0.010
1959	2.874	1.441	0.295	0.008
1960	2.874	1.441	0.295	0.008
1961	2.874	1.441	0.295	0.008
1962	2.874	1.441	0.295	0.008
1963	2.874	1.441	0.295	0.008
1964	4.493	2.253	0.460	0.012
1965	5.530	2.772	0.567	0.015
1966	6.76	3.389	0.693	0.019
1967	6.437	3.227	0.660	0.018
1968	5.557	2.786	0.570	0.016
1969	5.291	2.654	0.544	0.017
1970	4.928	2.473	0.509	0.018
1971	4.318	2.169	0.449	0.019
1972	3.674	1.847	0.385	0.020
1973	3.007	1.513	0.319	0.020
1974	2.464	1.242	0.264	0.020
1975	2.019	1.020	0.220	0.020

Table F-5. Geometric Mean based job-exposure matrix (JEM) for Marysville workers (continued)

Year	Trionizing (all jobs)	Plant maintenance[a]	Central maintenance[b]	Background[c]
1976	1.391	0.705	0.157	0.020
1977	0.150	0.090	0.030	0.020
1978	0.086	0.053	0.027	0.020
1979	0.077	0.044	0.017	0.010
1980	0.063	0.036	0.015	0.010
1981	0.063	0.036	0.015	0.010
1982	0.060	0.035	0.015	0.010
1983	0.060	0.035	0.015	0.010
1984	0.055	0.032	0.014[d]	0.010
1985	0.055	0.032	0.014	0.010
1986	0.052	0.031	0.014	0.010
1987	0.052	0.031	0.014	0.010
1988	0.052	0.031	0.014	0.010
1989	0.052	0.031	0.014	0.010
1990	0.052	0.031	0.014	0.010
1991	0.052	0.031	0.014	0.010
1992	0.052	0.031	0.014	0.010
1993	0.052	0.031	0.014	0.010
1994	0.052	0.031	0.014	0.010
1995−2000	0.052	0.031	0.014	0.010

[a]Assumes exposure occurs 50% in trionizing and 50% in background departments.
[b]Assumes exposure occurs 10% in trionizing and 90% in background departments.
[c]Background includes pilot plant, research, polyform, office, packaging, and warehouse.
[d]After 1983, central maintenance was outsourced, but some O.M. Scott workers continued in that position.

F.5.3. Derivation of a Job-Exposure Matrix (JEM) Based on Untransformed Data

The basic approach used by EPA for deriving a JEM based on the untransformed data was generally similar to that used for the log-transformed data, with the following exceptions:

- Nondetects were assigned a value of zero rather than the detection limit (Cameron and Trivedi, 2013; U.S. EPA, 2008; Haas et al., 1999; U.S. EPA, 1999).
- The IH data were fit to statistical models to characterize time trends, rather than using interpolation among data-rich years.

- Indoor trionizing jobs were modeled individually rather than combined into one data set.

The details of this approach are described below.

F.5.3.1. *Fitting Available Industrial Hygiene Data from 1972−1994*

F.5.3.1.1. ***Trionizing department data*.** Industrial hygiene data collected in the trionizing department between 1972 and 1994 were classified as being associated with nine different types of jobs (blender, cleanup, dryer, expander, feeder, mill, resin, track other, and track unload). Table F-6 provides summary statistics for these trionizing jobs. All values are shown to two significant figures.

Table F-6. Summary statistics for trionizing jobs

Job	1972–1975			1976–1980			1981–1984			1985–1990			1991–1994		
	n	**Mean**	**Max**	***n***	**Mean**	**Max**	***n***	**Mean**	**Max**	***n***	**Mean**	**Max**	***n***	**Mean**	**Max**
Blender	0	--	--	24	1.8×10^{-1}	1.2×10^{0}	3	1.4×10^{-2}	1.9×10^{-2}	0	--	--	0	--	--
Cleanup	1	5.3×10^{0}	5.3×10^{0}	52	7.5×10^{-1}	1.1×10^{1}	3	2.0×10^{-2}	5.0×10^{-2}	0	--	--	0	--	--
Dryer	2	1.2×10^{0}	2.1×10^{0}	6	6.1×10^{-2}	1.8×10^{-1}	11	5.0×10^{-2}	1.1×10^{-1}	27	2.1×10^{-2}	9.0×10^{-2}	0	--	--
Expander	64	5.7×10^{0}	5.9×10^{1}	157	1.6×10^{0}	4.8×10^{1}	24	6.3×10^{-2}	2.3×10^{-1}	23	3.7×10^{-2}	8.5×10^{-2}	8	5.6×10^{-2}	1.7×10^{-1}
Feeder	0	--	--	23	6.0×10^{0}	5.0×10^{1}	5	2.8×10^{-2}	1.0×10^{-1}	1	8.0×10^{-3}	8.0×10^{-3}	3	6.9×10^{-2}	1.0×10^{-1}
Mill	0	--	--	39	6.2×10^{-1}	6.1×10^{0}	13	4.9×10^{-2}	1.0×10^{-1}	18	4.2×10^{-2}	3.6×10^{-1}	7	6.8×10^{-2}	2.0×10^{-1}
Resin	0	--	--	13	7.1×10^{-2}	1.9×10^{-1}	12	5.4×10^{-2}	1.7×10^{-1}	3	5.7×10^{-3}	1.0×10^{-2}	0	--	--
Track other	0	--	--	33	1.2×10^{-1}	1.5×10^{0}	18	3.2×10^{-2}	1.3×10^{-1}	37	6.2×10^{-2}	1.5×10^{0}	14	6.0×10^{-2}	2.2×10^{-1}
Track unload	2	3.5×10^{0}	5.2×10^{0}	53	1.7×10^{1}	2.5×10^{2}	22	9.0×10^{0}	3.6×10^{1}	7	1.1×10^{0}	2.1×10^{0}	0	--	--

All concentration values are PCM f/cc.

As indicated, mean exposure levels vary among jobs, and also tend to decrease over time. Because the data are insufficient to calculate a reliable estimate of the arithmetic mean exposure level for each job for each year, the data for each job were fit to a statistical model to characterize the rate of change over time. Several different modeling approaches were evaluated, as described below.

F.5.3.1.1.1. ***Fitting method 1: local regression (LOESS)***. To investigate the form of the regression curve relating sample concentrations to date of sample, a flexible nonparametric fitting method was applied, using data for each job. Analyses were implemented by the SAS procedure PROC LOESS (SAS for Windows, Version 9.3). Linear functions of time were sequentially fit to "windows" of concentration values within a chosen radius (time span) of each concentration value. A smooth LOESS curve was then drawn through the fitted values. Fitting was performed by weighted least squares. The same radius was applied to each window of job-specific data. A "smoothing parameter" determined the radius of the fitting windows. The optimum smoothing parameter was determined by a grid search to identify the value that minimized the Akaike Information Criterion with Correction, a criteria for determining model fit.

These nonparametric plots generally reflect a decrease in exposure over time with a steeper decline in the mid-1970s followed by a shallower decline in later years. As shown in Figure F-5, a smooth fit was obtained for indoor trionizing jobs, but the results were more erratic and variable for the other jobs. This variability was judged to be related to variations in the *amount* of data available over various time windows rather than to authentic variations in concentration. On this basis, the LOESS approach was not pursued further. However, the results did suggest that exponential models could be a reasonable parametric form.

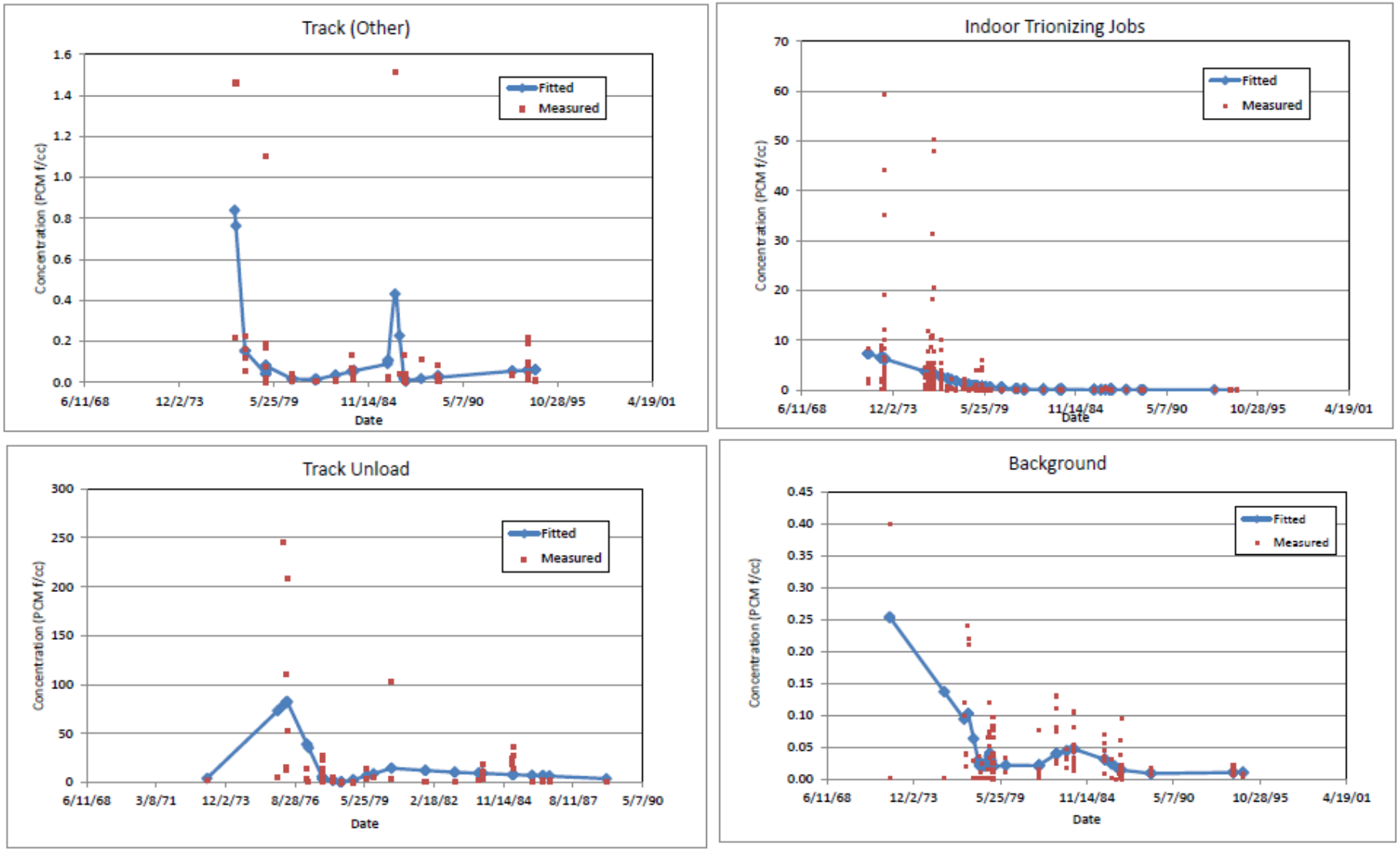


Figure F-5. Local regression (LOESS) fitting results.

F.5.3.1.1.2. ***Fitting method 2: exponential models with job-specific slopes.*** The second fitting method that was evaluated assumed a nonlinear regression model to describe the relationship between fiber concentrations and time. At time *t*, it was assumed that

$$C(t) = \mu(t) + e_t \quad \text{(F-1)}$$

where $\mu(t)$ = mean of $C(t)$ at time t, and e_t is a normally distributed error term with mean 0 and variance structure as discussed below.

A two parameter exponential function was used to model mean fiber concentration at time *t*:

$$\mu(t) = a \times \exp(-b \times t) \quad \text{(F-2)}$$

The intercept parameter (a) and the slope parameter (b) were expressed in terms of exponentiated functions [$a = \exp(a_0)$, $b = \exp(b_0)$] to guarantee that a, b, and $\mu(t)$ could only take on nonnegative values. Time t was coded as number of years from 1/1/1970 (an arbitrary frame of reference) to the date of sampling to facilitate model convergence.

When the data were grouped by job and by year, a plot of the natural logarithm (ln) of variance versus the natural logarithm of mean concentration revealed that ln-variance tended to increase approximately as a linear function of the ln-mean (see Figure F-6). Based on this, a "power of the mean" variance function was chosen to describe the mean-variance relation, where the dimension and value of the power parameter θ were determined from the data. This broad class of variance functions is commonly used in nonlinear regression analyses. Different models for the variance function were tried, including the 1-parameter function, $\mu(t)^{\theta}$, and 2-parameter function, $\theta_1 + \mu(t)^{\theta_2}$. Model convergence was consistently achieved with the 1-parameter power function model and was not achieved with the 2-parameter function. Consequently, the variance of the error term was modeled as a 1-parameter power function of the mean fiber concentration at time t, multiplied by a scale parameter σ^2 reflecting the overall level of precision in $C(t)$ (similar to σ^2 in ordinary linear regression):

$$\text{Var}\{C(t)\} = \sigma^2 \times \mu(t)^{\theta} \quad \text{(F-3)}$$

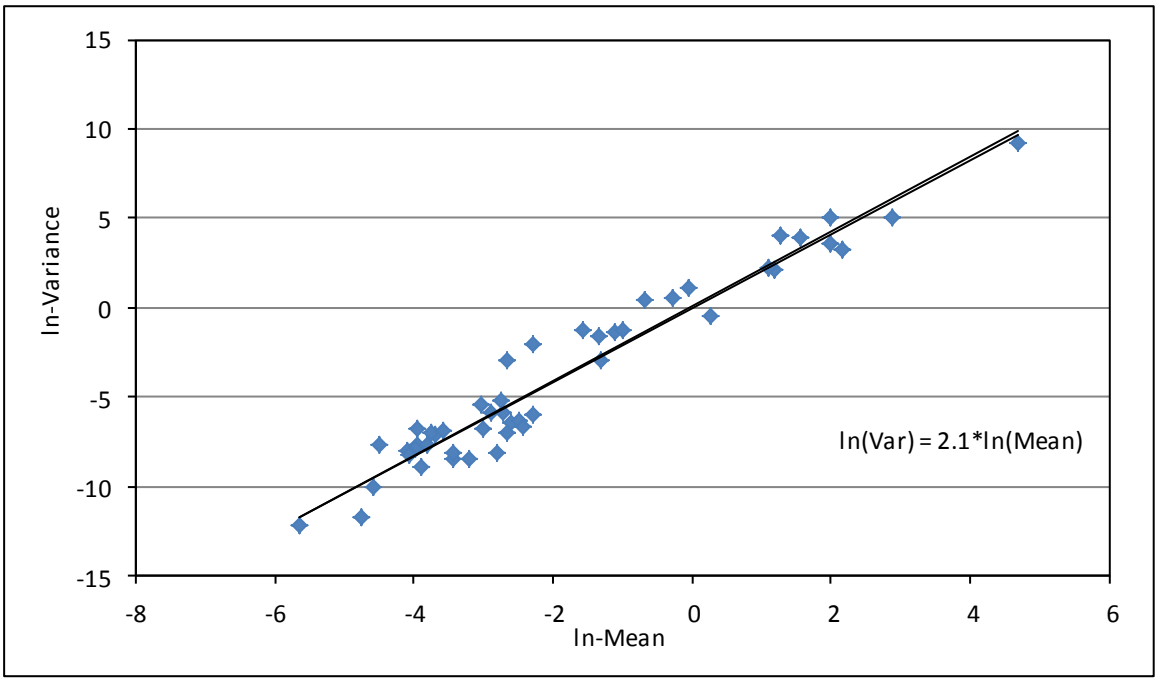


Figure F-6. Variance in industrial hygiene (IH) data as a function of the mean.

Regression parameters were estimated by iteratively reweighted least squares, in which estimates of the mean and the variance were alternately updated until convergence. Initially, the estimation of θ was incorporated into the estimation of regression parameters. However, this greatly increased data computations, and model convergence was usually not achieved. Therefore, the estimate of the parameter θ was obtained by including a grid search, which identified values for which model convergence was obtained and provided the value that best fit the data. A search of values from 0.1 to 2 was sufficient in each analysis to estimate θ. Post hoc sensitivity analyses were performed in which other values of θ were manually specified to confirm that the chosen θ was optimum. Results showed that a power of the mean model with θ−~1 allowed model convergence for all areas. After model parameters were estimated, σ^2 was estimated by calculating the mean-squared error (MSE), equal to the weighted sum of squared deviations of observed minus mean concentrations, divided by the sample size minus number of parameters (2 for this model). The weights were equal to the inverse of mean concentration to the power θ at each time. Analyses were implemented using the SAS procedure PROC NLIN (SAS for Windows, Version 9.3).

When each job was fit individually, most yielded reasonable fits (see Figure F-7). However, cleanup and blender yielded fits in which predicted concentrations for 1972−1973 were substantially higher than could be justified with known information about the manufacturing process. The results for cleanup and blender were likely a result of the absence of

data in the early time frame (1972−1973), and were considered to be unreliable. On this basis, this approach (use of independent parameters for each job) was not pursued further.

F.5.3.1.1.3. ***Fitting method 3: exponential models with common slopes for grouped jobs*****.** To avoid the unrealistic results generated when each job was allowed to have a separate slope term, a strategy of grouping jobs expected to show a similar rate of decline in airborne fiber levels was employed to obtain more reliable and realistic fits. Based on the expectation that the rate of decline in average exposure level was likely to be similar for trionizing jobs in the same general area, the trionizing jobs were grouped into two categories: jobs located inside the trionizing building (indoor trionizing jobs) and jobs located in the railroad yard (outdoor trionizing jobs). Indoor jobs included blender, cleanup, dryer, expander, feeder, mill, and resin, while outdoor jobs included track unload and track other. For each group, the data were fit to the model, requiring the slope parameter (b) to be the same for all jobs within the same group. Results are displayed in Figure F-8.

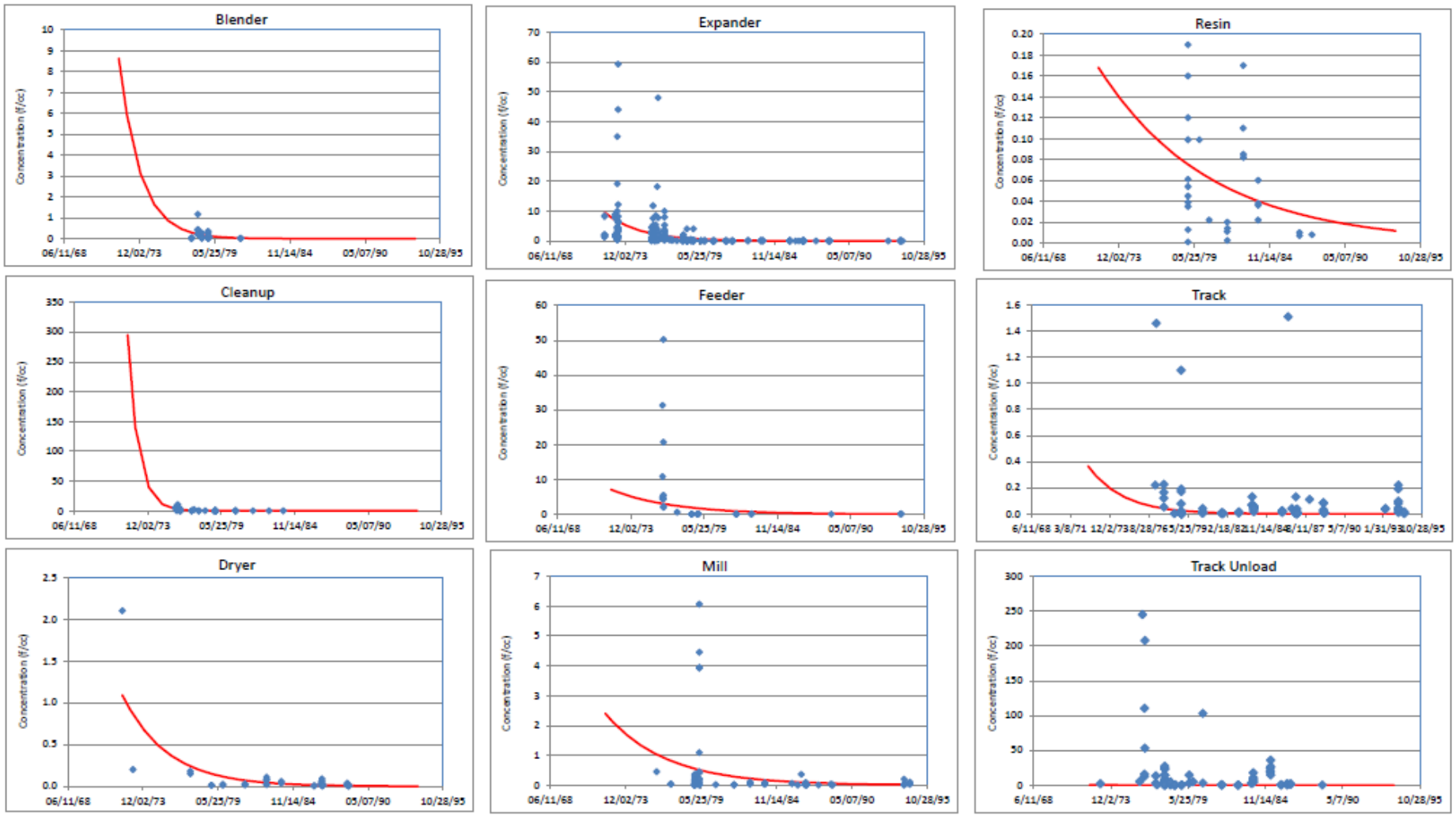


Figure F-7. Trionizing department data stratified by job. Variance-weight fitting with independent *b* terms.

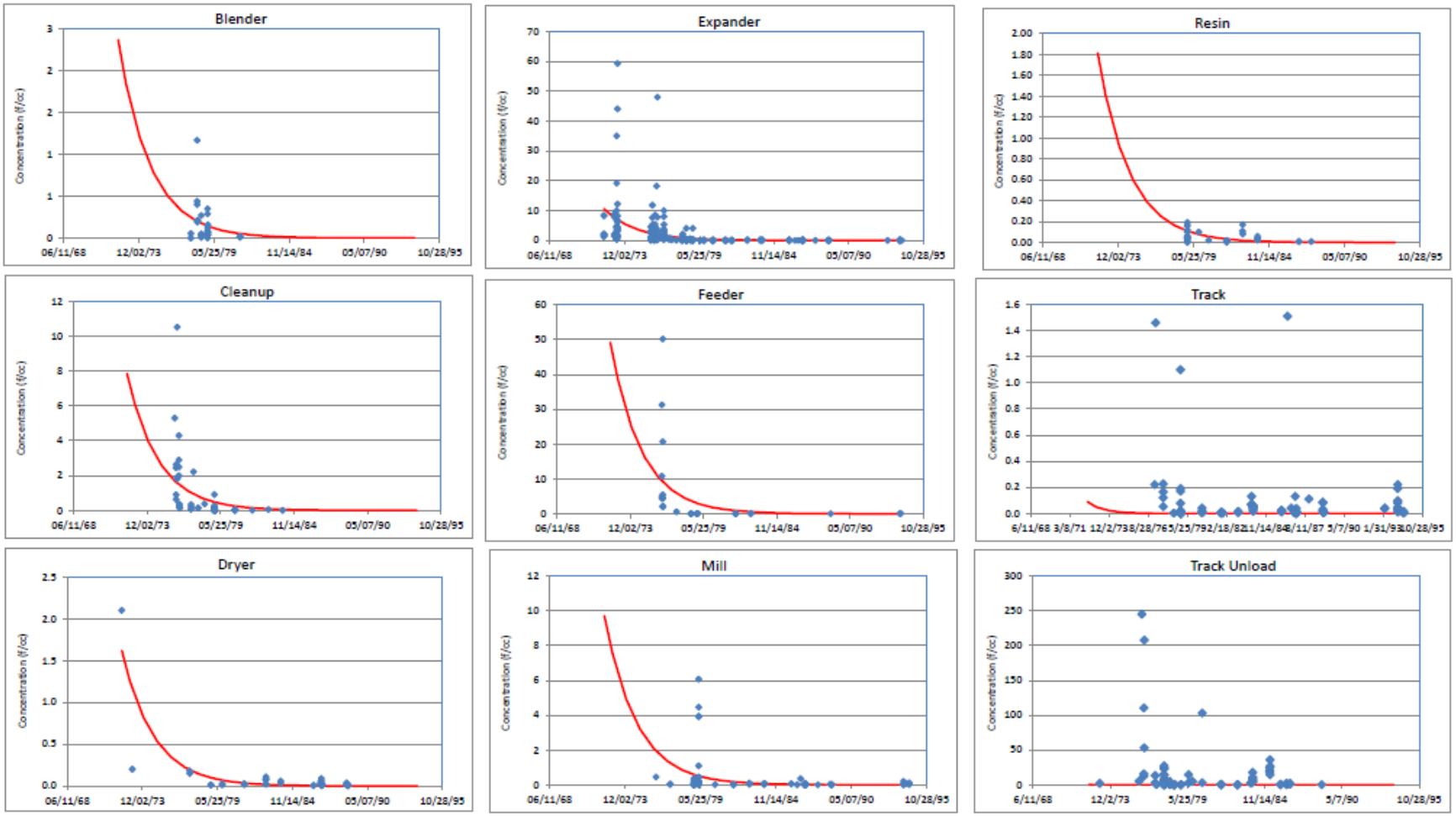


Figure F-8. Trionizing department data stratified by job. Variance-weight fitting with common *b* terms for indoor and outdoor jobs.

F.5.3.1.1.4. ***Fitting method 4: segmented exponential models***. The fourth approach evaluated was similar to the third approach, except the data were divided into two or three time segments, with different exponential curves fit to each segment. This approach was based on the expectation that the rate of decline in average exposure levels in the trionizing department was related to the timing and effectiveness of various engineering controls. As discussed in Section F.2, a number of different engineering controls were installed over time, with the largest decreases in dust level tending to occur in the 1976 to 1980 time frame. After 1980, Libby vermiculite was no longer used, and exposure levels tended to be low and relatively constant. Based on this, for indoor trionizing jobs, the data were fit using a three-segment approach, with the time segments defined as follows:

Segment 1: Before 1/1/1976.
Segment 2: 1/1/1976 to 12/31/1980.
Segment 3: 1/1/1981 and after.

Engineering controls installed to reduce indoor exposures in the trionizing department are not expected to have had significant impact on the outdoor exposure levels, so outdoor trionizing jobs (track other and track unload) were fit to a two-segment model, with the break point between segments occurring at 1/1/1981, when Libby vermiculite was no longer used. Results are shown in Figure F-9.

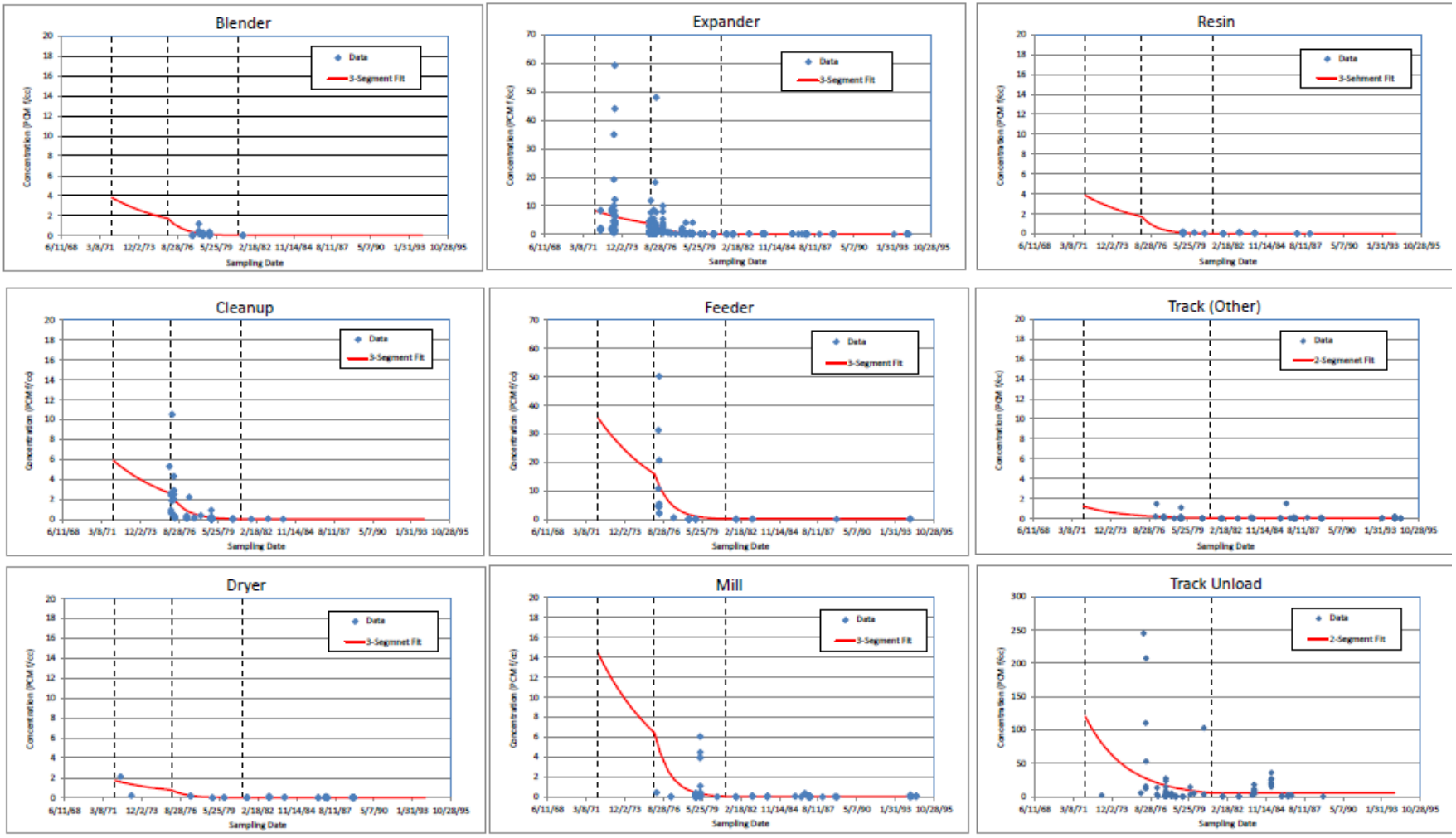


Figure F-9. Weighted exponential fits to indoor (3-segment) and outdoor (2-segment) trionizing jobs.

F.5.3.1.1.5. ***Selection of the preferred fitting approach.*** In choosing between fitting Strategy 3 and fitting Strategy 4, two factors were considered: (1) statistical goodness of fit of the model and (2) consistency with the general understanding of the impact of engineering controls at the Marysville facility.

The goodness of fit of the estimation model was determined by calculating the MSE, where MSE was calculated as the sum of the squared derivations between observed and predicted values divided by $n - p$, where n is the number of data points and p is the number of model parameters. For both indoor and outdoor jobs, the segmented approach (see Strategy 4) provided a lower MSE than the un-segmented approach (see Strategy 3), as shown in Table F-7:

Table F-7. Fitting statistics for trionizing jobs

Data set	No. of segments	MSE
Indoor	1	5.80
Trionizing	3	5.08
Outdoor	1	33.6
Trionizing	2	31.5

In addition, a segmented approach is consistent with the approach used by the University of Cincinnati for fitting the log-transformed data. This approach is also consistent with the available information regarding the implementation and effectiveness of various dust control techniques in the trionizing department. Hence, it is thought that the segmented approach better represents changes over time, even though the model is somewhat more complex with more regression parameters than the un-segmented models. The variance parameter θ of the segmented models was set at the value determined from the corresponding nonsegmented model, and was altered slightly, if necessary, to assure convergence. Post hoc sensitivity analyses were performed to validate that the optimum model fit was obtained. For these reasons, the segmented fits were selected for use in calculation of the arithmetic-mean-based JEM for trionizing jobs. Model parameters for the preferred models are shown in Table F-8.

Table F-8. Parameter values for segmented exponential fits to trionizing jobs

Parameter	Blender	Cleanup	Drier	Expander	Feeder	Mill	Resin	Track other	Track unload
a (Segment 1)	5.69×10^{0}	8.81×10^{0}	2.56×10^{0}	1.24×10^{1}	5.36×10^{1}	2.17×10^{1}	5.78×10^{0}	2.42×10^{0}	2.41×10^{2}
a (Segment 2)	4.34×10^{2}	6.72×10^{2}	1.95×10^{2}	9.44×10^{2}	4.09×10^{3}	1.66×10^{3}	4.41×10^{2}	5.46×10^{-2}	5.42×10^{0}
a (Segment 3)	1.66×10^{-2}	2.56×10^{-2}	7.45×10^{-3}	3.60×10^{-2}	1.56×10^{-1}	6.31×10^{-2}	1.68×10^{-2}	--	--
b (Segment 1)	2.02×10^{-1}	2.02×10^{-1}	2.02×10^{-1}	2.02×10^{-1}	2.02×10^{-1}	2.02×10^{-1}	2.02×10^{-1}	3.46×10^{-1}	3.46×10^{-1}
b (Segment 2)	9.25×10^{-1}	9.25×10^{-1}	9.25×10^{-1}	9.25×10^{-1}	9.25×10^{-1}	9.25×10^{-1}	9.25×10^{-1}	9.12×10^{-4}	9.12×10^{-4}
b (Segment 3)	6.14×10^{-6}	6.14×10^{-6}	6.14×10^{-6}	6.14×10^{-6}	6.14×10^{-6}	6.14×10^{-6}	6.14×10^{-6}	--	--

F.5.3.1.1.6. ***Calculation of job-weighted average exposure within the trionizing department.*** Workers in the trionizing department rotated among jobs, spending approximately equal amounts of time in each job during each work cycle, including equal time at each of the two dryer locations. When working at the outdoor track job, the employees reported that about 25% of the time was spent at track unload and 75% was spent at track other. Based on this, the job-weighting factors shown in Table F-9 were computed:

Table F-9. Job-weighting factors for trionizing department workers

Indoor							Outdoor	
Blender	**Cleanup**	**Dryer**	**Expander**	**Feeder**	**Mill**	**Resin**	**Track other**	**Track unload**
0.111	0.111	0.222	0.111	0.111	0.111	0.111	0.083	0.028

The job-weighted average exposure across all jobs (*j*) for each year (*t*) in the trionizing department was then calculated as:

$$\text{Job-weighted average } (t) = \sum C(j,t) \times JWF(j) \qquad \text{(F-4)}$$

where $C(j,t)$ = exposure concentration while working at job "*j*" in year "*t*."

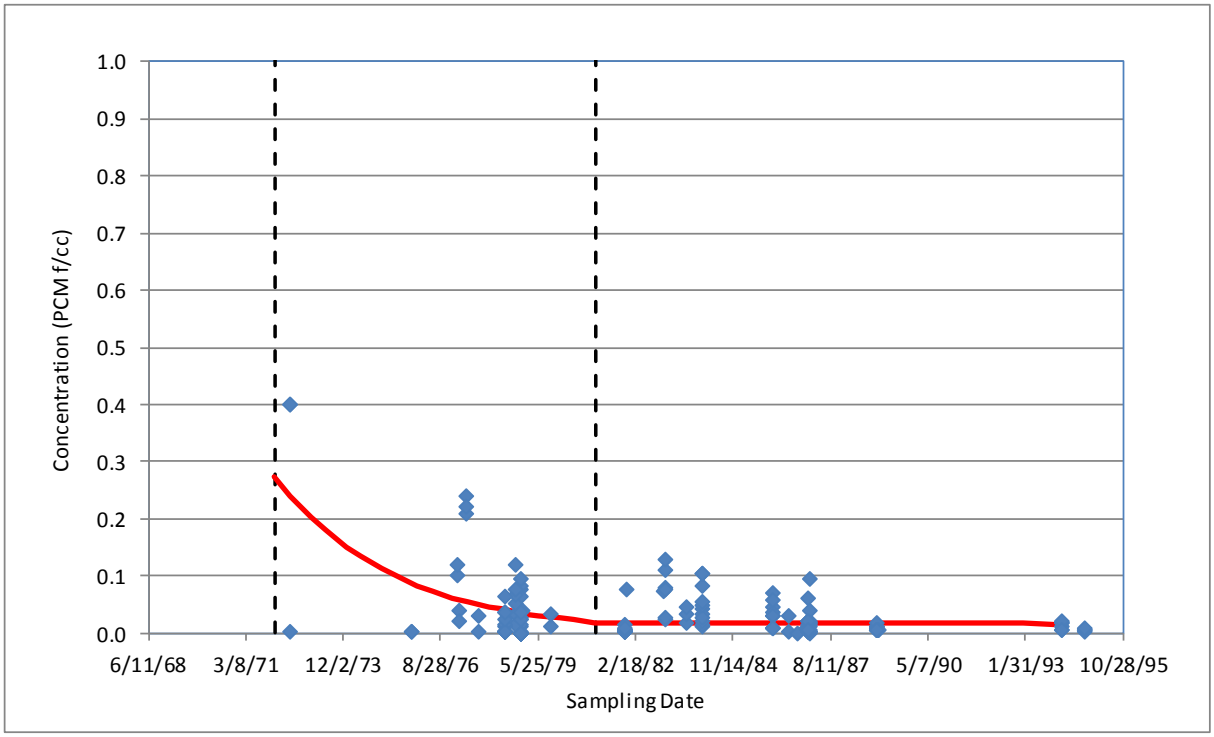
F.5.3.1.1.7. ***Data for other departments ("background").*** As discussed previously, industrial hygiene measurements in locations where only expanded vermiculite or no vermiculite was used were defined as having "plant background" exposure. These included measurements in polyform, office, research, pilot plant, warehouse, and packaging. Measurements of fibers in the air from these departments tended to be relatively low, with little distinction among departments. Therefore, data for all background jobs were combined and fit as a single data set.

Both the nonsegmented and two-segment exponential fitting strategies were tested for the background data set. Of these, the two-segment exponential approach was selected as being optimum because it better reflects known changes in processes, and the mean square error was slightly lower than for the nonsegmented model (see Table F-10).

Table F-10. Fitting statistics for background jobs

Data set	No. of segments	Mean square error
Background	1	0.020
	2	0.018

Figure F-10 shows the model parameters and the two-segment exponential fit for the background data set.



Parameter	Value
a (segment 1)	0.491
a (segment 2)	0.022
b (segment 1)	0.294
b (segment 2)	0.013

Figure F-10. Two-segment exponential fit to background jobs.

F.5.3.2. *Estimation of Exposure Levels from 1957 to 1971*

Extrapolation of model-predicted exposure concentrations in 1972 backwards in time to earlier years was performed as described in Section F.6.2. In brief, the extrapolation was based on a consideration of relative dust levels, the relative amounts of vermiculite from Libby or South Carolina, and the relative asbestos content of these types of vermiculite. The basic equation used for extrapolation is as follows:

$$C_{j,y} = \left(C_{j,1972}\right) \cdot Extrapolation\ factor_{j,y} \qquad \text{(F-5)}$$
$$Extrapolation\ factor_{j,y} = \ (Dust\ ratio)_{j,y}(F_L + k \times F_{SC})_y$$

where:

$C_{j,y}$ = Extrapolated fiber concentration for job "j" for year "y"

$C_{j,1972}$ = Estimated concentration of fiber in job "j" for 1972

Dust ratio$_{j,y}$ = Estimated ratio of dust in air for job "*j*" in year "*y*" compared to dust level in 1972

F_L = Fraction of vermiculite derived from Libby in year *y*

F_{SC} = Fraction of vermiculite derived from South Carolina in year *y*

k = Estimated relative concentration of fiber in South Carolina vermiculite compared to Libby vermiculite

As discussed in Section F.6.2.2, for the indoor trionizing jobs, the dust ratio in 1967 was assumed to be twice as high as in 1972, decreasing linearly over this time window. For all background and track jobs, the dust ratio was assumed to be 1:1. Data on the relative amounts of vermiculite from Libby and South Carolina were derived from company records (see Table F-3, above), and the relative asbestos content of Libby vermiculite to South Carolina vermiculite was estimated to be 8.7:1. Based on these values and estimates, extrapolation factors were calculated as summarized in Table F-11.

Table F-11. Extrapolation factors for 1957−1972

Department	Year	Dust ratio	F_L	F_{SC}	k	Extrapolation factor
Trionize (all indoor jobs)	1957	2.00	0.00	1.00	0.115	0.230
	1958	2.00	0.00	1.00	0.115	0.230
	1959	2.00	0.32	0.68	0.115	0.796
	1960	2.00	0.32	0.68	0.115	0.796
	1961	2.00	0.32	0.68	0.115	0.796
	1962	2.00	0.32	0.68	0.115	0.796
	1963	2.00	0.32	0.68	0.115	0.796
	1964	2.00	0.57	0.43	0.115	1.239
	1965	2.00	0.73	0.27	0.115	1.522
	1966	2.00	0.92	0.08	0.115	1.858
	1967	2.00	0.87	0.13	0.115	1.770
	1968	1.80	0.79	0.21	0.115	1.465
	1969	1.60	0.82	0.18	0.115	1.345
	1970	1.40	0.90	0.10	0.115	1.276
	1971	1.20	0.95	0.05	0.115	1.147
	1972	1.00	1.00	0.00	0.115	1.000
Trionize (outdoor jobs) and background	1957	1.00	0.00	1.00	0.115	0.115
	1958	1.00	0.00	1.00	0.115	0.115
	1959	1.00	0.32	0.68	0.115	0.398
	1960	1.00	0.32	0.68	0.115	0.398
	1961	1.00	0.32	0.68	0.115	0.398
	1962	1.00	0.32	0.68	0.115	0.398
	1963	1.00	0.32	0.68	0.115	0.398
	1964	1.00	0.57	0.43	0.115	0.619
	1965	1.00	0.73	0.27	0.115	0.761
	1966	1.00	0.92	0.08	0.115	0.929
	1967	1.00	0.87	0.13	0.115	0.885
	1968	1.00	0.79	0.21	0.115	0.814
	1969	1.00	0.82	0.18	0.115	0.841
	1970	1.00	0.90	0.10	0.115	0.911
	1971	1.00	0.95	0.05	0.115	0.956
	1972	1.00	1.00	0.00	0.115	1.000

Extrapolation factor = Dust ratio × (F_L + k × F_{SC}).
k = 1/ratio; ratio = 8.7.

F.5.3.3. ***Results: Job-Exposure Matrix (JEM) Based on Arithmetic Mean Exposure Levels***

As described above, IH measurements from the plant were used to estimate yearly arithmetic mean (AM) exposure levels in the trionizing department and in all other departments (background) from 1957 to 2000. As described previously, plant maintenance workers were assumed to be exposed 50% of the time in the trionizing department and 50% of the time in background departments, and central maintenance workers were assumed to be exposed 10% of the time in the trionizing department and 90% of the time in background departments. Table F-12 provides the AM-based JEM developed using this methodology.

Table F-12. Arithmetic Mean (AM)-based job-exposure matrix (JEM) for Marysville workers

Year	Trionizing (all jobs)	Plant maintenance[a]	Central maintenance[b]	Background[c]
1957	2.078	1.053	0.232	0.027
1958	2.078	1.053	0.232	0.027
1959	7.200	3.647	0.804	0.094
1960	7.200	3.647	0.804	0.094
1961	7.200	3.647	0.804	0.094
1962	7.200	3.647	0.804	0.094
1963	7.200	3.647	0.804	0.094
1964	11.201	5.673	1.252	0.146
1965	13.761	6.970	1.538	0.179
1966	16.802	8.511	1.877	0.219
1967	16.002	8.105	1.788	0.209
1968	13.487	6.839	1.521	0.192
1969	12.651	6.425	1.444	0.198
1970	12.334	6.275	1.427	0.215
1971	11.483	5.854	1.351	0.225
1972	10.498	5.367	1.262	0.236
1973	8.210	4.193	0.978	0.175
1974	6.484	3.307	0.766	0.130
1975	5.138	2.618	0.601	0.097
1976	3.164	1.618	0.382	0.073
1977	1.473	0.764	0.196	0.054
1978	0.745	0.392	0.111	0.040
1979	0.409	0.219	0.068	0.030
1980	0.244	0.133	0.044	0.022
1981	0.189	0.104	0.036	0.019
1982	0.189	0.104	0.036	0.019
1983	0.189	0.104	0.036	0.019
1984	0.189	0.104	0.035[d]	0.018
1985	0.188	0.103	0.035	0.018
1986	0.188	0.103	0.035	0.018
1987	0.188	0.103	0.035	0.018
1988	0.189	0.103	0.035	0.017
1989	0.188	0.102	0.034	0.017
1990	0.188	0.102	0.034	0.017

Table F-12. Arithmetic Mean (AM) based job-exposure matrix (JEM) for Marysville workers (continued)

Year	Trionizing (all jobs)	Plant maintenance[a]	Central maintenance[b]	Background[c]
1991	0.187	0.102	0.034	0.017
1992	0.188	0.102	0.034	0.017
1993	0.187	0.102	0.033	0.016
1994	0.187	0.102	0.033	0.016
1995–2000	0.187	0.102	0.033	0.016

[a]Assumed exposure 50% in trionizing and 50% in background departments.
[b]Assumed exposure 10% in trionizing and 90% in background departments.
[c]Background includes pilot plant, research, polyform, office, packaging, and warehouse.
[d]After 1983, central maintenance was outsourced, but some O.M. Scott workers continued in that job.

F.5.4. Selection of the Preferred Job-Exposure Matrix (JEM)

In occupational epidemiology and industrial health studies, evaluations of worker exposure are often based on estimates of the geometric mean exposure concentration (Seixas et al., 1988). However, EPA traditionally employs the arithmetic mean exposure level in computing exposure and risk (U.S. EPA, 1994), and toxicity values employed by EPA in risk quantification are based on arithmetic mean exposures. For this reason, EPA determined that the JEM based on untransformed data (as described in Section F.6.3) is the most appropriate for use in calculating cumulative worker exposure, as described in the following section, and for use in deriving the reference concentration (RfC).

F.6. DEVELOPMENT OF A CUMULATIVE HUMAN EQUIVALENT EXPOSURE CONCENTRATION

F.6.1. Basic Equation

In most occupational studies of worker exposure to asbestos, cumulative exposure (*CE*) is expressed in units of fiber/cc-years, which is calculated as the product of average exposure concentration at work ($\bar{C}$, fiber/cc) and exposure duration (*ED*, the number of years at work):

$$CE(\text{f/cc-yrs}) = \bar{C}\ (\text{f/cc}) \times ED\ (\text{yrs}) \qquad \text{(F-6)}$$

F.6.2. Extrapolation from Workplace Exposure to Continuous Exposure

When exposure-response data based on workers are used as the basis for evaluating exposures and risks in people with continuous exposure (e.g., full-time residents), it is necessary to convert the cumulative exposure value for each worker to a value that is appropriate for a resident with continuous exposure:

$$CE\ (continuous) = CE\ (workplace) \times Adj.\ factor \quad \text{(F-7)}$$

This adjustment accounts for the fact that workers are exposed only part of the day (while at work), and also accounts for different breathing rates between the workplace and the residence. In the absence of site-specific data, the adjustment factor for asbestos is calculated as follows (U.S. EPA, 2014, 1994):

$$Adj\ factor = \frac{(BR \cdot ET \cdot ED)_{occupational}}{(BR \cdot ET \cdot ED)_{continuous}} \quad \text{(F-8)}$$

$$= \frac{(1.25\ m^3\ per\ hr) \cdot (8\ hrs\ per\ day) \cdot (5\ work\ days\ per\ week)}{(0.8333\ m^3\ per\ hr) \cdot (24\ hrs\ per\ day) \cdot (7\ days\ per\ week)} = \frac{50\ m^3}{140\ m^3} = 0.3571 \quad \text{(F-9)}$$

In the case of the Marysville cohort, a more complex adjustment is needed to convert from workplace exposure to continuous exposure, because employees at the Marysville plant often worked extended work schedules, both in terms of hours per day and days per week, and these schedules depended on the time of year (season) due to seasonal variations in product demand (OSHA, 1979). The focus groups were used to gain a more complete understanding of these work schedules. The groups were comprised of long-term workers with pre- and post-1972 experience across all departments. Therefore, these groups were uniquely qualified to elucidate the plant work schedules over the full time frame of interest, beginning in 1957.

Based on this understanding of plant operations, six departments were identified that had a unique set of season-specific exposure parameters (hours/day, days per season):

1. Trionizing (including track other and track unload).
2. Plant maintenance.
3. Central maintenance.
4. Polyform.
5. Background (office, research lab, pilot plant).
6. Background with extra time (warehouse, packaging).

For each of these departments, a seasonal adjustment factor was calculated using the following general equation:

$$Seasonal\ adj.factor_{d,i} = \left(\frac{1.25\ m^3\ per\ hr}{0.8333\ m^3\ per\ hr}\right)\left(\frac{ET_{d,i}}{24}\right)\left(\frac{ED_{d,i}}{N_i}\right) \quad \text{(F-10)}$$

where:

$ET_{d,i}$ = Exposure time (hours/day) in department "*d*" during season "*i*"
$ED_{d,i}$ = Number of days worked in department "*d*" during season "*i*"
N_i = Number of days in season "*i*"

For each worker, the date of any job change among these six departments was adjusted so the change occurred at the starting month for the nearest season. Department-specific and season-specific values of *ET*, *ED*, and *N* are provided below, along with the corresponding seasonal adjustment factors.

F.6.2.1. ***Trionizing, Plant Maintenance, Polyform, Warehouse, and Packaging***

Each of these departments was characterized by a complex work schedule that included substantial overtime, with the level of overtime work depending on season:

Spring
Season = January 1 to May 31
N = 151.25 days (includes 0.25 days to account for leap years)
Work schedule = 7 days/week, 12 hours/day, with New Years' Day off
ED = 151.25 − 1 = 150.25
ET = 12 hours/day
Seasonal adj. factor = (1.25/0.8333) × [12/24 × 150.25/151.25] = 0.745

Summer
Season = June 1 to August 31
N = 92 days
Work schedule = 5 days/week, 8 hours/day, with 2 week summer vacation
ED = (92 − 14) × 5/7 = 55.71 days
ET = 8 hours/day
Seasonal adj. factor = (1.25/0.8333) × [8/24 × 55.71/92] = 0.3028

Fall
Season = September 1 to December 31
N = 122 days
Work schedule = 5 days/week, 12 hours/day plus 2 days/week, 8 hours/day, with Christmas Day off
*ED*1 = 121 days × 5/7 = 86.43 days
*ET*1 = 12 hours/day
*ED*2 = 121 × 2/7 = 34.57 days
*ET*2 = 8 hours/day
Seasonal adj. factor = (1.25/0.8333) × [(12/24 × 86.43) + (8/24 × 34.57)]/122 = 0.6730

F.6.2.2. ***Office, Pilot Plant, Research, and Central Maintenance***

Each of these departments was characterized by a normal work schedule that did not include overtime.

Spring
Season = January 1 to May 31
N = 151.25
Work schedule = 5 days/week, 8 hours/day, with New Years' Day off
ED = 150.25 days × 5/7 = 107.32 days

ET = 8 hours/day
Seasonal adj. factor = (1.25/0.8333) × [8/24 × 107.32/151.25] = 0.3548

Summer
Season = June 1 to August 31
N = 92 days
Work schedule = 5 days/week, 8 hours/day, with 2 week summer vacation
ED = (92 − 14) × 5/7 = 55.71 days
ET = 8 hours/day
Seasonal adj. factor = (1.25/0.8333) × [8/24 × 55.71/92] = 0.3028

Fall
Season = September 1 to December 31
N = 122 days
Work schedule = 5 days/week, 8 hours/day, with Christmas Day off
ED = (122 − 1) × 5/7 = 86.43
ET = 8 hours/day
Season adj. factor = (1.25/0.8333) × [8/24 × 86.43/122] = 0.3542

In summary, the seasonal adjustment factors are as shown in Table F-13:

Table F-13. Seasonal adjustment factors

Departments	Spring	Summer	Fall
Trionizing, plant maintenance, polyform, warehouse, packaging	0.7450	0.3028	0.6730
Office, pilot plant, research, central maintenance	0.3548	0.3028	0.3542

F.6.3. Calculation of Average Exposure Concentrations

Calculation of the average exposure concentration ($\bar{C}$) for each worker is complicated by the fact that some workers did not spend 100% of the time at work in a single location.

According to the focus group data, each worker was allowed approximately a 30-minute break for lunch and two 15-minute breaks during the day. Therefore, regardless of job, every worker was considered to have at least 1 hour of the total time at work spent at a background exposure location. There was no documentation that a third 15-minute break was provided when working longer than 8 hours in a day.

In addition, when overtime hours (more than 8 hours/day) were worked, workers in some departments spent some of their extra hours in other departments. According to focus group data, the only workers that worked extra hours outside of their own departments were those in trionizing and polyform. Thus, a decision was needed on how to appropriate the amount of overtime spent outside trionizing and polyform.

1. Extra hours for polyform workers—According to the focus groups, polyform workers first worked in their own department, and went to trionizing to work extra hours. According to workers, about 75% of the daily overtime was in their own department. Therefore, for each 4 hours worked beyond the normal 8 hour day, it is estimated that polyform workers spent 3 hours in polyform and 1 hour in trionizing.

2. Extra hours for trionizing workers—As with polyform workers above, it is estimated that for every 4 hours of overtime worked by trionizing workers, 3 hours were spent in trionizing and 1 hour was spent in polyform.

In accord with these exposure parameters, the value of $\bar{C}_{d,i}$ for each department "*d*" for each season "*i*" was calculated as indicated in Table F-14.

Table F-14. Equations for calculating $\overline{C}_{d,i}$ values that account for breaks and interdepartment overtime

Department (*d*)	Season (*i*)		
	Spring	**Summer**	**Fall**
Trionizing	10/12 × *Ct* + 2/12 × *Cb*	7/8 × *Ct* + 1/8 × *Cb*	5/7 × (10/12 × *Ct* + 2/12 × *Cb*) + 2/7 × (7/8 × Ct + 1/8 × *Cb*)
Polyform	1/12 × *Ct* + 11/12 × *Cb*	*Cb*	5/7 × (1/12 × *Ct* + 11/12 × *Cb*) + 2/7 × *Cb*
Plant maintenance	11/12 × *Cpm* + 1/12 × *Cb*	7/8 × *Cpm* + 1/8 × *Cb*	5/7 × (11/12 × *Cpm* + 1/12 × *Cb*) + 2/7 × (7/8 × *Cpm* + 1/8 × *Cb*)
Central maintenance	7/8 × *Ccm* + 1/8 × *Cb*	7/8 × *Ccm* + 1/8 × *Cb*	7/8 × *Ccm* + 1/8 × *Cb*
Warehouse, packaging, office, pilot plant, research	*Cb*	*Cb*	*Cb*

Ct = Concentration in trionizing department.
Cb = Concentration in background departments.
Cpm = Average exposure while performing plant maintenance activities.
Ccm = Average exposure while performing central maintenance activities.

F.6.4. Calculation of Cumulative Human Equivalent Exposure Concentration (CHEEC)

Given the department-specific seasonal adjustment factors, the cumulative human equivalent exposure concentration (CHEEC) for each worker is calculated as follows:

$$\text{CHEEC (f/cc-year)} = \sum\left(\bar{C}_{d,i} \times \text{Seasonal Adj. factor}_{d,i} \times N_{\text{i}}/365.25\right) \quad \text{(F-11)}$$

where $\bar{C}_{d,i}$ is the average concentration of fibers inhaled by a worker in department "*d*" during season "*i*", N_i is the number of days in season "*i*", and the sum is calculated across all seasons that the worker is exposed.

F.6.5. Verification of the Calculations

To verify the accuracy of the CHEEC calculations, several quality control checks were conducted. The distribution was evaluated by reviewing the mean, median, standard deviation, highest 10 values, and lowest 10 values. Several workers were also randomly selected and their values were hand calculated to ensure all programming was appropriate.

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APPENDIX G. EXTRA RISK AND UNIT RISK CALCULATION

G.1. MESOTHELIOMA MORTALITY

The increased risk of mesothelioma mortality attributable to continuous fiber exposure was estimated using a life-table procedure based on the general U.S. population. The life-table procedure involved the application of the estimated Libby Amphibole asbestos[15]-specific toxicity to a structured representation of the general U.S. population in such a manner as to yield age-specific risk estimates for mesothelioma mortality in the absence and presence of exposure to Libby Amphibole asbestos. Baseline all-cause mortality rates were included in the life-table in such a way as to enable computation of the specific absolute risk of mesothelioma mortality while accounting for other competing causes of mortality. For each age-interval in the life-table, the effect estimates of the Poisson regression model analysis (the absolute risk) were used to estimate mesothelioma mortality at a particular exposure level. These age-specific absolute risks can then be summed over a lifetime. Different exposure levels are evaluated to ascertain what magnitude of exposure would be expected to produce 1% absolute risk of mesothelioma mortality. By this method, the exposure-response relationship determined in the Libby worker cohort is used to estimate mesothelioma mortality in the general U.S. population that would be expected from continuous lifetime environmental exposure to various concentrations of Libby Amphibole asbestos.

Assuming no background risk for mesothelioma, extra risk is the same as absolute risk. Absolute risk estimates were calculated using the effect estimates derived from the modeling of the mesothelioma mortality risk and a life-table analysis program that accounts for competing causes of death.[16] The unit risk of mesothelioma is computed using the 95% upper bound to estimate an upper bound for extra risk of mesothelioma due to Libby Amphibole asbestos exposure. The upper bound calculation is specific to the exposure metric parameters; the effect of metric uncertainty in these values is discussed in Section 5.4.5.3. Because this human health assessment derived a combined inhalation unit risk (IUR) for both mesothelioma and lung cancer mortality, an interim value based on the central effect estimate (rather than the upper bound) is also computed to avoid statistical concerns regarding the combination of upper bounds. Details are shown in Section 5.4.5.3. In accordance with EPA's *Supplemental Guidance for Assessing Susceptibility from Early Life Exposure to Carcinogens* (U.S. EPA, 2005b), the application of

[15]The term "Libby Amphibole asbestos" is used in this document to identify the mixture of amphibole mineral fibers of varying elemental composition (e.g., winchite, richterite, tremolite, etc.) that have been identified in the Rainy Creek complex near Libby, MT. It is further described in Section 2.2.

[16]This program is an adaptation of the approach previously used by the Committee on the Biological Effects of Ionizing Radiation (BEIR, 1988). A spreadsheet containing the extra risk calculation for the derivation of the LEC01 for mesothelioma mortality is presented in Tables G-1.

the age dependent adjustment factors for substances that act through a mutagenic mode of action is not recommended (see Section 5.4.5.3).

U.S. age-specific all-cause mortality rates from the 2010 *National Vital Statistics Report (NVSR)* for deaths in 2007 among all race and gender groups combined (Xu et al., 2010) were used to specify the all-cause background mortality rates (R_o) in the life-table analysis. The risk with exposure (R_x) was computed up to age 85 years,[17] assuming continuous environmental exposure to Libby Amphibole asbestos. Conversions between occupational Libby Amphibole asbestos exposures and continuous environmental asbestos exposures were made to account only for differences in the amount of air inhaled per day during a higher effort occupational shift (8 hours; 10 m^3) compared to a standard 24-hour (20 m^3) day (U.S. EPA, 1994) because results were already based on a 365-day calendar year. The computation of the unit risk involved three steps. The first step was to compute the unit risk for adults. This was achieved by initiating exposure at age 16 years and maintaining continuous exposure throughout the remainder of life while allowing for the incremental mathematical decay of previously accumulated exposure.[18]

An age of 16 years was used because it roughly matched the youngest age of a worker in the subcohort and was consistent with the application of a similar life-table methodology when the age-dependent adjustment factors (ADAFs) are applied; however, the application of age-dependent adjustment factors was not recommended in this case (see Section 4.6.2.2). An adjustment was also made in the life-table for the lag period, so that the age-specific risk calculations began at 16+ (the length of the lag period) years of age. The standard assumption used by the U.S. Environmental Protection Agency (EPA) is that the average lifetime spans 70 years. Because the adult-only-exposure unit risk excluded the first 16 years, the adult-only-exposure unit risk based on 54 years was then rescaled for an entire lifetime of continuous exposure by multiplying the interim value for adult-only-exposure by 70/54 to cover the childhood years (<16 years) to compute the "adult-based" unit risk. After rescaling, the resulting "adult-based" lifetime unit risk estimate (in contrast to the unscaled "adult-only-exposure" unit risk estimate obtained from the life-table calculations) may be prorated for less-than-lifetime exposure scenarios in the same manner as would be used for an "adult-based" unit risk estimate derived from a rodent bioassay.

Consistent with the *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005), the same data and methodology were also used to estimate the exposure level effective concentration (EC_x) and the associated 95% lower confidence limit of that exposure level effective concentration (LEC_x) corresponding to an absolute risk of 1% ($x = 0.01$). A 1%-risk level is commonly used for the determination of the point of departure (POD) for low-dose extrapolation

[17]Note that 85 years is not employed here as an average lifespan but, rather, as a cut-off point for the life-table analysis, which uses actual age-specific mortality rates.
[18]Exposures in the life-tables were computed at the mid-point of each age interval and appropriately lagged.

from epidemiological data, and the LEC value corresponding to that risk level was used as the actual POD.

The following table illustrates the computational details of the unit risks for mesothelioma mortality (see Table G-1). The result of Table G-1 is shown in Table 5-49 and is not adjusted for the underascertainment of mesothelioma described in Section 5.4.5.1.1. The unit risks adjusted for underascertainment are shown in Table 5-49.

Column Definitions for Table G-1:

Column A: Age interval up to age 85.

Column B: All-cause mortality rate for interval i ($\times 10_5$/year) (Xu et al., 2010).

Column C: All-cause hazard rate for interval i ($h \times {}_i$) (= all-cause mortality rate × number of years in age interval).

Column D: Probability of surviving interval i (q_i) [= $\exp(-h \times {}_i)$].

Column E: Probability of surviving up to interval i (S_i) ($S_1 = 1$; $S_i = S_{i-1} \times q_{i-1}$, for $I > 1$).

Column F: Lagged exposure at midinterval (x dose) assuming constant exposure was initiated at age 16.

Column G: Mesothelioma mortality hazard rate in exposed people for interval. To estimate the LEC_{01}, i.e., the 95% lower bound on the continuous exposure giving an extra risk of 1%, the 95% upper bound on the regression coefficient is used.

Column H: All-cause hazard rate in exposed people for interval i ($h \times x_i$) [= $h \times {}_I + (hx_i - h_i)$].

Column I: Probability of surviving interval i without dying from mesothelioma for exposed people (qx_i) [= $\exp(-h \times x_i)$].

Column J: Probability of surviving up to interval i without dying from mesothelioma for exposed people (Sx_i) ($Sx_1 = 1$; $Sx_i = Sx_{i-1} \times qx_{i-1}$, for $I > 1$).

Column K: Conditional probability of dying from mesothelioma in interval i for exposed people [= $(hx \div h \times x_i) \times Sx_i \times (1 - qx_i)$] ($R_x$, the lifetime probability of dying from mesothelioma for exposed people = the sum of the conditional probabilities across the intervals).

Note that the life-tables for mesothelioma mortality estimate the extra risk as the absolute risk as there is no assumption of a background risk in the absence of exposure. In each of the life-tables, inhalation exposure commences at age 16 years and continues at the same exposure concentration for the duration of the life-table. This allows for the computation of an

"adult-only-exposure" occupational lifetime unit risk, which is then scaled by a ratio of 70:54 to account for risk over the standard 70-year lifetime. While exposure is initiated in the life-table at age 16 years, this exposure is lagged to match the corresponding exposure-response models, which provide the hazard rates per unit of exposure. For example, in Table G-1, Column F shows exposure lagged by 10 years so that no lagged exposure appears in the table prior to age 26 years (16 + 10). Note that risks are initially shown in 1-year intervals because children's risk intervals can be smaller, and there was a need to be able to begin exposures at 16 years.

Table G-1. Mesothelioma extra risk calculation for environmental exposure to 0.1479 fibers/cc Libby Amphibole asbestos using the metric of cumulative exposure with a 10-year exposure lag and a 5-year half-life of exposure, as described in Section 5.4.5.3

A	B	C	D	E	F	G	H	I	J	K
Age int.	**All-cause mortality (×105/yr)**	**All-cause hazard rate (*h*×)**	**Prob. of surviving interval (*q*)**	**Prob. of surviving up to interval (*S*)**	**Lagged exp. mid. int. (*X*dose)**	**Exposed meso. hazard rate (*hx*)**	**Exposed all-cause haz. rate (*h* × *x*)**	**Exposed prob. of surviving interval (*qx*)**	**Exposed prob. of surviving up to int. (*Sx*)**	**Exposed cond. prob. of meso. in interval (*Rx*)**
<1	684.5	0.0068	0.9932	1.0000	0.000	0.0000	0.0068	0.9932	1.0000	0.0000
1	28.6	0.0003	0.9997	0.9932	0.000	0.0000	0.0003	0.9997	0.9932	0.0000
2	28.6	0.0003	0.9997	0.9929	0.000	0.0000	0.0003	0.9997	0.9929	0.0000
3	28.6	0.0003	0.9997	0.9926	0.000	0.0000	0.0003	0.9997	0.9926	0.0000
4	28.6	0.0003	0.9997	0.9923	0.000	0.0000	0.0003	0.9997	0.9923	0.0000
5	13.7	0.0001	0.9999	0.9920	0.000	0.0000	0.0001	0.9999	0.9920	0.0000
6	13.7	0.0001	0.9999	0.9919	0.000	0.0000	0.0001	0.9999	0.9919	0.0000
7	13.7	0.0001	0.9999	0.9918	0.000	0.0000	0.0001	0.9999	0.9918	0.0000
8	13.7	0.0001	0.9999	0.9916	0.000	0.0000	0.0001	0.9999	0.9916	0.0000
9	13.7	0.0001	0.9999	0.9915	0.000	0.0000	0.0001	0.9999	0.9915	0.0000
10	18.7	0.0002	0.9998	0.9914	0.000	0.0000	0.0002	0.9998	0.9914	0.0000
11	18.7	0.0002	0.9998	0.9912	0.000	0.0000	0.0002	0.9998	0.9912	0.0000
12	18.7	0.0002	0.9998	0.9910	0.000	0.0000	0.0002	0.9998	0.9910	0.0000
13	18.7	0.0002	0.9998	0.9908	0.000	0.0000	0.0002	0.9998	0.9908	0.0000
14	18.7	0.0002	0.9998	0.9906	0.000	0.0000	0.0002	0.9998	0.9906	0.0000
15	61.9	0.0006	0.9994	0.9904	0.000	0.0000	0.0006	0.9994	0.9904	0.0000
16	61.9	0.0006	0.9994	0.9898	0.000	0.0000	0.0006	0.9994	0.9898	0.0000
17	61.9	0.0006	0.9994	0.9892	0.000	0.0000	0.0006	0.9994	0.9892	0.0000

Table G-1. Mesothelioma extra risk calculation for environmental exposure to 0.1479 fibers/cc Libby Amphibole asbestos using the metric of cumulative exposure with a 10-year exposure lag and a 5-year half-life of exposure, as described in Section 5.4.5.3 (continued)

A	B	C	D	E	F	G	H	I	J	K
18	61.9	0.0006	0.9994	0.9886	0.000	0.0000	0.0006	0.9994	0.9886	0.0000
19	61.9	0.0006	0.9994	0.9880	0.000	0.0000	0.0006	0.9994	0.9880	0.0000
20	98.3	0.0010	0.9990	0.9874	0.000	0.0000	0.0010	0.9990	0.9874	0.0000
21	98.3	0.0010	0.9990	0.9864	0.000	0.0000	0.0010	0.9990	0.9864	0.0000
22	98.3	0.0010	0.9990	0.9854	0.000	0.0000	0.0010	0.9990	0.9854	0.0000
23	98.3	0.0010	0.9990	0.9845	0.000	0.0000	0.0010	0.9990	0.9845	0.0000
24	98.3	0.0010	0.9990	0.9835	0.000	0.0000	0.0010	0.9990	0.9835	0.0000
25	99.4	0.0010	0.9990	0.9825	0.000	0.0000	0.0010	0.9990	0.9825	0.0000
26	99.4	0.0010	0.9990	0.9815	0.144	0.0001	0.0011	0.9989	0.9815	0.0001
27	99.4	0.0010	0.9990	0.9806	0.401	0.0002	0.0012	0.9988	0.9805	0.0002
28	99.4	0.0010	0.9990	0.9796	0.626	0.0003	0.0013	0.9987	0.9793	0.0003
29	99.4	0.0010	0.9990	0.9786	0.821	0.0004	0.0014	0.9986	0.9780	0.0004
30–34	110.8	0.0055	0.9945	0.9777	1.268	0.0006	0.0062	0.9938	0.9767	0.0006
35–39	145.8	0.0073	0.9927	0.9723	1.701	0.0009	0.0082	0.9919	0.9706	0.0008
40–44	221.6	0.0111	0.9890	0.9652	1.918	0.0010	0.0121	0.9880	0.9628	0.0009
45–49	340.0	0.0170	0.9831	0.9546	2.026	0.0010	0.0180	0.9821	0.9512	0.0010
50–54	509.0	0.0255	0.9749	0.9385	2.080	0.0011	0.0265	0.9738	0.9342	0.0010
55–59	726.3	0.0363	0.9643	0.9149	2.107	0.0011	0.0374	0.9633	0.9098	0.0010
60–64	1,068.3	0.0534	0.9480	0.8823	2.121	0.0011	0.0545	0.9470	0.8764	0.0009
65–69	1,627.5	0.0814	0.9218	0.8364	2.127	0.0011	0.0825	0.9209	0.8299	0.0009
70–74	2,491.3	0.1246	0.8829	0.7710	2.131	0.0011	0.1256	0.8819	0.7642	0.0008

Table G-1. Mesothelioma extra risk calculation for environmental exposure to 0.1479 fibers/cc Libby Amphibole asbestos using the metric of cumulative exposure with a 10-year exposure lag and a 5-year half-life of exposure, as described in Section 5.4.5.3 (continued)

A	B	C	D	E	F	G	H	I	J	K
75–79	3,945.9	0.1973	0.8209	0.6807	2.132	0.0011	0.1984	0.8201	0.6740	0.0007
80–84	6,381.4	0.3191	0.7268	0.5588	2.133	0.0011	0.3202	0.7260	0.5527	0.0005
Absolute Rx = 0.0100										

exp. = exposure, haz. = hazard, int. = interval, meso. = mesothelioma, mid. = midinterval, Prob. = probability.
Absolute risk = 0.01000, exp. Level = 0.1479; occupational lifetime unit risk = 0.01/0.1479 = 0.0676 (based on occupational exposures beginning at age 16 yr); scaled occupational lifetime unit risk = 0.0876 (scaled by ratio of 70:54 to account for risk over 70-yr lifetime).

G.2. LUNG CANCER MORTALITY

Lung cancer mortality risk computations are very similar to mesothelioma mortality computations above (see Section G.1), with one important difference that extra risk is used for lung cancer. Extra risk is defined as equaling $(R_x - R_o) \div (1 - R_o)$, where R_x is the lifetime lung cancer mortality risk in the exposed population and R_o is the lifetime lung cancer mortality risk in an unexposed population (i.e., the background risk). U.S. age-specific all-cause mortality rates from the 2010 *National Vital Statistics Report* (Xu et al., 2010) for deaths in 2007 among all race and gender groups combined were used to specify the all-cause background mortality rates (R_o) in the life-table analysis. Cause-specific background mortality rates for cancers of the lung, trachea, and bronchus were obtained from a Surveillance, Epidemiology, and End Results (SEER) report on mortality during 2003−2007 (2003–2007 Surveillance Epidemiology and End Results Table 15.10, age-specific U.S. death rates).

The following tables show details of the computations of the unit risks for lung cancer mortality (see Tables G-2). The result of Table G-2 is shown in Table 5-52.

Column Definitions for Tables G-2:

Column A: Age interval up to age 85.

Column B: All-cause mortality rate for interval *i* ($\times 10_5$/year) (Xu et al., 2010).

Column C: Lung cancer mortality rate for interval *i* ($\times 10_5$/year) (2003–2007 Surveillance, Epidemiology and End Results Table 15.10, age-specific U.S. death rates).

Column D: All-cause hazard rate for interval *i* ($h \times {}_i$) (= all-cause mortality rate × number of years in age interval).

Column E: Probability of surviving interval *i* (q_i) [$= \exp(-h \times {}_i)$].

Column F: Probability of surviving up to interval *i* (S_i) ($S_1 = 1$; $S_i = S_{i-1} \times q_{i-1}$, for $I > 1$).

Column G: Lung cancer mortality hazard rate for interval *i* (h_i) (= lung cancer mortality rate × number of years in interval).

Column H: Conditional probability of dying from lung cancer in interval *I* [$= (h_i \div h \times {}_i) \times S_i \times (1 - q_i)$], i.e., conditional upon surviving up to interval *i* (R_o, the background lifetime probability of dying from lung cancer = the sum of the conditional probabilities across the intervals).

Column I: Lagged exposure at midinterval (*x* dose) assuming constant exposure was initiated at age 16.

Column J: Lung cancer mortality hazard rate in exposed people for interval. To estimate the LEC_{01}, i.e., the 95% lower bound on the continuous exposure

giving an extra risk of 1%, the 95% upper bound on the regression coefficient is used, i.e., maximum likelihood estimate + 1.645 × standard error.

Column K: All-cause hazard rate in exposed people for interval *i* ($h \times x_i$) [= $h \times {}_I + (hx_i - h_i)$].

Column L: Probability of surviving interval *i* without dying from lung cancer for exposed people (qx_i) [= $\exp(-h \times x_i)$].

Column M: Probability of surviving up to interval *i* without dying from lung cancer for exposed people (Sx_i) ($Sx_1 = 1$; $Sx_i = Sx_{i-1} \times qx_{i-1}$, for $I > 1$).

Column N: Conditional probability of dying from lung cancer in interval *i* for exposed people [= $(hx_i \div h \times x_i) \times Sx_i \times (1 - qx_i)$] ($R_x$, the lifetime probability of dying from lung cancer for exposed people = the sum of the conditional probabilities across the intervals).

In each of the life-tables, inhalation exposure commences at age 16 years and continues at the same exposure concentration for the duration of the life-table. This allows for the computation of an "adult-only-exposure" occupational lifetime unit risk, which is then scaled by a ratio of 70:54 to account for risk over the standard 70-year lifetime. While exposure is initiated at age 16 years, this exposure is lagged to match the corresponding exposure-response models, which provide the hazard rates per unit of exposure. For example, in Tables G-2, Column I shows exposure lagged by 10 years so that no lagged exposure appears prior to age 26 years.

Table G-2. Lung cancer extra risk calculation for environmental exposure to 0.191 fibers/cc Libby Amphibole asbestos using a linear exposure-response model based on the metric of cumulative exposure with a 10-year exposure lag, as described in Section 5.4.5.3

A	B	C	D	E	F	G	H	I	J	K	L	M	N
Age Int.	All-cause mortality (×105/yr)	Lung CA mortality (×105/yr)	All cause hazard rate (*h*×)	Prob. of surviving interval (*q*)	Prob. of surviving up to interval (*S*)	Lung CA hazard rate (*h*)	Cond. prob. of lung CA mortality in interval (*Ro*)	Lagged exp. mid. int. (*X*dose)	Exposed lung CA hazard rate (*hx*)	Exposed all-cause haz. rate (*h* × *x*)	Exposed prob. of surviving interval (*qx*)	Exposed prob. of surviving up to int. (*Sx*)	Exposed cond. prob. of lung CA in interval (*Rx*)
<1	684.5	0	0.0068	0.9932	1.0000	0.0000	0.0000	0.00	0.0000	0.0068	0.9932	1.0000	0.0000
1	28.6	0	0.0003	0.9997	0.9932	0.0000	0.0000	0.00	0.0000	0.0003	0.9997	0.9932	0.0000
2	28.6	0	0.0003	0.9997	0.9929	0.0000	0.0000	0.00	0.0000	0.0003	0.9997	0.9929	0.0000
3	28.6	0	0.0003	0.9997	0.9926	0.0000	0.0000	0.00	0.0000	0.0003	0.9997	0.9926	0.0000
4	28.6	0	0.0003	0.9997	0.9923	0.0000	0.0000	0.00	0.0000	0.0003	0.9997	0.9923	0.0000
5	13.7	0	0.0001	0.9999	0.9920	0.0000	0.0000	0.00	0.0000	0.0001	0.9999	0.9920	0.0000
6	13.7	0	0.0001	0.9999	0.9919	0.0000	0.0000	0.00	0.0000	0.0001	0.9999	0.9919	0.0000
7	13.7	0	0.0001	0.9999	0.9918	0.0000	0.0000	0.00	0.0000	0.0001	0.9999	0.9918	0.0000
8	13.7	0	0.0001	0.9999	0.9916	0.0000	0.0000	0.00	0.0000	0.0001	0.9999	0.9916	0.0000
9	13.7	0	0.0001	0.9999	0.9915	0.0000	0.0000	0.00	0.0000	0.0001	0.9999	0.9915	0.0000
10	18.7	0	0.0002	0.9998	0.9914	0.0000	0.0000	0.00	0.0000	0.0002	0.9998	0.9914	0.0000
11	18.7	0	0.0002	0.9998	0.9912	0.0000	0.0000	0.00	0.0000	0.0002	0.9998	0.9912	0.0000
12	18.7	0	0.0002	0.9998	0.9910	0.0000	0.0000	0.00	0.0000	0.0002	0.9998	0.9910	0.0000
13	18.7	0	0.0002	0.9998	0.9908	0.0000	0.0000	0.00	0.0000	0.0002	0.9998	0.9908	0.0000
14	18.7	0	0.0002	0.9998	0.9906	0.0000	0.0000	0.00	0.0000	0.0002	0.9998	0.9906	0.0000
15	61.9	0	0.0006	0.9994	0.9904	0.0000	0.0000	0.00	0.0000	0.0006	0.9994	0.9904	0.0000
16	61.9	0	0.0006	0.9994	0.9898	0.0000	0.0000	0.00	0.0000	0.0006	0.9994	0.9898	0.0000

Table G-2. Lung cancer extra risk calculation for environmental exposure to 0.191 fibers/cc Libby Amphibole asbestos using a linear exposure-response model based on the metric of cumulative exposure with a 10-year exposure lag, as described in Section 5.4.5.3 (continued)

A	B	C	D	E	F	G	H	I	J	K	L	M	N
Age Int.	All-cause mortality (×105/yr)	Lung CA mortality (×105/yr)	All cause hazard rate (*h*×)	Prob. of surviving interval (*q*)	Prob. of surviving up to interval (*S*)	Lung CA hazard rate (*h*)	Cond. prob. of lung CA mortality in interval (*Ro*)	Lagged exp. mid. int. (*X*dose)	Exposed lung CA hazard rate (*hx*)	Exposed all-cause haz. rate (*h* × *x*)	Exposed prob. of surviving interval (*qx*)	Exposed prob. of surviving up to int. (*Sx*)	Exposed cond. prob. of lung CA in interval (*Rx*)
17	61.9	0	0.0006	0.9994	0.9892	0.0000	0.0000	0.00	0.0000	0.0006	0.9994	0.9892	0.0000
18	61.9	0	0.0006	0.9994	0.9886	0.0000	0.0000	0.00	0.0000	0.0006	0.9994	0.9886	0.0000
19	61.9	0	0.0006	0.9994	0.9880	0.0000	0.0000	0.00	0.0000	0.0006	0.9994	0.9880	0.0000
20	98.3	0.1	0.0010	0.9990	0.9874	0.0000	0.0000	0.00	0.0000	0.0010	0.9990	0.9874	0.0000
21	98.3	0.1	0.0010	0.9990	0.9864	0.0000	0.0000	0.00	0.0000	0.0010	0.9990	0.9864	0.0000
22	98.3	0.1	0.0010	0.9990	0.9854	0.0000	0.0000	0.00	0.0000	0.0010	0.9990	0.9854	0.0000
23	98.3	0.1	0.0010	0.9990	0.9845	0.0000	0.0000	0.00	0.0000	0.0010	0.9990	0.9845	0.0000
24	98.3	0.1	0.0010	0.9990	0.9835	0.0000	0.0000	0.00	0.0000	0.0010	0.9990	0.9835	0.0000
25	99.4	0.2	0.0010	0.9990	0.9825	0.0000	0.0000	0.00	0.0000	0.0010	0.9990	0.9825	0.0000
26	99.4	0.2	0.0010	0.9990	0.9815	0.0000	0.0000	0.10	0.0000	0.0010	0.9990	0.9815	0.0000
27	99.4	0.2	0.0010	0.9990	0.9806	0.0000	0.0000	0.29	0.0000	0.0010	0.9990	0.9806	0.0000
28	99.4	0.2	0.0010	0.9990	0.9796	0.0000	0.0000	0.48	0.0000	0.0010	0.9990	0.9796	0.0000
29	99.4	0.2	0.0010	0.9990	0.9786	0.0000	0.0000	0.67	0.0000	0.0010	0.9990	0.9786	0.0000
30–34	110.8	0.5	0.0055	0.9945	0.9777	0.0000	0.0000	1.24	0.0000	0.0055	0.9945	0.9777	0.0000
35–39	145.8	2.1	0.0073	0.9927	0.9723	0.0001	0.0001	2.20	0.0001	0.0073	0.9927	0.9722	0.0001
40–44	221.6	7.9	0.0111	0.9890	0.9652	0.0004	0.0004	3.15	0.0004	0.0111	0.9890	0.9652	0.0004
45–49	340.0	20.2	0.0170	0.9831	0.9546	0.0010	0.0010	4.11	0.0011	0.0171	0.9831	0.9545	0.0010

Table G-2. Lung cancer extra risk calculation for environmental exposure to 0.191 fibers/cc Libby Amphibole asbestos using a linear exposure-response model based on the metric of cumulative exposure with a 10-year exposure lag, as described in Section 5.4.5.3 (continued)

A	B	C	D	E	F	G	H	I	J	K	L	M	N
Age Int.	**All-cause mortality (×105/yr)**	**Lung CA mortality (×105/yr)**	**All cause hazard rate (*h*×)**	**Prob. of surviving interval (*q*)**	**Prob. of surviving up to interval (*S*)**	**Lung CA hazard rate (*h*)**	**Cond. prob. of lung CA mortality in interval (*Ro*)**	**Lagged exp. mid. int. (*X*dose)**	**Exposed lung CA hazard rate (*hx*)**	**Exposed all-cause haz. rate (*h* × *x*)**	**Exposed prob. of surviving interval (*qx*)**	**Exposed prob. of surviving up to int. (*Sx*)**	**Exposed cond. prob. of lung CA in interval (*Rx*)**
50–54	509.0	39.8	0.0255	0.9749	0.9385	0.0020	0.0018	5.06	0.0022	0.0257	0.9747	0.9384	0.0020
55–59	726.3	74.7	0.0363	0.9643	0.9149	0.0037	0.0034	6.02	0.0042	0.0368	0.9639	0.9146	0.0038
60–64	1,068.3	139.8	0.0534	0.9480	0.8823	0.0070	0.0060	6.97	0.0080	0.0544	0.9470	0.8815	0.0069
65–69	1,627.5	220.9	0.0814	0.9218	0.8364	0.0110	0.0089	7.93	0.0129	0.0832	0.9201	0.8348	0.0103
70–74	2,491.3	304.3	0.1246	0.8829	0.7710	0.0152	0.0110	8.88	0.0181	0.1275	0.8803	0.7682	0.0131
75–79	3,945.9	369.5	0.1973	0.8209	0.6807	0.0185	0.0114	9.84	0.0224	0.2013	0.8177	0.6762	0.0137
80–84	6,381.4	379.4	0.3191	0.7268	0.5588	0.0190	0.0091	10.79	0.0235	0.3236	0.7236	0.5529	0.0111
Ro = 0.0531								Rx = 0.0625					

CA = cancer, cond. = conditional, exp. = exposure, haz. = hazard, int. = interval, mid. = mid-interval, Prob. = probability.
Extra risk = 0.01001; exp. Level = 0.191; occupational lifetime unit = 0.01/0.191 = 0.0524 (based on occupational exposures beginning at age 16 yr); scaled occupational lifetime unit = 0.0679 (scaled by ratio of 70:54 to account for risk over 70-yr lifetime).

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APPENDIX H. GLOSSARY OF ASBESTOS TERMINOLOGY

The definitions associated with asbestos literature often vary depending on the source or publication in which it is used. There are definitions applied to industrial, interdisciplinary, medical, mineralogical, and regulatory usage of terms associated with the discipline involved with mineral fiber reporting. The definitions are a source of ongoing debate within the asbestos community centering on nomenclature. From the academic, industrial, and regulatory literature, it is clear that there is disagreement and perhaps misunderstanding regarding some of the terminology used by workers in various asbestos-related fields. For many of the definitions contained herein and for perspectives on the evolution of these terms, the reader is referred to Lowers and Meeker (2002) and NRC (1984).

Acicular: The very long and very thin, often needle-like shape, that characterizes some prismatic crystals. (Prismatic crystals have one elongated dimension and two other dimensions that are approximately equal.) Acicular crystals or fragments do not have the strength, flexibility, or other properties often associated with asbestiform fibers.

Actinolite: A calcic amphibole mineral in the tremolite-ferroactinolite solid solution series. Actinolite can occur in both asbestiform and nonasbestiform mineral habits. The asbestiform variety is often referred to as actinolite asbestos.

Amosite: A magnesium-iron-manganese-lithium amphibole mineral in the cummingtonite-grunerite solid solution series that occurs in the asbestiform habit. The name amosite is a commercial term derived from the acronym for "Asbestos Mines of South Africa." Amosite is sometimes referred to as "brown asbestos."

Amphibole: A group of silicate minerals that may occur either in massive or fibrous (asbestiform) habits.

Anthophyllite: A magnesium-iron-manganese-lithium amphibole mineral in the anthophyllite gedrite solid solution series that can occur in both the asbestiform and nonasbestiform mineral habits. The asbestiform variety is referred to as anthophyllite asbestos.

Asbestiform (mineralogical): A specific type of mineral fibrosity in which the fibers and fibrils are long and thin and possess high tensile strength and flexibility.

Asbestiform (regulatory): A specific type of fibrosity in which the fibers and fibrils possess high tensile strength and flexibility.

Asbestos: A group of highly fibrous silicate minerals that readily separate into long, thin, strong fibers that have sufficient flexibility to be woven, are heat resistant and chemically inert, are electrical insulators, and are therefore suitable for uses where incombustible, nonconducting, or chemically resistant materials are required.

Asbestos Structure: A term applied to any connected or overlapping grouping of asbestos fibers or bundles, with or without other particles.

Aspect Ratio: The ratio of the length of a particle to its diameter.

Biopersistence: The ability to remain in the lung or other tissue. Biopersistence of mineral fibers is a function of their fragility, solubility, and clearance.

Bundle*:* A group of fibers occurring side by side with parallel orientations.

Chrysotile: A mineral in the serpentine mineral group that occurs in the asbestiform habit. Chrysotile generally occurs segregated as parallel fibers in veins or veinlets and can be easily separated into individual fibers or bundles. Often referred to as "white asbestos," chrysotile is used commercially in cement or friction products and for its good spinnability in the making of textile products.

Cleavage Fragment: A fragment produced by breakage of a crystal in directions that are related to the crystal structure and are always parallel to possible crystal faces. A mineral on an approximately planar surface on a mineral that is controlled by its crystal structure.

Cluster*:* A group of overlapping fibers oriented at random.

Crocidolite: A sodic amphibole mineral in the glaucophane-riebeckite solid solution series. Crocidolite, commonly referred to as "blue asbestos," is a varietal name for the asbestiform habit of the mineral riebeckite.

Durability: The tendency of particles to resist degradation in body fluids.

Edenite: A calcic amphibole mineral in the hornblende solid solution series. Edenite occurs in a blocky massive form or as fibrous asbestiform. It is present in trace levels in Libby Amphibole asbestos.

Fiber (mineralogical)*:* The smallest, elongate crystalline unit that can be separated from a bundle or appears to have grown individually in that shape, and that exhibits a resemblance to organic fibers.

Fiber (regulatory)*:* A particle that has an aspect ratio (length of the particle divided by its width), and depending on the analytical methods used, a particle is considered a fiber if it has a greater than 3:1 (by PCM) or 5:1 (by transmission electron microscopy [TEM]) aspect ratio).

Fibril*:* An individual unit of structure, single, elementary fibers that have a small width. A substructure of a fiber.

Fibrous: The occurrence of a mineral in bundles of fibers, resembling organic fibers in texture, from which the fibers can usually be separated. Crystallized in elongated, thin, needle-like grains or fibers.

Fragility: The tendency of particles to break into smaller particles.

Libby Amphibole Asbestos (LAA): The term used in this document to identify the mixture of amphibole mineral fibers of varying elemental composition (e.g., winchite, richterite, tremolite, etc.) that have been identified in the Rainy Creek complex near Libby, MT, as described in Section 2.2.

***Magnesio-arfvedsonite**:* A sodic amphibole mineral in the magnesio-arfvedsonite-arfvedsonite solid solution series. It occurs in asbestiform and nonasbestiform habit. It occurs in trace levels in Libby Amphibole asbestos.

***Magnesio-riebeckite**:* A sodic amphibole mineral the magnesio-riebeckite-riebeckite solid solution series. It occurs in nonasbestifiorm, blocky, massive and asbestiform habit. In Libby Amphibole asbestos, it is infrequently identified in the asbestiform habit. It occurs in trace levels in Libby Amphibole asbestos.

***Massive**:* A mineral form that does not contain fibrous crystals.

***Matrix**:* A particle of nonasbestos material that has one or more fibers associated with it.

Nonasbestiform: The term used to describe fibers not having an asbestiform habit. The massive nonfibrous forms of the asbestos minerals have the same chemical formula and internal crystal structure as the asbestiform variety but have crystal habits in which growth is more equivalent in two or three dimensions instead of primarily one dimension. When milled or crushed, nonasbestiform minerals generally do not break into fibers/fibrils but rather into fragments resulting from cleavage along the two or three growth planes. Often, cleavage fragments can appear fibrous.

Parting: The tendency of a crystal or grain to break along crystallographic planes weakened by inclusions or structural defects. Different specimens of the same mineral may or may not exhibit parting. Twinned crystals often part along composition planes, which are lattice planes and, therefore, potentially crystal faces. Parting is similar to cleavage.

***Phase Contrast Microscopy (PCM)**:* A form of light microscopy used to count fibers collected on 25-mm or 37-mm cellulose ester air filters following NIOSH Method 7400 (commonly referred to as PCM fibers). Fiber counting criteria include: fibers longer than 5 µm in length, >0.25 µm in diameter with an aspect ratio of 3:1 or greater. Commonly used to assess occupational exposures to mineral fibers.

Phased Contrast Microscope Equivalent (PCME): A subset of fibers counted by transmission electron microscopy following ISO 10312 that were collected on cellulose filters. Fibers are counted following the PCM counting rules. PCME fibers will be a subset of the total structures counted under ISO 10312.

***Prismatic**:* Having blocky, pencil-like elongated crystals that are thicker than needles.

Refractory Ceramic Fiber (RCF): An amorphous, synthetic fiber produced by melting and blowing or spinning calcined kaolin clay or a combination of alumina (Al_2O_3) and silicon dioxide (SiO_2). Oxides (such as zirconia, ferric oxide, titanium oxide, magnesium oxide, and calcium oxide) and alkalis may be added.

Richterite: A sodic-calcic amphibole mineral in the richterite-ferro-richterite solid solution series. It occurs in fibrous and nonfibrous habits.

Solid Solution Series: A grouping of minerals that includes two or more minerals in which the cations in secondary structural position are similar in chemical properties and size and can be present in variable but frequently limited ratios.

***Structure**:* A term used mainly in microscopy, usually including asbestos fibers, bundles, clusters, and matrix particles that contain asbestos.

Thoracic-Size Particle: A particle with an aerodynamic equivalent diameter that enables it to be deposited in the airways of the lung or the gas exchange region of the lung when inhaled.

Tremolite: A calcic amphibole mineral in the series tremolite-ferroactinolite. Tremolite can occur in both fibrous and nonfibrous mineral habits. The asbestiform variety is often referred to as tremolite asbestos. Due only to changes in the International Mineralogical Association's amphibole nomenclature, subsets of what was formerly referred to as tremolite asbestos are now mineralogically specified as asbestiform winchite and asbestiform richterite.

Winchite: A sodic-calcic amphibole mineral in the barroisite-ferro-barroisite solid solution series. It occurs in fibrous and nonfibrous habits. It was formerly referred to as soda-tremolite when first described in the Rainy Creek complex.

H.1. REFERENCES

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APPENDIX I. EVALUATION OF LOCALIZED PLEURAL THICKENING IN RELATION TO PULMONARY FUNCTION MEASURES

The outcome used to derive the reference concentration in this Toxicological Review is localized pleural thickening (LPT) (in the absence of asbestosis, defined as small interstitial opacities ≥1/0), as described by the International Labor Organization (ILO, 2002) and implemented by Rohs et al. (2008). LPT is a persistent structural change to the pleura, and as shown in this appendix, LPT is associated with decrements in pulmonary function. The U.S. Environmental Protection Agency (EPA) sought information pertaining to the impact and progression of LPT by conducting a systematic evaluation of cross-sectional and longitudinal studies examining the relationship between LPT and pulmonary function, focusing on forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV_1) as the primary measures of pulmonary function.

LPT was not defined by the ILO until the 2000 guidelines were published (ILO, 2002). Previously, the 1980 ILO guidelines defined only circumscribed pleural thickening (plaques) and diffuse pleural thickening (DPT), either with or without costophrenic angle obliteration. The 2000 ILO revision defines LPT as the union of what was previously defined as plaques found on the chest wall or in other locations (e.g., diaphragm) in the 1980 guidelines, and what was previously defined as DPT without costophrenic angle obliteration. Neither classification for pleural thickening (LPT or DPT) in the 2000 ILO guidelines corresponds with the previous ILO classification systems for pleural thickening; LPT is defined more broadly than the previous category of pleural plaques, while DPT is defined more narrowly due to the requirement for costophrenic angle obliteration.

Different researchers have used different terminology for circumscribed pleural thickening or plaques when implementing the 1980 ILO guidelines, most often using the terms "pleural plaques." Although not specified in the 1980 ILO guidelines, some studies did account for plaques in sites other than the chest wall, and some required costophrenic angle obliteration (e.g., García-Closas and Christiani, 1995) as an additional criterion for diffuse pleural thickening even before implementation of the 2000 ILO revision. Other studies did not explicitly describe the consideration of plaques in other sites and/or costophrenic angle obliteration other than citing a reference (e.g., ILO, 1980).

Because the "LPT" designation is fairly recent, few studies provide data for this specific outcome. Therefore, EPA considered studies examining the relationship between circumscribed pleural thickening (plaques) as defined in the 1980 ILO guidelines (as noted above, a subset of the current designation of LPT) and pulmonary function, with the understanding that the plaques definition may not fully capture the effects of LPT as defined in the 2000 ILO guidelines.

The research question addressed by this review concerns the functional impact of LPT (or pleural plaques): Is the presence of LPT (or pleural plaques) associated with decrements in

percent predicted pulmonary function? The search was conducted in September 2013 using the PubMed and Web of Science databases; ToxNet, a toxicology database, was not used because the focus of this review was on epidemiology studies. The search strings used in specific databases are shown in Table I-1 and the search strategy is summarized in Figure I-1, with additional details of the process described below.

Table I-1. Summary of search terms—asbestos, localized pleural thickening, and pulmonary function

Database, search date	Terms	Hits
PubMed 9/25/2013 No date restriction	((“asbestos” [MeSH Terms] OR “asbestos”[All Fields] OR “libby”[MeSH Terms] OR “libby”[All Fields]) AND (“pulmonary function” [All Fields] OR “spirometry”[MeSH Terms] OR “spirometry”[All Fields] OR FEV[All Fields] OR FVC[All Fields] OR VC[All Fields] OR TLC[All Fields] OR “dyspnea”[All Fields]) AND (“pleural thickening”[All Fields] OR “pleural plaque”[All Fields] OR “pleural plaques”[All Fields] OR “chest x-ray”[All Fields] OR “radiographic”[All Fields] OR “computed tomography”[All Fields] OR hrct[All Fields] OR profusion[All Fields])) AND (“humans”[MeSH Terms] AND English[lang])	184
Web of Science 9/25/2013 No date restriction	Topic = ((asbestos AND ("pulmonary function" OR "spirometry" OR FEV OR "forced expiratory volume" OR FVC OR "forced vital capacity" OR VC OR "vital capacity" OR TLC OR "total lung capacity" OR dyspnea) AND ("pleural thickening" OR "pleural plaque" OR "pleural plaques" OR "chest x-ray" OR radiographic OR "computed tomography" OR HRCT OR profusion)))	183
Merged reference set		367
	Duplicates eliminated through electronic screen (*n* = 47) Additional duplicates eliminated through HERO (*n* = 58)	320 262

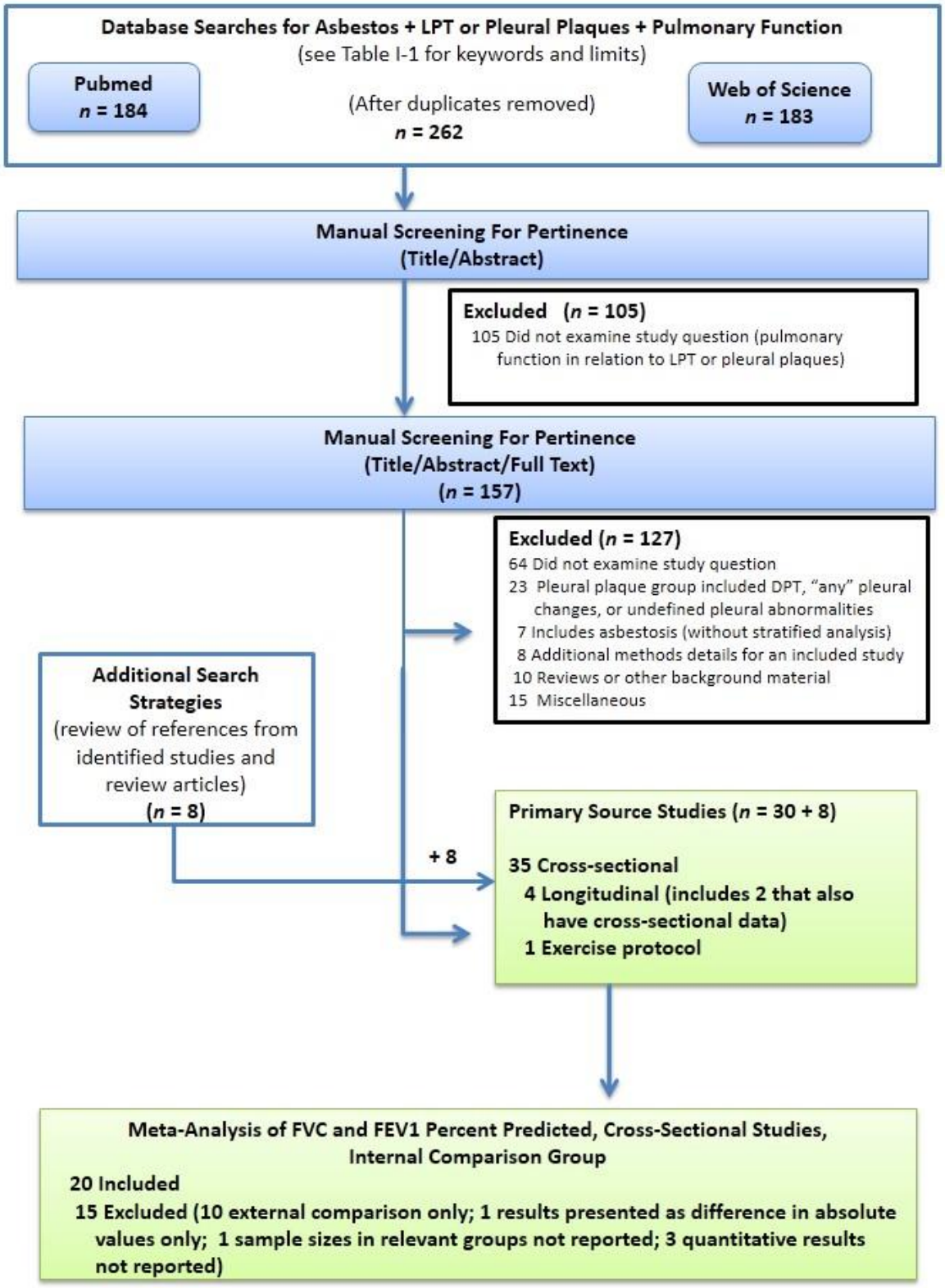

Figure I-1. Summary of literature search for studies of relation between localized pleural thickening (LPT) or pleural plaques and pulmonary function.

Based on the initial title and abstract screen, 58 additional duplicate citations were found and 105 citations were excluded because they were not directly relevant to the study question (e.g., no pulmonary measurements). The remaining 157 citations were selected for full-text review by a group of three reviewers to determine whether any contained an analysis that addressed the study question. Each paper was reviewed independently by two of the three reviewers. In cases of disagreements or uncertainty (e.g., questions about the definition of pleural abnormality used), the third reviewer also reviewed the paper and participated in the consensus-building discussions. Studies were excluded at this step if the analysis group included individuals with DPT (as defined in a way that would include the DPT category in ILO 2000) or was based on undefined pleural abnormalities (n = 23), or if they included individuals with parenchymal abnormalities (defined as x-ray profusion score greater than 1/0, or high resolution computed tomography [HRCT] evidence of parenchymal abnormality) without presenting a stratified analysis showing the results for the effect of pleural plaques in the absence of asbestosis (n = 7). Thirty studies were selected for inclusion through this process, and eight additional references were identified through (1) a review of references in reviews and in the identified primary source studies and (2) by searching the Table of Contents of relevant journals for newly released papers (September−December 2013) of selected journals (*American Journal of Industrial Medicine, Occupational and Environmental Medicine, American Journal of Epidemiology, Epidemiology, Annals of Epidemiology*) for a total of 38 primary source studies. In some instances, more than one publication presented data on the same study participants or on a subset of the study participants, or provided additional methodological details about a study. In these cases, these publications are treated as one related set of studies (i.e., one entry in the summary tables and analysis). The references reviewed through this process can be found on the Health and Environmental Research Online (HERO) website (http://hero.epa.gov/Libby Amphibole Asbestos (Draft 2011)/).

In the next step of this review process, each of the selected studies was evaluated for attributes related to study methods. Again, two of the three reviewers independently abstracted information pertaining to selection of participants, protocols for x-ray or HRCT readings, protocols for spirometry measurements, analytic approach, and consideration of smoking as a potential confounder (see Table I-2). This information was used to identify studies with limitation(s) of sufficient magnitude to potentially affect the interpretation of the study results.

Table I-2. Information abstracted for initial study evaluation

	Information abstracted	Notes regarding potential limitations
Study participants	Geographic location Source of exposure Age Duration of exposure Time since first exposure (TSFE) Smoking history Current or retired workers	A short time since first exposure (i.e., <10 yr) or no information on time since first exposure in a relatively young study population (i.e., mean age <40 yr) considered a limitation, with potential for "false negative" results (i.e., these studies would miss an association that would be observed with longer follow-up). Imbalance in smoking prevalence between comparison groups (i.e., pleural plaque vs. no pleural plaque groups) that was not addressed in the analysis considered a limitation; impact on risk estimate would depend on direction of the imbalance; similar considerations for age, gender, and height if absolute values, rather than predicted values, of pulmonary function parameters were used.
Selection process	Source, recruitment process Exclusion/inclusion criteria Comparison group: source, recruitment, matching Participation rates, final *n*	Clinic-based studies, studies based on recruitment for medico-legal evaluations, or general screening studies with very low participation rates (<20%) considered a limitation because of concerns this process would result in differential selection based on symptoms or other effects and exposure.
Measures: x-ray or HRCT	Type of x-ray views, number of readers, training Standards for classifying findings (e.g., ILO, 1980) Blinding to exposure and medical history Definition, size of pleural abnormality group	Use of only one reader or of different readers in different locations without discussion of training and reliability testing considered a limitation because of concerns of outcome misclassification resulting, in large studies, in attenuation of the association of LPT with pulmonary function (direction of bias is difficult to assess with small sample sizes). Lack of blinding to exposure history, medical history, and other readings considered a limitation.
Measures: spirometry	Protocol reference for administration of pulmonary function tests; number of technicians, number of trials Blinding to exposure and medical history Reproducibility (and use of nonreproducible results) Source of reference values or equations	Use of absolute values, rather than predicted values, of pulmonary function parameters considered a limitation (even if adjustment for age, gender, and height was addressed in the analysis) because it is difficult to compare to the majority of studies reporting predicted values. Lack of any details regarding procedures used in spirometry considered a limitation, but no study provided all of the desired details.
Analysis	Confirm that study includes analysis of the association between LPT and pulmonary function measures with an appropriate comparison group Prevalence of smoking or mean pack-yr by group; use of smoking variable in the analysis	Analysis of "external comparison" only (i.e., comparison to an unexposed referent group rather than an internal comparison to an exposed referent group) or studies that provided pulmonary function results (percentage predicted) for LPT or pleural plaque group without a comparison group considered a limitation because of issues of the comparability of the populations. No adjustment for smoking when there is either no indication of the degree of difference in smoking between groups or when there was a large difference in smoking between groups (e.g., smoking prevalence >10% higher or mean pack-yr >10 pack-yr higher in pleural plaque group) considered a limitation.
Other	Miscellaneous (e.g., discrepancies in sample size or reported results)	

For the purpose of developing a summary effect estimate across studies, EPA considered cross-sectional studies separately from longitudinal studies. Among the cross-sectional studies, 25 used an internal comparison group (i.e., comparison of pleural plaque versus no pleural plaque groups among individuals with asbestos exposure), and ten included only an external comparison group (i.e., the comparison was between asbestos-exposed individuals with pleural plaques and people without asbestos exposure). Internal comparisons provide a better approach to addressing issues of comparability and potential confounding (i.e., produce groups with greater similarity with regards to exposure and other factors, such as smoking, socioeconomic status, work status, and general health). Based on these considerations, the 10 studies with only an external comparison group (Schneider et al., 2012; Ameille et al., 2004; Kilburn and Warshaw, 1991; Hillerdal, 1990; Kilburn and Warshaw, 1990; Hjortsberg et al., 1988; Fridriksson et al., 1981) were not included in the quantitative analysis.

The abstracted information relating to study methods are shown in a set of supplemental tables included at the end of this appendix (see Supplemental Table I-A (cross-sectional studies, internal comparison), Supplemental Table I-B (longitudinal studies), and Supplemental Table I-C (cross-sectional studies, external comparison only).

I.1. ANALYSIS

After the initial evaluation of study attributes, the studies were again reviewed by sets of two reviewers, focusing in more detail on the analysis and results. The reviewer assignments allowed each of the three reviewers to have the responsibility for each of the papers either in the initial abstraction of the methods details or of the results. The results were then displayed in tabular form. Specific sets of studies were also displayed in graphical form, grouping results of similar type (e.g., difference in percentage predicted [%predicted] FVC), as described in detail below.

Each of the identified 20 cross-sectional, internal comparison studies that provided usable data on (1) the number of individuals with and without pleural plaques and (2) mean values for the respiratory measures of interest in each group were included in further analysis. Most, but not all studies, also included either standard deviations (SDs) or standard errors (SEs) for these estimates, as described below. Four studies reported vital capacity (VC) rather than FVC; these four studies (Rui et al., 2004; van Cleemput et al., 2001; Singh et al., 1999; Järvholm and Larsson, 1988) were included in the analysis together with the rest of the studies. In total, 15 x-ray studies and 5 HRCT studies were used for the analysis of mean difference in FVC; 10 x-ray studies and 5 HRCT studies were used for the analysis of mean difference in FEV_1. Summaries of the included studies are shown in Table I-3; the five excluded studies are summarized in Table I-4, with reasons for exclusions noted.

Table I-3. Cross-sectional studies used in meta-analysis of mean difference in percentage predicted forced vital capacity (FVC) or forced expiratory volume (FEV_1)

Reference, methods details	Results			
X-ray studies				
Bresnitz et al. (1993) Philadelphia Construction—elevator (union) Selection bias: *n* total eligible not available Information bias: x-rays—two B Readers, blinded; spirometry—procedure reference, no details Confounding: internal comparison; excluded profusion scores ≥1/0	From Table 2.			
	Mean (SD) percentage predicted, by group			
		Bilateral and unilateral pleural thickening (*n* = 20)	**No pleural abnormalities (*n* = 71)**	**Mean difference**
	FVC	85.8 (10.6)	89.4 (16.2)	−3.6
	FEV_1	86.3 (11.8)	86.1 (19.7)	0.2
Di Lorenzo et al. (1996) Italy Asbestos cement factory Selection bias: 86% participation Information bias: x-rays—two readers, blinding not reported; spirometry—procedure reference, some details Confounding: internal comparison, percentage predicted; excluded profusion scores ≥1/1	From Table 3.			
	Mean (SD) percentage predicted, by group			
		Pleural plaques (*n* = 10)	**No bronchial, parenchymal or pleural disease on x-ray (*n* = 9)**	**Mean difference**
	FVC	83.2 (12.2)	92.4 (13.4)	−9.2
	FEV_1	76.5 (14.3)	86.9 (9.6)	−10.4
Dujić et al. (1993) Croatia Asbestos cement factory Selection bias: 92% of current workers and 52% of retired workers participated Information bias: x-rays—two ILO trained readers, blinded; spirometry—procedure reference, some details Confounding: internal comparison, percentage predicted with additional covariates; potentially inadequate consideration of smoking; excluded profusion scores ≤ 1/1	From Tables 2 and 4.			
	Mean (SD) percentage predicted, by group, unadjusted			
		Pleural plaques (*n* = 55)	**No plaques (*n* = 252)**	**Mean difference**
	FVC	75.8 (12.7)[a]	92.2 (9.9)	−16.4
	FEV_1	86.8 (10.6)[a]	89.0 (12.0)	−2.2
	DL_{CO}	89.9 (11.6)[a]	98.8 (12.6)	−8.9
	DL_{CO} (with carboxyhemoglobin correction)	90.6 (12.6)[a]	96.8 (12.7)	−6.2
	[a]Statistically significant difference between groups with and without pleural plaques; difference in FVC was also significant in model adjusting for exposure and smoking.			
	***N* (%), by group**			
		Pleural plaques (*n* = 55)	**No plaques (*n* = 252)**	**RR[a] (95% CI)**
	Restriction	23 (41.9)	41 (16.2)	2.6 (1.7, 3.9)
	Obstruction	4 (7.2)	23 (9.2)	0.80 (0.23, 2.2)
	Restriction: FVC <80 %pred and FEV% ≥70%. Obstruction: FEV_1 <80 %pred and FEV% <70%. [a]Calculated by EPA. RR = relative risk.			

Table I-3. Cross-sectional studies used in meta-analysis of mean difference in percentage predicted forced vital capacity (FVC) or forced expiratory volume (FEV_1) (continued)

<table>
<tr><th>Reference, methods details</th><th>Results</th></tr>
<tr><td rowspan="11">García-Closas and Christiani (1995)
Massachusetts
Construction—carpenters (union)
Selection bias: 16% of current workers and 3% of retired workers participated
Information bias: x-rays—two B Readers, blinded; spirometry—procedure reference, some details
Confounding: internal comparison, percentage predicted with additional covariates; excluded profusion scores ≥0/1</td><td>From Tables III, IV, and V.</td></tr>
<tr><td>Mean (SD) percentage predicted, by group</td></tr>
<tr><td><table>
<tr><th></th><th>Pleural plaques (n = 64)</th><th>No asbestosis or DPT on x-ray (n = 457)</th><th>p-value (unadjusted, adjusted[a])</th><th>Mean difference</th></tr>
<tr><td>FVC</td><td>94.2 (14.7)</td><td>99.1 (12.0)</td><td>(<0.01, 0.11)</td><td>−4.9</td></tr>
<tr><td>FEV_1</td><td>87.3 (16.4)</td><td>94.4 (13.6)</td><td>(<0.01, 0.13)</td><td>−7.1</td></tr>
</table></td></tr>
<tr><td>Prevalence, by group</td></tr>
<tr><td><table>
<tr><th></th><th>Pleural plaques (n = 64) n (%)</th><th>No asbestosis or DPT on x-ray (n = 457) n (%)</th><th>Adjusted OR (95% CI)</th></tr>
<tr><td>Restriction (n = 27, 4.2%)</td><td>5 (7.8)</td><td>18 (3.9)</td><td>1.27 (0.41, 3.94)</td></tr>
<tr><td>Obstruction (n = 96, 15.2%)</td><td>10 (15.6)</td><td>42 (9.2)</td><td>1.03 (0.47, 2.22)</td></tr>
<tr><td>Mixed (n = 24, 3.8%)</td><td>4 (6.5)</td><td>6 (1.3)</td><td>3.76 (1.45, 12.33)</td></tr>
</table></td></tr>
<tr><td>Restriction: FVC <80 %pred and FEV% >75%.
Obstruction: FEV_1 <80 %pred and FEV% ≤75%.
Mixed; FVC <80 %pred and FEV_1 <80 %pred and 60 <FEV% <75.</td></tr>
<tr><td>[a]Adjusted for yr in trade, smoking status, pack-yr, occupation (carpenter, millwright, other), and interstitial fibrosis.
DPT definition requires costophrenic angle blunting/obliteration.</td></tr>
<tr><td rowspan="5">Hilt et al. (1987)
Norway
Asbestos-exposed workers
Selection bias: 96% of people with abnormalities participated in repeat exam
Information bias: x-rays—departmental radiologist followed by one B Reader, blinding not reported; spirometry—procedure reference, some details
Confounding: internal comparison, percentage predicted with smoking variable; did not discuss details of profusion scores
Other refs: Hilt et al. (1986b); Hilt et al. (1986a)</td><td>From Table IV.</td></tr>
<tr><td>Percentage predicted, by group[a]</td></tr>
<tr><td><table>
<tr><th></th><th>Pleural plaques (n = 363)</th><th>No abnormal x-ray findings (n = 98)</th><th>Mean difference</th></tr>
<tr><td>FVC</td><td>95.2</td><td>97.8</td><td>−2.6</td></tr>
<tr><td>FEV_1</td><td>93.5</td><td>94.3</td><td>−0.8</td></tr>
</table></td></tr>
<tr><td>[a]EPA calculations from observed and predicted values, SD not available.</td></tr>
</table>

Table I-3. Cross-sectional studies used in meta-analysis of mean difference in percentage predicted forced vital capacity (FVC) or forced expiratory volume (FEV_1) (continued)

Reference, methods details	Results			
Järvholm and Sandén (1986) Sweden (Gothenburg) Selection bias: *n* total eligible not available Information bias: x-rays—one reader from group of three chest physicians, blinding not reported; spirometry procedure reference not given, some details Confounding: internal comparison, percentage predicted; limited to nonsmokers; did not discuss details of profusion scores	From Table 2 (no plaques) and Table 3 (Plaques).			
	Mean (SD) percentage predicted [subgroup *n*]			
		Pleural plaques (*n* = 56)	**Normal x-ray (*n* = 88)**	**Mean difference**
	FVC			
	Low	96.6 (10.8) [23]	100.0 (10.3) [54]	−3.4
	Heavy	90.9 (12.9) [33]	99.1 (14.0) [34}	−8.2
	Weighted average[a]	93.2 (12.1)	99.7 (11.9)	−6.5
	FEV_1			
	Low	108.0 (14.0) [23]	110.9 (13.1) [54]	−2.9
	Heavy	102.2 (17.5) [33]	110.7 (15.1) [34]	−8.5
	Weighted average[a]	104.6 (16.2)	110.8 (13.9)	−6.2
	[a]Calculated by EPA.			
Järvholm and Larsson (1988) Sweden (Gothenburg) Asbestos-exposed workers Selection bias: participation rate not reported Information bias: x-rays—one reader from group of readers, blinding not reported; spirometry—procedure reference not given, some details Confounding: internal comparison, percentage predicted, stratified by smoking; did not discuss details of profusion scores	From Table 5.			
	Mean (SD) percentage predicted			
	Current smokers[a]	**Pleural plaques (*n* = 53)**	**No pleural plaques by x-ray (*n* = 425)**	**Mean difference**
	VC	94.4 (10.5)	96.7 (12.0)	−2.3
	FEV_1	103.1 (13.4)	102.6 (14.6)	0.5
	[a]Data for former smokers and never smokers were not used because sample sizes for these two groups were not reported.			
Miller et al. (1992) United States and Canada Insulation workers Selection bias: approximately 40% participation; some information on mortality by participation status Information bias: x-rays—one B Reader, blinded; spirometry—procedure reference, some details Confounding: internal comparison, percentage predicted; potentially inadequate consideration of smoking; stratified by profusion score (0/- and 0/0)	From Table 3 (0/- and 0/0 groups).			
	Percentage predicted[a]			
		Circumscribed pleural thickening (*n* = 121)	**No pleural thickening (*n* = 203)**	**Mean difference**
	FVC	86.8	89.8	−3.0
	[a]EPA assumed reported values are means; SD or SE not reported. DPT definition required costophrenic angle blunting/obliteration.			
Miller et al. (2013) United States (four states) Selection bias: screening for medico-legal evaluation Information bias: x-rays—one B Reader, blinded; spirometry—procedure reference, no details Confounding: internal comparison, percentage predicted; potentially inadequate consideration of smoking; stratified by profusion score (0/0)	From Table VI and Table VII.			
	Mean (SD) percentage predicted			
		LPT group[a]	**Normal x-ray (*n* = 1,096)**	**Mean difference**
	FVC	91.6 (16.35)	96.6 (15.87)	−5.0
	DL_{CO}	89.5 (21.68)	98.6 (19.09)	−9.1
	[a]Calculated by EPA, based on sample-size weighted average of circumscribed only (*n* = 290), and diaphragm (*n* = 83).			

Table I-3. Cross-sectional studies used in meta-analysis of mean difference in percentage predicted forced vital capacity (FVC) or forced expiratory volume (FEV_1) (continued)

Reference, methods details	Results			
(Ohlson et al. (1985); Ohlson et al. (1984)) Sweden Asbestos cement plant Selection bias: 96% participation Information bias: x-rays—one qualified reader, blinding not reported; spirometry—procedure reference not given, some details Confounding: internal comparison, percentage predicted stratified by exposure group; did not discuss details of profusion scores	From Table 4 of Ohlson et al. (1985) (combine exposure categories, assuming constant proportion of pleural plaques across exposure levels).			
	Mean percentage predicted (SD or SE not reported)[a]			
		Pleural plaques (n = 24)	**No pleural plaques (n = 51)**	**Mean difference**
	FVC	97.8	92.6	5.2
	FEV_1	97.0	91.5	5.5
	Results support the statement in Ohlson et al. (1984) that pulmonary function values among men with and without pleural plaques did not differ significantly (quantitative results not reported). [a]Calculated by EPA.			
Oliver et al. (1988) United States (Pennsylvania) Railroad workers Selection bias: Information bias: one B + one other reader, blinding not reported; spirometry—procedure reference, some details Confounding: internal comparison, percentage predicted stratified by exposure duration and smoking status; excluded profusion scores ≥0/1 **Related reference: Oliver et al. (1985)**	From text: smoking adjusted FVC = −4.3% (p = 0.0306); FEV_1 = −2.15 (p = 0.39). From Table II.			
	Mean (SD) percentage predicted			
		Plaque (n = 81)	**No plaque (n = 278)**	**Mean difference**
	FVC	86.0 (0.17)[a,b]	92.7 (0.14)[b]	−6.7
	FEV_1	80.3 (21.3)[a]	87.3 (0.19)[b]	−7.0
	DL_{CO}	97.0 (21.3)	101.9 (19.7)	−4.9
	FVC <80% [n]	18.5 [15][a]	9.0 [25]	RR (95% CI)[b] 2.1 (1.1, 3.7)
	[a]p < 0.05 vs. no plaque. [b]EPA noted that these SDs are considerably different from those reported in other studies and so used imputed SD values for this study in the meta-analysis. EPA used smoking adjusted results in the meta-analysis.			
Schwartz et al. (1990) United States (Iowa) Selection bias: 46% participation Information bias: one experienced reader (plus 10% validation study), blinded; spirometry—procedure reference, some details Confounding: internal comparison, percentage predicted; excluded profusion scores ≥1/0 **Related reference: Broderick et al. (1992)**	From Table 9 (excludes interstitial changes).			
	Percentage predicted[a] (SD)			
		Circumscribed pleural fibrosis (n = 178)	**No pleural fibrosis (n = 797)**	**Mean difference**
	FVC	90.3 (13.4)	94.7 (16.8)	−4.4
	[a]EPA assumed reported values are means.			
Singh et al. (1999) Australia Selection bias: clinic-based recruitment Information bias: one experienced reader, blinding not reported; spirometry—procedure reference not given, no details Confounding: small n; potentially inadequate consideration of smoking; did not discuss details of profusion scores	From Table 2.			
	Mean (SD) percentage predicted			
		Pleural plaques (n = 12)	**No pleural disease (n = 7)**	**Mean difference**
	VC	98.0 (15.6)	101.2 (10.6)	−3.2
	[a]Calculated by EPA, based on reported SEs (4.5 and 4.0, respectively, for pleural plaques and no pleural disease groups). Pleural abnormality definition excludes costophrenic angle blunting/obliteration.			

Table I-3. Cross-sectional studies used in meta-analysis of mean difference in percentage predicted forced vital capacity (FVC) or forced expiratory volume (FEV_1) (continued)

Reference, methods details	Results			
Weill et al. (2011) Montana (Libby) Community-based Selection bias: 79% participation Information bias: x-rays—two out of three B Readers consensus, blinding not reported; spirometry—procedure reference, some details Confounding: internal comparison, percentage predicted with additional covariates; excluded profusion scores ≥1/0	From Table 6, men.			
		Beta (difference in percentage predicted) for plaques compared with no abnormalities groups		
	Men			
	Never smokers	−4.28	($p < 0.05$)	
	Ever smokers	−4.43	($p < 0.05$)	
	Women			
	Never smokers	Not reported	($p > 0.05$)	
	Ever smokers	Not reported	($p > 0.05$)	
	From Table 4.			
	Mean (SD[a]) percentage predicted			
		Circumscribed pleural thickening (n = 482)	**Normal (n = 4,065)**	**Mean difference**
	FVC	95.63 (16.7)	103.15 (15.9)	−7.5
	DPT definition requires costophrenic angle blunting/obliteration. [a]Calculated by EPA, based on reported SEs (0.76 and 0.25, respectively, for pleural thickening and normal groups). EPA also noted discrepancies between the text and Table 4 with respect to definition of DPT and sample size in different groups. EPA used Table 6 results for men in the meta-analysis.			
Zavalić and Bogadi-Sare (1993) Croatia Shipyard workers Selection bias: participation rate not reported Information bias: x-rays—two out of three B Readers consensus, blinding not reported; spirometry—procedure reference not provided, some details Confounding: internal comparison, percentage predicted; excluded profusion scores ≥1/0	From Table 5 and Table 6.			
		Mean (SD) percentage predicted, by group		
		Pleural plaques[a] (n = 68)	**No pleural plaques (n = 101)**	**Mean difference**
	FVC	88.4 (17.4)	90.9 (21.2)	−2.5
	FEV_1	85.7 (13.6)	86.0 (17.2)	−0.3
	DL_{CO}	91.3 (29.8)	90.1 (16.2)	1.2
	[a]Calculated by EPA, based on sample-size weighted average within each table, and then averaged across tables.			
HRCT Studies				
Clin et al. (2011) France Exposed workers (retired or inactive) Selection bias: participation rate not reported Information bias: HRCT—two readers, blinded; Spirometry—procedure reference not provided, multiple locations Confounding: internal comparison, percentage predicted with additional covariates **Related ref:** **Paris et al. (2009)**	From Table 3.			
	Mean (SD) percentage predicted, by group			
		Isolated pleural plaques (n = 403)	**Normal CT scan (n = 1,802)**	**Mean difference**
	FVC	96.6 (16.6)	100.4 (16.6)	−3.8
	FEV_1	97.9 (19.4)	101.9 (19.2)	−4.0
	Adjusted for age, gender, body mass index (BMI), smoking, location of pulmonary function testing, yr asbestos exposure, cumulative exposure index.			

Table I-3. Cross-sectional studies used in meta-analysis of mean difference in percentage predicted forced vital capacity (FVC) or forced expiratory volume (FEV_1) (continued)

Reference, methods details	Results			
Oldenburg et al. (2001) Germany Exposed workers Selection bias: participation rate not reported Information bias: HRCT—reading protocol not reported; spirometry—procedure reference not provided Confounding: internal comparison, percentage predicted	From Table 1.			
	Mean (SD) percentage predicted, by group			
		Plaques (*n* = 21)	**No plaques (*n* = 22)**	***p*-value for difference**
	FVC	88.8 (13.89)	89.89 (11.86)	>0.05
	FEV_1	91.67 (20.25)	86.58 (28.09)	>0.05
	Mean percentage predicted, by group			
	Current and former smokers	*n* = 16	*n* = 15	
	FVC	86.5	86.97	Not reported
	FEV_1	86.28	78.76	Not reported
	Nonsmokers	*n* = 5	*n* = 7	Not reported
	FVC	96.16	96.13	Not reported
	FEV_1	108.95	103.36	Not reported
Rui et al. (2004) Italy Referrals to an occupational medicine clinic Selection bias: participation rate not reported; participants had evidence of pleural plaques on x-ray and subsequent referral for HRCT Information bias: HRCT—one reader, blinding not reported. Spirometry—procedure reference, some details Confounding: internal longitudinal comparison, percentage predicted	From Table 2—Results from last follow-up visit.			
	Mean (SD) percentage predicted, by group			
		Plaques (*n* = 36)	**No plaques (*n* = 67)**	***p*-value for difference**
	VC	90 (10)	96 (11)	<0.05
	FEV_1	95 (14)	102 (13)	<0.05
Soulat et al. (1999) France Former nitrate fertilizer plant workers Selection bias: 66.9% participation (48.6% of all identified using company records) Information bias: HRCT—one reader, blinded; Spirometry—no procedure reference Confounding: internal comparison, percentage predicted; potentially inadequate consideration of smoking	From Table 4.			
	Mean (SE) percentage predicted, by group			
		Plaques (*n* = 84)	**No abnormalities (*n* = 51)**	***p*-value for difference**
	FVC	110.2 (2.03)	108.9 (2.60)	Not reported
	FEV_1	112.6 (2.40)	108.4 (3.15)	Not reported

CI = confidence interval; DL_{CO} = diffusing capacity of lung for carbon monoxide

Table I-4. Cross-sectional studies excluded from meta-analysis of mean difference in percentage predicted forced vital capacity (FVC) or forced expiratory volume (FEV_1)

Reference, methods details	Results, reason for exclusion
van Cleemput et al. (2001) Belgium Asbestos cement factory Selection bias: 83% participation Information bias: Three readers, blinded; used x-ray rather than HRCT to exclude individuals with asbestosis from study population Spirometry—procedure reference, some details Confounding: internal comparison, percentage predicted; potentially inadequate consideration of smoking	From Table 3. **Mean (SD) percentage predicted, by group** **Plaques (*n* = 51)** | **No plaques (*n* = 22)** | **Mean difference** VC: 110.5 (13.4) | 109.8 (14.9) | 0.7 FEV_1: 104.1 (12.9) | 103.8 (13.7) | 0.3 DL_{CO}: 102.0 (16.5) | 97.2 (15.5) | 4.8
X-ray studies	
Bourbeau et al. (1990) Canada (Quebec) Construction—insulators (union) Selection bias: 85% participation Information bias: x-rays—two B Readers, blinding not reported; spirometry—Renzetti (1979) procedures with some details Confounding: internal comparison, percentage predicted with additional covariates	From Table 5. **Mean difference (liters) in absolute value, pleural plaques compared with no pleural plaques:** **Difference** | **(SE)** FVC: −0.20 | (0.09) FEV_1: −0.35 | (0.1) (Excludes costophrenic angle obliteration and profusion ≥1/0; adjusted for age, height, smoking, and parenchymal disease (based on Gallium-67 uptake quantitation). Excluded because results presented for absolute difference rather than difference in percentage predicted; *n* for pleural plaques group after exclusions not reported (approximately 50).
Rosenstock et al. (1988) United States (Washington) Plumbers and pipefitters Selection bias: participation rate 20% in Seattle, 7% in Tacoma Information bias: x-rays—two readers, blinded; spirometry—procedure reference not reported, some details provided Confounding: internal comparison; potentially inadequate consideration of confounding	From Figure 4, profusion score 0/− or 0/0: Mean difference in percentage predicted FVC approximately 98 and 94%, respectively in the no pleural disease and bilateral discrete groups. Excluded because sample sizes in relevant groups not reported.
HRCT	
Lebedova et al. (2003) Czech Republic Asbestos-processing plants Selection bias: approximately 30% of random selection from within groups defined on the basis of x-rays taken in 2000 Information bias: HRCT—readers not reported; blinding not reported Confounding: internal comparison, adjusted for smoking	From Table 5. *p*-value **Pleural lesions** | **Fibrosis** | **Pleural—fibrosis interaction** FVC: 0.0019 | 0.0003 | 0.0580 FEV_1: 0.0057 | <0.0001 | 0.1498 Adjusted for smoking, chronic bronchitis, BMI, and ischemic heart disease. Excluded because quantitative results not presented.

Table I-4. Cross sectional studies excluded from meta analysis of mean difference in percentage predicted forced vital capacity (FVC) or forced expiratory volume (FEV_1) (continued)

Reference, methods details	Results, reason for exclusion
Neri et al. (1996) Italy Exposed workers Selection bias: 119/161 participated, reasons for exclusion unlikely to be related to both exposure and outcome; Information bias: HRCT—two readers, blinded to exposure; Spirometry—ATS guidelines; Confounding: internal comparison	States that "No significant difference of pulmonary function tests was observed between the subjects with pleural plaques detected on HRCT and workers with normal pleura in absence of parenchymal involvement." Excluded because quantitative results not presented.
Staples et al. (1989) United States (California[a]) Exposed workers Selection bias: participation rate not reported Information bias: two readers, blinded; Spirometry—procedure reference not reported, some details provided Confounding: internal comparison [a] Location not explicitly stated; EPA assumed to be California based on affiliation of authors.	From text, page 1,507: Analysis of "normal" group (n = 76) divided into with and without plaques; VC and FEV_1 percentage predicted reported as "not significantly different" but quantitative results not reported. Excluded because quantitative results not reported.

ATS = American Thoracic Society.

Three of the included studies did not have the required data on pulmonary function for the overall pleural-plaque and no-plaque groups, but did provide these data broken down by another variable (exposure level or size of pleural plaque); for these three studies, data were pooled across categories (weighted by number of individuals in each category) before inclusion in the analysis (Zavalić and Bogadi-Sare, 1993; Järvholm and Sandén, 1986; Ohlson et al., 1985). Miller et al. (2013) used 1980 ILO guidelines but presented data for circumscribed pleural plaques and plaques on the diaphragm separately. The combination (weighted average) of these two groups was used in the analysis. Additionally, Ohlson et al. (1985) only reported the overall number of individuals with and without pleural plaques, rather than numbers within each category of exposure; thus, the number of individuals within each category was considered proportional to the numbers in the entire study group.

Three studies did not provide SDs or standard errors for respiratory measures (Miller et al., 1992; Hilt et al., 1987; Ohlson et al., 1985). In addition, two studies (Weill et al., 2011; Oliver et al., 1988) reported overall SDs but did not present variance estimates for the smoking-adjusted results (males only results for Weill et al., 2011) used in the meta-analyses. For these five studies, SDs were imputed as the linear average of reported SDs in other studies, weighted by sample size, across the pleural-plaque and no-pleural-plaque groups. For Järvholm and Larsson (1988), only data on smokers (in both the pleural-plaque and no-pleural-plaque

groups) were used, because no information was included on the number of former smokers and nonsmokers.

All of the x-ray studies used in these meta-analyses used the outcome of plaques as defined by the 1980 ILO revision. However, one x-ray study used a modification in which DPT required the presence of costophrenic angle obliteration and reported plaques in locations other than the chest wall (Singh et al., 1999; García-Closas and Christiani, 1995); thus, the data presented in this study are equivalent to the 2000 ILO LPT definition. The studies using HRCT, published between 1999 and 2011, used a variety of descriptions to describe the pleural-plaque group (see Supplemental Table I-A); standardized guidelines for classification of pleural abnormalities identified using HRCT are not currently available.

Data entry was performed independently by two people and any inconsistencies were resolved by discussion and verification with the original study. All statistical analyses were performed in R software; the R package Metafor (Viechtbauer, 2010) was used for conducting the meta-analyses. Both x-ray and HRCT studies were included in the analysis. Analyses stratified into these two groups were also conducted to investigate potential differences based on detection method. HRCT has been reported to have greater sensitivity and specificity compared to chest x-ray for the detection of pleural abnormalities (e.g., Larson et al., 2014); only 50−80% of cases of pleural thickening documented by HRCT are identified on x-ray (ATS, 2004). HRCT is better able to differentiate such thickening from subpleural fat pads and identify parenchymal abnormalities.

A random-effects model was used for both FVC and FEV_1, as was done in a recent meta-analysis (Wilken et al., 2011). This model examined the pulmonary effects of all types of pleural abnormalities in combination, as well as the pulmonary effects of asbestos exposure in the absence of any type of pleural abnormality. Summary estimates and the 95% confidence intervals (CIs) are reported for each outcome.

All inferences are based on a comparison between exposed individuals with no radiographic or HRCT abnormalities and exposed individuals with pleural plaques only (i.e., without any other radiographic or HRCT abnormalities). The outcomes are %predicted values for FVC and FEV_1, where predicted values are adjusted for age, gender, and height. The potential confounding effects of smoking were addressed in various ways by 14 of the studies: stratification (Järvholm and Larsson, 1988), adjustment (Clin et al., 2011; Weill et al., 2011; Oliver et al., 1988), exclusion of ever smokers (Järvholm and Sandén, 1986), and indication that there was no or only a small difference in the smoking distribution between groups (Di Lorenzo et al., 1996; García-Closas and Christiani, 1995; Bresnitz et al., 1993; Zavalić and Bogadi-Sare, 1993; Schwartz et al., 1990; Hilt et al., 1987; Ohlson et al., 1985). Clin et al. (2011) and Weill et al. (2011) additionally controlled for the effects of body mass index (BMI). One study (Ohlson et al., 1985) presented results stratified by exposure level, and three studies (Clin et al., 2011; Di Lorenzo et al., 1996; Oliver et al., 1988) adjusted for a cumulative asbestos exposure index or

duration of exposure. These factors (smoking, BMI, and asbestos exposure) were not measured in all studies, but the use of an internal comparison group (i.e., exposed workers) should have minimized differences in these factors when comparing workers with no radiographic or HRCT abnormalities to workers with pleural plaques.

Among the studies identified for the meta-analyses, specific limitations pertaining to participant selection, data collection, and analysis were noted as follows:

- Recruitment through clinic setting, or other attributes of recruitment, that may have led to overselection of symptomatic individuals (Miller et al., 2013; Singh et al., 1999; García-Closas and Christiani, 1995)

- Only one x-ray reader or different readers in different locations (without validation sample) (Miller et al., 2013; Singh et al., 1999; Miller et al., 1992; Järvholm and Larsson, 1988; Järvholm and Sandén, 1986; Ohlson et al., 1985)

- Lack of blinding (or lack of reporting of blinding) of x-ray or HRCT readers to asbestos exposure or medical history (Weill et al., 2011; Singh et al., 1999; Zavalić and Bogadi-Sare, 1993; Järvholm and Larsson, 1988; Oliver et al., 1988; Hilt et al., 1987; Järvholm and Sandén, 1986; Ohlson et al., 1985)

- Potentially inadequate consideration of smoking as a potential confounder (Miller et al., 2013; van Cleemput et al., 2001; Singh et al., 1999; Dujić et al., 1993; Miller et al., 1992)

These 16 studies were not excluded from further consideration, but additional analyses were conducted to evaluate the potential effect of these identified limitations on the results of the meta-analyses.

I.2. RESULTS

I.2.1. Meta-Analyses of Cross-Sectional Studies

Figures I-2 (FVC) and I-3 (FEV_1) show individual study results as well as the summary effect estimates resulting from the meta-analyses. The summary effect estimates for both FVC and FEV_1 are statistically significant, showing a change of −4.09 %pred (95% CI: −5.86, −2.31) and −1.99 %pred (95% CI: −3.77, −0.22), respectively. The results of larger studies are very consistent in showing a decrease in FVC (see Figure I-2). In contrast, fewer large studies are available for FEV_1, and results are less consistent. The use of random-effect models was supported for both pulmonary measures, as the tests for heterogeneity were statistically significant, and the I^2 was 80 and 57% for FVC and FEV_1, respectively (where I^2 represents the proportion of the total variation across studies due to study heterogeneity instead of chance).

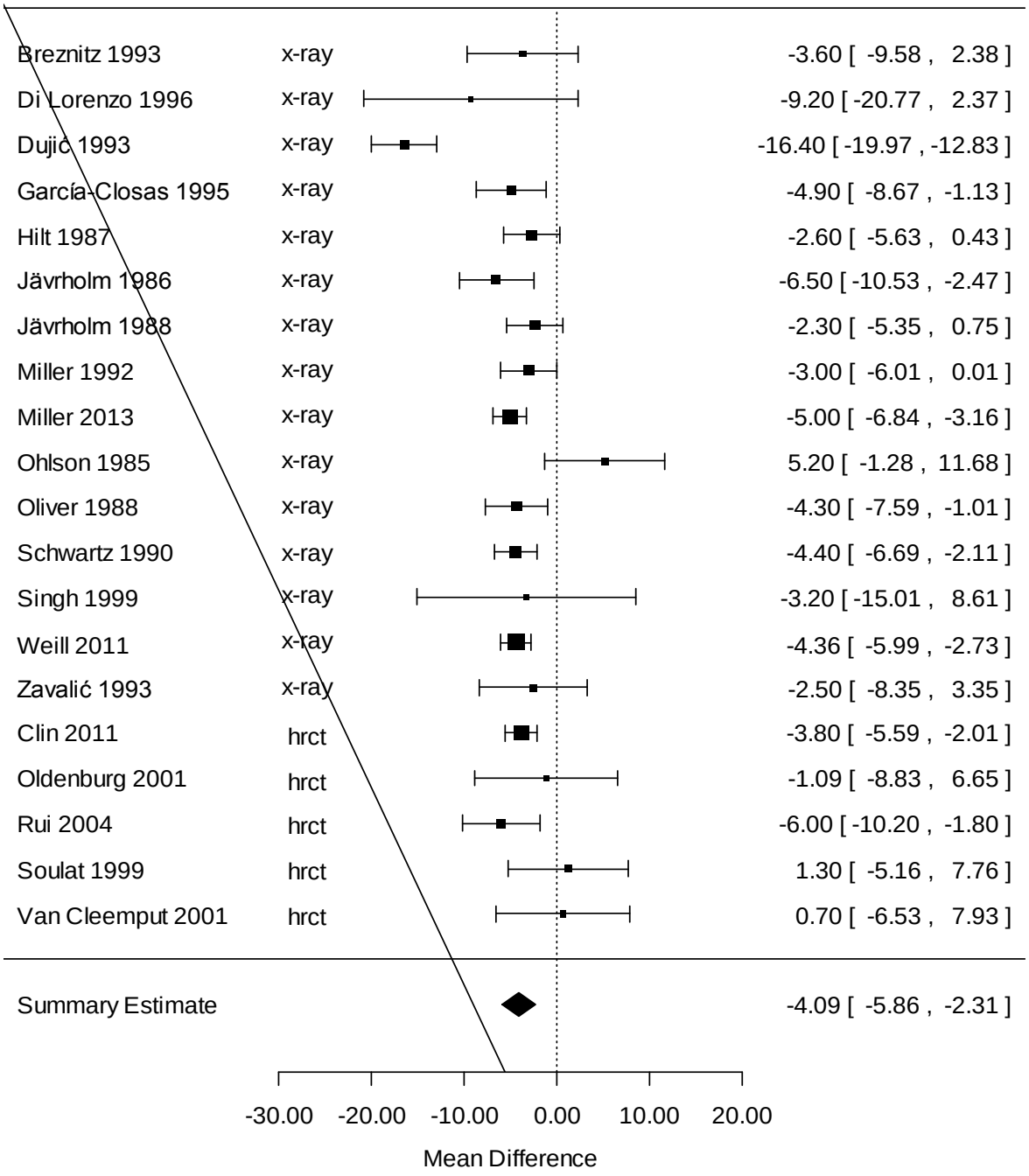

Figure I-2. Study-specific and summary effect estimates for change in percentage predicted forced vital capacity (FVC) comparing asbestos-exposed groups with and without localized pleural thickening (LPT) or pleural plaques, x-ray and high resolution computed tomography (HRCT) cross-sectional studies. Data are mean values; bars and values in brackets are 95% CI, size of data point is proportional to study size.

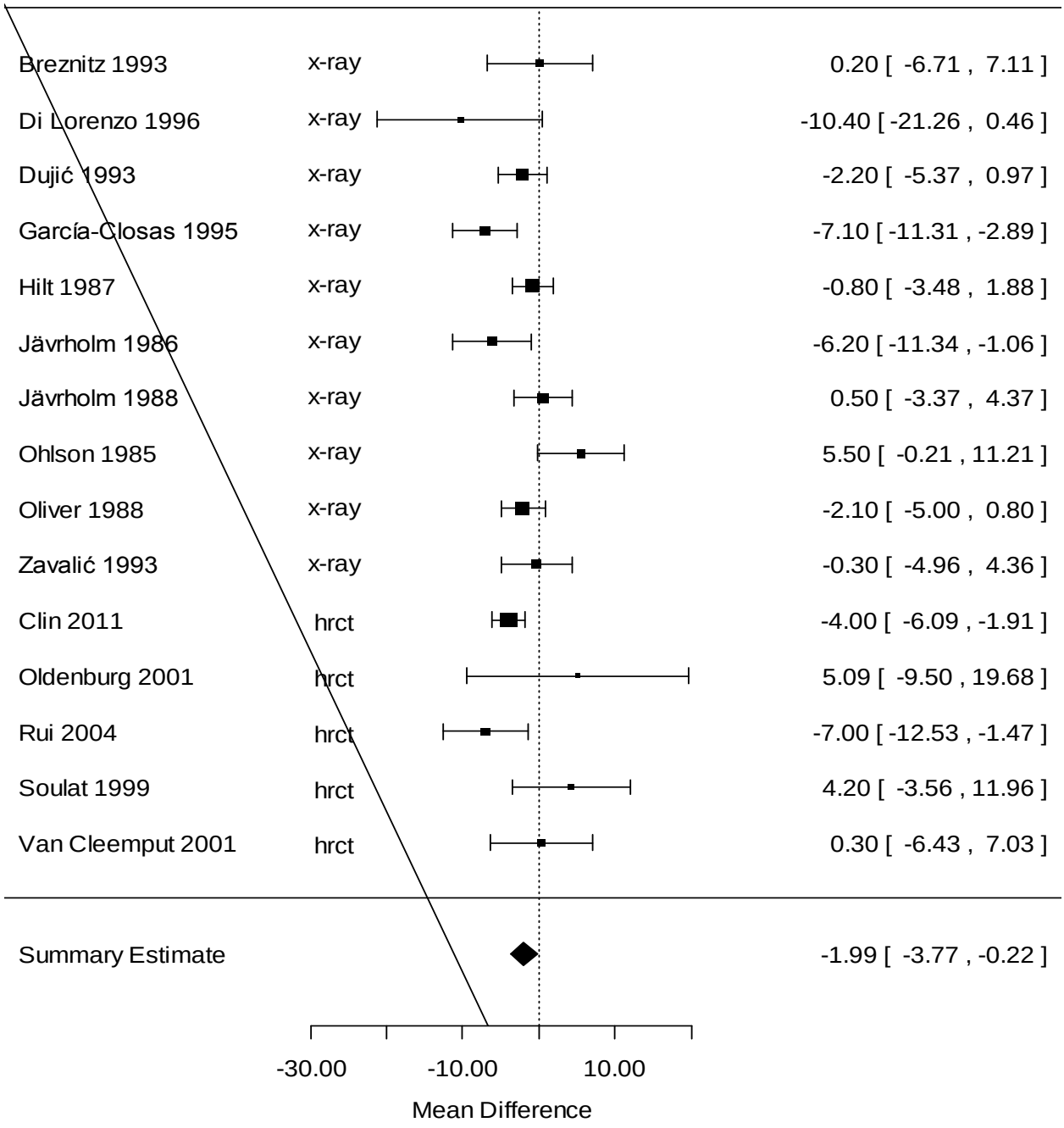

Figure I-3. Study-specific and summary effect estimates for change in percentage predicted forced expiratory volume (FEV_1) comparing asbestos-exposed groups with and without localized pleural thickening (LPT) or pleural plaques, x-ray and high resolution computed tomography (HRCT) cross-sectional studies. Data are mean values; bars and values in brackets are 95% CI, size of data point is proportional to study size.

1

Analyses of x-ray and HRCT studies separately are shown in Figures I-4 (FVC) and I-5 (FEV_1). For both measures of lung function, the results for x-ray and HRCT studies considered separately are quite similar in magnitude to overall results (combining the two study types). For FVC, results from both HRCT and x-ray studies considered as separate sets are statistically significant: −3.30 %pred (95% CI: −5.25, −1.34) and −4.55 %pred (95% CI: −6.73, −2.38), respectively. FEV_1 results for HRCT and x-ray studies considered separately were very similar in magnitude to the combined results but are not statistically significant: −1.96 %pred (95% CI: −6.01; 2.09) and −1.87 %pred (95% CI: −3.96, 0.23), respectively. Given that the overall (combined) results for FEV_1 are statistically significant, this discrepancy is likely due to the smaller sample sizes when x-ray and HRCT studies are separated.

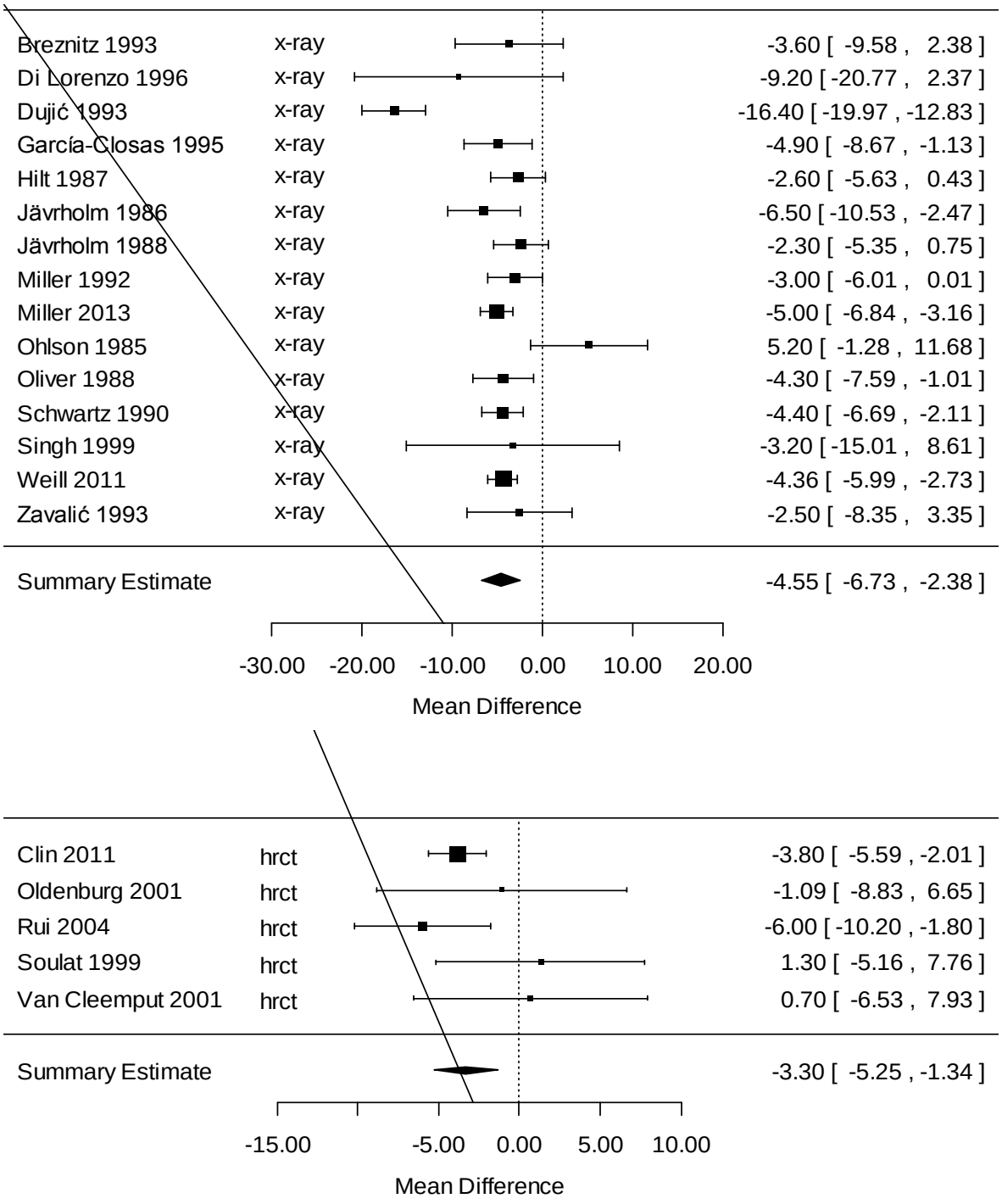

Figure I-4. Study-specific and summary effect estimates for change in percentage predicted forced vital capacity (FVC) comparing asbestos-exposed groups with and without localized pleural thickening (LPT) or pleural plaques, for x-ray (top panel) and high resolution computed tomography (HRCT) (bottom panel) cross-sectional studies. Data are mean values; bars and values in brackets are 95% CI, size of data point is proportional to study size.

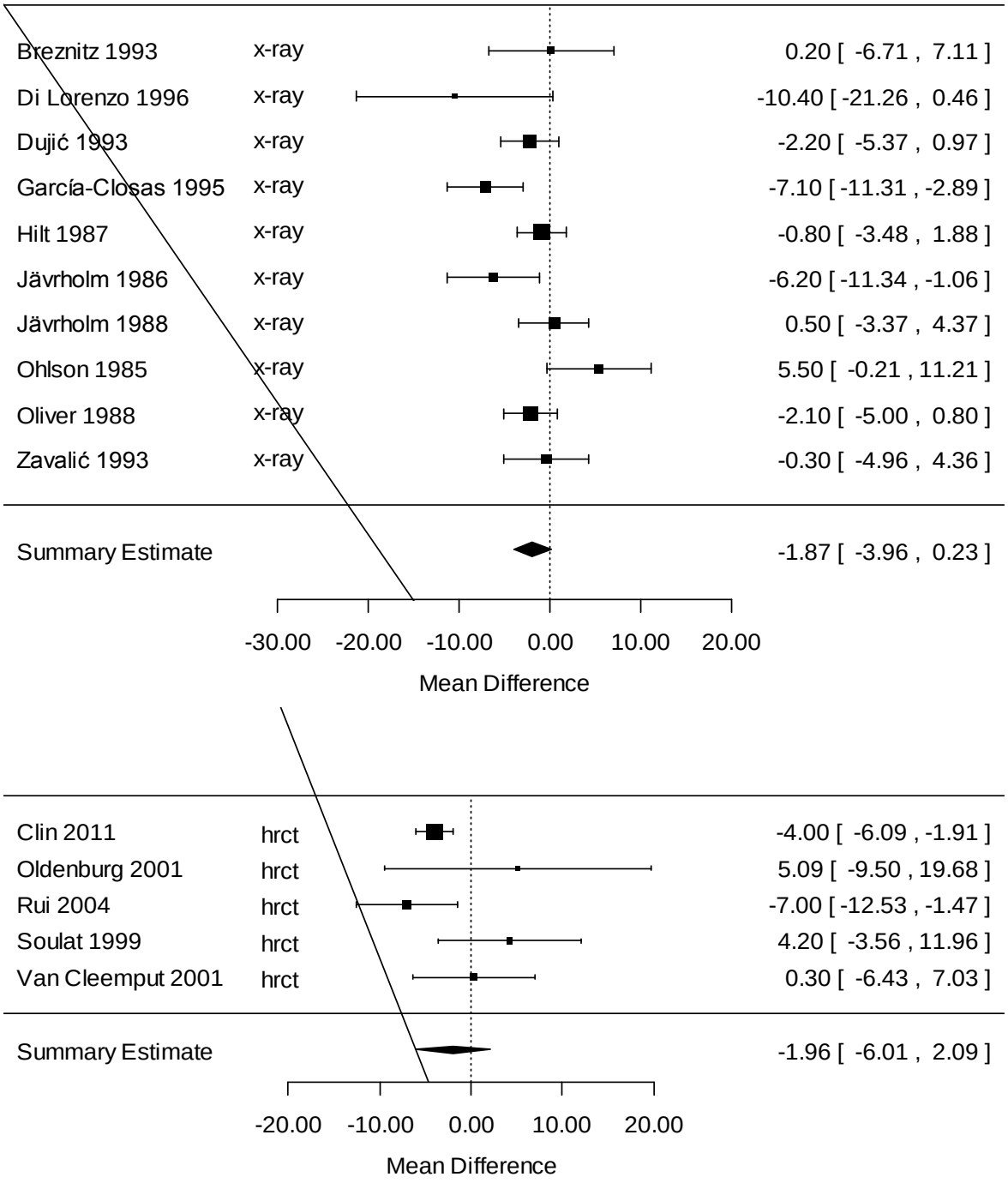

Figure I-5. Study-specific and summary effect estimates for change in percentage predicted forced expiratory volume (FEV_1) comparing asbestos-exposed groups with and without localized pleural thickening (LPT) or pleural plaques, for x-ray (top panel) and high resolution computed tomography (HRCT) (bottom panel) cross-sectional studies. Data are mean values; bars and values in brackets are 95% CI, size of data point is proportional to study size.

1

There were no clear asymmetries in the examination of funnel plots for all the analyses (although the HRCT analyses had few data points) suggesting that publication bias in not an issue in these analyses. Exclusion of all of the studies with the limitations noted previously (16 in the FVC meta-analysis and 12 in the FEV_1 analysis) resulted in more consistent results (narrower CI despite a smaller number of studies) with a summary effect estimate of −4.08 %pred (95% CI: −5.44; −2.71) for FVC (based on four studies: Clin et al., 2011; Di Lorenzo et al., 1996; Bresnitz et al., 1993; Schwartz et al., 1990) and an effect for FEV_1 that is almost doubled compared to the full set analysis (−3.87 %pred, 95% CI: −5.84; −1.90) (based on three studies: Clin et al., 2011; Di Lorenzo et al., 1996; Bresnitz et al., 1993). In addition, examination of the studies excluded because of analysis or reporting issues (see Table I-4) indicates that the results of this additional set of studies are also consistent with the pattern see in Figures I-2 and I-3, with three of the five studies in Table I-4 indicating a decrement in FVC in the pleural-plaque group, compared with the no-pleural-plaque group (two studies did not state whether there was a decrease or increase).

Of the five studies (Miller et al., 2013; van Cleemput et al., 2001; Dujić et al., 1993; Zavalić and Bogadi-Sare, 1993; Oliver et al., 1988) that also reported diffusing capacity (DL_{CO}), only two (Zavalić and Bogadi-Sare, 1993; Oliver et al., 1988) did not have potential limitations related to adjustment for smoking. (Oliver et al., 1988) showed a borderline statistically significant ($p = 0.055$) decrease in DL_{CO} (−4.9 %pred), while Zavalić and Bogadi-Sare (1993), showed a slight (statistically nonsignificant) increase in DL_{CO} (1.2 %pred) for individuals with pleural plaques relative to those without pleural plaques.

I.2.1.1. *Relationship Between Pulmonary Function Measures and Extent of Pleural Plaques*

Four cross-sectional studies also presented analyses of the extent of pleural plaques in relation to degree of decrement in pulmonary function (Clin et al., 2011; van Cleemput et al., 2001; Zavalić and Bogadi-Sare, 1993; Lilis et al., 1991b). Lilis et al. (1991b) is a publication related to the Miller et al. (1992) study included in the meta-analysis, and so is not counted as a separate primary study in the literature search results. In Clin et al. (2011), the decrease in FVC seen with increasing maximum cumulative plaque extent was statistically significant, and for FEV_1 the decrease was marginally significant ($p = 0.06$); there was a difference of approximately −4 %pred in both FVC and FEV_1 when comparing the lowest to the highest plaque extent category. In Lilis et al. (1991b), a higher index score (indicating increased pleural plaque size) was significantly associated with a larger decrement of 5−10 %pred FVC (accounting for smoking and time since first exposure) than was a low index score. van Cleemput et al. (2001) reported a statistically nonsignificant decrease in both %predicted VC and %predicted FEV_1 with increasing total surface area of pleural plaques; however, on average those with pleural plaques had slightly better lung function than those without pleural plaques. Although van Cleemput et al. (2001) concluded that neither the presence nor the extent of the plaques was correlated with

pulmonary function parameters, this is a small study of only 73 workers compared to more than 2,000 workers in the study by Clin et al. (2011); these are both HRCT studies. _ENREF_9Zavalić and Bogadi-Sare (1993) reported that %predicted FVC and %predicted FEV_1 both tended to decrease with increased plaque length. Additionally, the longitudinal study by Sichletidis et al. (2006) demonstrated that after 15 years of follow-up, the total surface area of pleural plaques increased twofold and pulmonary function was statistically significantly decreased over that period. Although increased plaque surface area was not statistically significantly associated with the observed reductions in %predicted FVC or %predicted FEV_1, the reduction in total lung capacity (TLC) was associated with plaque surface area ($r = -0.486$, $p = 0.041$). Taken together, these studies strongly suggest that the extent of the decrease in pulmonary function is associated with the extent (size or total surface area) of pleural plaques.

I.2.1.2. *Analysis by Categorical, Rather Than Continuous Measures of Pulmonary Function*

Three studies presented analyses in terms of difference in the proportion of individuals within a group below a specified value for the pulmonary function test or combination of tests. In Oliver et al. (1988), the proportion with FVC <80 %pred was approximately doubled in the pleural-plaque group (18.5%) compared with the group with no pleural plaques (9.0%) (relative risk: 2.1, 95% CI: 1.1, 3.7); the smoking-adjusted mean difference between these two groups was −4.3 %pred FVC. Restrictive disease was defined slightly differently in other studies. García-Closas and Christiani (1995) observed a statistically nonsignificant increase in the proportion classified as having restrictive disease (defined as FVC <80 %pred and FEV_1/FVC >75%), from 3.9% in the group with no pleural plaques to 7.8% in the pleural plaques group. In Dujić et al. (1993), the estimated relative risk for restrictive disease (defined as FVC <80 %pred and FEV_1/FVC ≥70%) in the group with pleural plaques, compared to the group with no pleural plaques, was 2.6 (95% CI 1.7, 3.9); the results in terms of mean difference in %predicted FVC between groups were notably larger than that of other studies in Figure I-2. The relative risks for obstructive disease in these studies were close to 1.0 (indicating no difference in those with plaques compared to those without pleural plaques); obstructive disease was defined as FEV_1 <80 %pred and either FEV_1/FVC <70% (Dujić et al., 1993) or FEV_1/FVC ≤75% (García-Closas and Christiani, 1995). However, the increase in the proportion of individuals with mixed-pattern disease (FVC and FEV_1 <80 %pred, and 60% <FEV_1/FVC <75%), from 1.3% in the no-plaques group to 6.5% in the plaques group, was significant in the study by García-Closas and Christiani (1995).

I.2.1.3. *Possible Underestimation of Effects of Localized Pleural Thickening (LPT) Due to Reliance Mostly on Studies of Pleural Plaques*

As noted previously, while the statistical inference shown here is mostly based on studies reporting the pulmonary effects of plaques as defined according to the 1980 ILO guidelines

(ILO, 1980) (with only 1 out of 20 studies for FVC and no FEV_1 studies using definitions equivalent to the 2000 ILO designation of LPT), the interest for this assessment is in the pulmonary effects of LPT, as defined by the 2000 ILO guidelines (ILO, 2002). There is some evidence in the literature (Miller et al., 2013; Kilburn and Warshaw, 1991) that DPT without costophrenic angle obliteration leads to more pronounced decrements in pulmonary function compared to pleural plaques alone. Kilburn and Warshaw (1991) reported additional decreases of 5.7% for percent predicted FVC and 4.3% for percent predicted FEV_1 in people with DPT without costophrenic angle obliteration compared to those with pleural plaques alone. Only one very small study (Singh et al., 1999) specifically reported diaphragmatic plaques and listed costophrenic angle obliteration as a criterion for DPT in its methods, so no numerical conclusion about the possible underestimation of the effect of LPT on pulmonary function is possible based on this systematic review.

I.2.1.4. *Evidence That the Observed Effect Is Not Due to Undetected Parenchymal Changes Detectable by High Resolution Computed Tomography (HRCT)*

The x-ray studies in the primary analysis used different radiographic criteria to define asbestosis. EPA conducted additional meta-analyses of x-ray studies that excluded individuals with any evidence of radiographic asbestosis (i.e., evaluated only those with ILO profusion scores of 0/0). These included three x-ray studies (García-Closas and Christiani, 1995; Dujić et al., 1993; Oliver et al., 1988), with two additional studies presenting data for the 0/0 profusion category separately (Miller et al., 2013; Miller et al., 1992). The resulting meta-analyses of FVC (five studies) and FEV_1 (three studies) produced statistically significant summary estimates that were noticeably larger than in the primary analysis: −6.66 %pred (95% CI: −11.37; −1.96) for FVC and −3.46 %pred (95% CI: −6.37; −0.61) for FEV_1.

HRCT may be more sensitive than x-ray as a test used to exclude individuals with parenchymal abnormalities (e.g., Lebedova et al., 2003; Janković et al., 2002; Šimundić et al., 2002); note that in some cases, these studies identified parenchymal abnormalities detected using HRCT even in the group with normal (i.e., 0/0) x-ray profusion scores. In a study of 162 subjects without radiographic (ILO 0/0) evidence of parenchymal fibrosis, Lebedova et al. (2003) found parenchymal changes were detectable in the HRCT scans of 46.3% of the participants. Asbestosis was found in 17 (10.5%) persons and suspected asbestosis in 58 (35.8%). Furthermore, parenchymal abnormalities were significantly more frequent in the subjects with pleural lesions than in those without pleural lesions (67.0% versus 15.4%, $p < 0.0001$). Analysis of HRCT studies alone showed that undetected parenchymal changes in x-ray examinations (but which would be detectable using HRCT) are not likely to explain the observed effects on pulmonary function. As shown in Figures I-4 and I-5, the decrease in FVC observed in HRCT studies was somewhat smaller than that shown in x-ray studies (although still

statistically significant); for FEV_1 there was little difference in the effect size, although this estimated effect was not statistically significant in the smaller set of HRCT studies.

I.2.2. Analysis of Longitudinal Studies

Longitudinal studies provide a basis for evaluating the progression of LPT or pleural plaques over time, as seen by an increase in the extent of pleural plaques or thickening and a corresponding increase in pulmonary function deficits with the passage of time. Only four longitudinal studies were found in the literature search, all using the 1980 ILO guidelines. The mean length of follow-up varied among these studies from 3.7 to 15 years, with the longer follow-up periods providing evidence supporting an association between pleural plaques and increased rate or degree of pulmonary impairment (see Table I-5). The presence of pleural plaques was not related to differences in decline in FVC or FEV_1 measures in the studies with the shortest follow-up (3.7−4 years) (Rui et al., 2004; Ohlson et al., 1985). In a case-control study with a 7-year follow-up, decreases in FVC of 31 ± 12 (mean ± SE) and 15 ± 6 mL/year were seen in those with and without pleural plaques, respectively, but this difference between groups was not statistically significant (Ostiguy et al., 1995). In the small study of people with plaques only, but with the longest follow-up period, the size of pleural plaques grew more than twofold (from 8.5 to 17.2 cm^2) over approximately 15 years (Sichletidis et al., 2006), and there was a large and statistically significant decrease of 14.6 %pred FVC and 4.3 %pred FEV_1 over the follow-up period. A statistically significant association was not seen between the declines in FVC and FEV_1 and the increase in plaque surface area, but was seen between TLC decline and plaque surface area. In Sichletidis et al. (2006), the use of percentage predicted values accounts for the expected decline due to increased age over the follow-up period. In addition, the observed pulmonary decrements are unlikely to be the result of continued asbestos exposure. Ostiguy et al. (1995) stated that additional exposure during the follow-up period was low, while Sichletidis et al. (2006) stated that there was no additional exposure during the follow-up period.

Table I-5. Longitudinal studies examining forced vital capacity (FVC) or forced expiratory volume (FEV_1)

<table>
<tr><th>Reference, methods details</th><th>Results</th></tr>
<tr><td rowspan="5">Ohlson et al. (1985)
Sweden
Asbestos cement plant
4 yr follow-up; no continuing exposure
Selection bias: 96% participation
Information bias: x-rays—one qualified reader, blinding not reported; spirometry—procedure reference not given, some details
Confounding: internal comparison, adjusted for covariates
Related reference: Ohlson et al. (1984)</td><td>From Table 6.</td></tr>
<tr><td>Adjusted percent decline (compared with baseline assessment)</td></tr>
<tr><td>
<table>
<tr><th></th><th>Pleural plaques (n = 24)</th><th>No pleural plaques (n = 50)</th><th>Mean difference in amount of loss</th></tr>
<tr><td>FVC</td><td>6.34</td><td>6.74</td><td>0.40</td></tr>
<tr><td>FEV_1</td><td>6.43</td><td>7.39</td><td>0.96</td></tr>
</table>
</td></tr>
<tr><td>Adjusted for height, age, tracheal area, cumulative exposure, and smoking.</td></tr>
<tr><td></td></tr>
<tr><td rowspan="5">Rui et al. (2004)
Italy
Referrals to an occupational medicine clinic
3.7 yr follow-up
Selection bias: participation rate not reported; participants had evidence of pleural plaques on x-ray and subsequent referral for HRCT
Information bias: HRCT—one reader, blinding not reported. Spirometry—procedure reference, some details
Confounding: internal longitudinal comparison, percentage predicted</td><td>From Table 2.</td></tr>
<tr><td>Mean (SD) percentage predicted, by group</td></tr>
<tr><td>
<table>
<tr><th></th><th colspan="2">First examination</th><th colspan="2">Last examination</th><th>Mean reduction (95% CI) for those with plaques[a]</th></tr>
<tr><th></th><th>Plaques (n = 36)</th><th>No plaques (n = 67)</th><th>Plaques (n = 36)</th><th>No plaques (n = 67)</th><th></th></tr>
<tr><td>VC</td><td>91 (10)</td><td>97 (10)</td><td>90 (10)</td><td>96 (11)</td><td>−3.4 (−7.9, 1.0)</td></tr>
<tr><td>FEV_1</td><td>97 (13)</td><td>103 (12)</td><td>95 (14)</td><td>102 (13)</td><td>−1.5 (−7.1, 4.0)</td></tr>
</table>
</td></tr>
<tr><td>[a]Adjusted for smoking habit and seniority.</td></tr>
<tr><td rowspan="5">Ostiguy et al. (1995)
Canada
Copper refinery; asbestos removal and threshold limit values not exceeded over study period
7 yr follow up
Selection bias: loss to follow-up not reported
Information bias: x-rays—two experienced readers, blinded; spirometry—Renzetti (1979) procedures, some details
Confounding: internal comparison</td><td>From Table 7.</td></tr>
<tr><td>Mean SEM annual loss (mL/yr)</td></tr>
<tr><td>
<table>
<tr><th></th><th>Pleural plaques (n = 51)</th><th>No pleural plaques (n = 211)</th><th>Mean difference in rate of loss</th></tr>
<tr><td>FVC</td><td>31 (12)</td><td>15 (6)</td><td>16 mL/yr</td></tr>
</table>
</td></tr>
<tr><td></td></tr>
<tr><td></td></tr>
<tr><td rowspan="5">Sichletidis et al. (2006)
Greece (residential exposure); no continuing exposure
15 yr follow-up
Selection bias: 78% follow-up
Information bias: x-rays—two experienced readers, blinding not reported; spirometry procedure reference not given, some details
Confounding: internal comparison
Related reference: Sichletidis et al. (1992)</td><td>From Table II.</td></tr>
<tr><td>Mean (SD) among people with pleural plaques (n = 18)</td></tr>
<tr><td>
<table>
<tr><th></th><th>1988</th><th>2003</th><th>Difference, 2003 minus 1988</th></tr>
<tr><td>FVC %predicted</td><td>94.74 (17.98)</td><td>80.12 (13.76)</td><td>−14.62</td></tr>
<tr><td>FEV_1 %predicted</td><td>93.43 (13.56)</td><td>89.1 (10.84)</td><td>−4.33</td></tr>
</table>
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SEM = standard error of the mean.

I.3. DISCUSSION

This systematic review demonstrates statistically significant decrements of 4.09 %pred FVC (95% CI: 2.31, 5.86) and 1.99 %pred FEV_1 (95% CI: 0.22; 3.77) in people exposed to asbestos with pleural plaques relative to exposed people with no pleural plaques. Cross-sectional studies suggest that an increased extent of pleural plaques is associated with greater decrements in pulmonary function. Two smaller studies (van Cleemput et al., 2001; Zavalić and Bogadi-Sare, 1993) both found a tendency for pulmonary function to decrease with plaque size, although these associations were not statistically significant. The association between plaque size and pulmonary function was statistically significant for %predicted FVC in two larger studies (Clin et al., 2011; Lilis et al., 1991b).

Few longitudinal studies are available, and two of these had very short follow-up periods of <5 years (Rui et al., 2004; Ohlson et al., 1985). In a case-control study with intermediate follow-up (7 years) and subjects matched on age, Ostiguy et al. (1995) observed a tendency for a more rapid decline in FVC in individuals with pleural plaques compared to those without pleural plaques (31 ± 12 [mean ± SE] versus 15 ± 6 mL/year, respectively). The study with the longest follow-up period (15 years, Sichletidis et al., 2006) was conducted among people exposed to asbestos in a community setting from whitewash material, rather than an occupational setting. This small study observed a statistically significant decrease in percentage predicted FVC and FEV_1 of 14.6 %pred and 4.3 %pred, respectively, among individuals with pleural plaques. Although these decreases were not significantly associated with the increase in plaque surface area, the reduction in TLC over the 15-year period was significantly associated with the increase in plaque surface area ($r = -0.486$, $p = 0.041$).

The analysis of HRCT studies alone showed similar results to both the overall (combined) results, and to the x-ray studies alone. Thus, undetected parenchymal abnormalities that could be detected by HRCT are unlikely to influence observed decrements. It is also unlikely that the observed association between pleural plaques and decrements in pulmonary function can be explained by the independent effects of asbestos exposure. The largest HRCT study (Clin et al., 2011) controlled for cumulative exposure, as well as other potential confounders, and demonstrated significant pulmonary function decreases consistent with our summary effect estimate. Similar results were obtained in a large x-ray study (Oliver et al., 1988) that controlled for duration of exposure. A smaller study that stratified for exposure observed a tendency for better lung function among workers with versus without pleural plaques (Ohlson et al., 1985). Overall, these results indicate that differences in asbestos exposure are unlikely to fully explain the observed differences in lung function. It is possible, however, that people more sensitive to the effect of asbestos exposure, given the same level of exposure, develop pleural plaques and also have a larger decrease in pulmonary function. In that case, plaques may not be the cause of the decrease in pulmonary function, but are a marker for susceptibility to pulmonary effects of asbestos.

Specific aspects of the design or analysis of these studies indicate that the demonstrated association of pleural plaques and pulmonary function decrease are unlikely to be explained by other causes of pulmonary function loss, such as demographic characteristics, smoking, or other lung disease. Height, age, and gender were accounted for by use of percentage predicted values that incorporate these variables. The sensitivity analysis addressed limitations or potential biases noted through a systematic review of study methods conducted prior to evaluation of the results, including limitations in the way in which smoking was addressed and lack of an explicit statement that some kind of blinding procedure was used for the reading of the x-ray or HRCT. In this sensitivity analysis, pulmonary decrements were essentially the same for FVC or increased almost twofold for FEV_1 compared with the analysis that included all of the studies, and the decrements remained statistically significant. Medical reasons for pulmonary decrease were explicitly accounted for through exclusion of individuals with lung diseases in seven studies (Clin et al., 2011; Singh et al., 1999; Zavalić and Bogadi-Sare, 1993; Järvholm and Larsson, 1988; Hilt et al., 1987; Järvholm and Sandén, 1986). Because this type of exclusion is a common practice, it may have been performed but not mentioned in some papers because reporting of details of the participant recruitment and selection process was often limited.

The association between LPT and decrements in pulmonary function are likely to be underestimated in this systematic review. First, LPT comprises both pleural plaques as defined in 1980 ILO in addition to plaques in other locations and what was formerly defined as DPT without costophrenic angle obliteration. Thus, the pulmonary decrements associated with LPT are likely to be greater than those estimated for pleural plaques alone. There is mechanistic evidence in the literature for lung function decrease associated with plaques on the diaphragm (Singh et al., 1999). There is also evidence (Kilburn and Warshaw, 1991) for larger lung function decrements in individuals having DPT without costophrenic angle obliteration (n = 129, 88.8 %pred FVC, 86.2 %pred FEV_1) than those with plaques on the chest wall alone (n = 98, 94.5 %pred FVC, 90.5 %pred FEV_1) (Kilburn and Warshaw, 1991), although the workers in this study exhibited obstructive lung disease (even among nonsmokers). A second reason for possible underestimation is that researchers may have included individuals with costophrenic angle obliteration only (but no pleural thickening) in the "no-pleural-plaques" group in x-ray studies (e.g., Miller et al., 1992). Because isolated costophrenic angle obliteration is known to be associated with decrements in pulmonary function (e.g., Miller et al., 2013), inclusion of these individuals in the comparison group could attenuate the differences when comparing individuals with and without pleural plaques, although costophrenic angle obliteration by itself may be rare, especially in a group with profusion scores of 0/0 (e.g., Miller et al., 2013).

Subpleural fat may be mistaken for LPT on radiographic examination (e.g., Larson et al., 2014), and thus individuals with greater BMI may have a greater chance of misclassification when examined with x-ray rather than HRCT. In this analysis, the results from HRCT studies considered separately indicate that misclassification due to the presence of subpleural fat (as

indicated by higher BMI) is not likely to explain the observed association of pleural plaques and decrements in lung function.

A second effect of BMI is to potentially confound the relationship between pleural plaques and pulmonary function; if the proportion of individuals with increased BMI differed between those with and without pleural plaques, and in addition BMI was associated with the pulmonary outcomes studied, BMI could be a potential confounder. EPA does not consider this to be a likely explanation for the findings, because the prediction equations for FVC and FEV_1 take into account height, age, race, and gender, and studies have found that given these factors, adding weight to the equation does not improve prediction for these pulmonary function parameters in cross-sectional studies (e.g., Hankinson et al., 1999). Weight gain over time has been associated with small decreases in lung function (e.g., Wang et al., 1999; Wang et al., 1997), but this would not likely affect results based on cross-sectional evaluations (as is the case for the studies included in our meta-analysis). Thus, BMI would not be associated with the pulmonary outcomes and could not be a confounder of the relationship between pleural plaques and pulmonary function.

The impact of the observed decrease in pulmonary function should be considered on both the individual level and the population level. At the individual level, the decrement in FVC or FEV_1 may or may not have a noticeable effect for a given patient. While no medical society has expressed a consensus statement on the individual-level effects of the pulmonary deficits associated with LPT as defined by the ILO 2000 guidelines, there have been such statements regarding the impact of deficits associated with plaques as defined by the ILO 1980 guidelines. The American Thoracic Society (ATS, 2004) stated that "Although pleural plaques have long been considered inconsequential markers of asbestos exposure, studies of large cohorts have shown a significant reduction in pulmonary function attributable to the plaques, averaging about 5% of FVC, even when interstitial fibrosis (asbestosis) is absent radiographically. Decrements, when they occur, are probably related to early subclinical fibrosis." However, the analyses of x-ray and HRCT studies individually (see Figures I-4 and I-5) suggest that subclinical fibrosis does not fully explain the observed associations between pleural plaques and pulmonary function decrements. The ATS document (ATS, 2004) went on to state that "There is a significant but small association between the extent of circumscribed pleural plaques and FVC, which is not seen with diffuse pleural thickening. Even so, most people with pleural plaques alone have well-preserved pulmonary function." In addition to the ATS document, the American College of Chest Physicians (ACCP; Banks et al., 2009) published a Delphi study conducted to gauge consensus among published asbestos researchers, and found that these researchers statistically rejected the statement that "Pleural plaques alter pulmonary function to a clinically significant degree" (although noting that some researchers strongly agreed with the statement, and the response rate was relatively low at <40%).

At the population level, ATS (2000) stated that "any detectable level of permanent pulmonary function loss attributable to air pollution exposure should be considered as adverse" and that

> "It should be emphasized that a small but significant reduction in a population mean FEV_1, or $FEV_{0.75}$, is probably medically significant, as such a difference may indicate an increase in the number of persons with respiratory impairment in the population. In other words, a small part of the population may manifest a marked change that is medically significant to them, but when diluted with the rest of the population the change appears to be small."

Thus, even small changes in the average (mean) of a distribution of pulmonary function parameters can result in a much larger proportion of the exposed population shifted down into the lower "tail" of the pulmonary function distribution. In the study by Oliver et al. (1988), a doubling (18.5% in pleural plaque group and 9% in no pleural plaque group, relative risk: 2.1, 95% CI: 1.1, 3.7) of the proportion of individuals with a <80 %pred FVC was seen among people with pleural plaques; there was a group mean difference (smoking-adjusted) of 4.3 %pred FVC. A similar situation is seen in the example of early childhood exposure to lead and decrements in intelligence as measured by IQ (U.S. EPA, 2013). A mean deficit of 2 IQ points would not be expected to be "clinically relevant" for an individual, but from a population perspective, a downward shift of the entire IQ distribution by 2 IQ points would be quite significant. By a similar argument, a shift in distribution of pulmonary function would result in a considerable increase in the proportion of individuals with a significant degree of pulmonary impairment below a clinically adverse level. At the same time, this shift would reduce the proportion of individuals with high pulmonary function.

In summary, pleural plaques (and correspondingly LPT) represent a persistent structural alteration of the pleura. The statistical association between pleural plaques and declines in pulmonary function identified herein is consistent with plaques being an indicator of asbestos exposure and indicate that pleural plaques and LPT are associated with declines in pulmonary function. Although the decrements in mean pulmonary function measures associated with the presence of pleural plaques or LPT may not be generally considered clinically significant, the relation between plaque size and degree of decrement, and the increase in size over time indicate these changes may be consequential even on the individual level. In addition, even small mean differences can have a large impact on a population level.

Supplemental Table I-A. Localized pleural thickening (LPT) pulmonary function studies evaluation: cross-sectional studies, internal comparison (alphabetical within x-ray and high resolution computed tomography [HRCT] groups)

Reference, population[a]	Selection	X-ray or HRCT measures	Spirometry	Consideration of exposure and smoking	Analysis
X-ray Studies					
Bourbeau et al. (1990) Quebec Construction—insulators (union) Mean (SD) age 44.3 (4.8) yr[a] Mean (SD) duration 17.3 (7.4) yr[a] Mean (SD) TSFE 24.0 (5.6) yr[a] 53% current smokers[a] Mean pack-yr 22[a] Percentage currently working not reported	Invited for pulmonary function tests in 1983−1984. Included if: Age 35 to <50 yr Not receiving compensation for asbestosis in 1982 Within 30 km of Montreal *n* = 110 out of 129 (85%) participated	P-A view Two B Readers Blinding not described ILO (1980) **Pleural plaques without obliteration of costophrenic angle and without small opacity profusion ≥1/0 (*n* = 58, 52.5%)**	Renzetti (1979) procedures, best of three values One of two trained technicians Reference values not reported (other than Renzetti (1979) reference) FEV_1, FVC	Duration, not used in analysis Smoking data for pleural plaque and no pleural plaque groups, respectively: 53 and 46% current smokers; mean 22 and 15 pack-yr; adjusts for smoking in analysis	Adjusted for age, height, smoking, parenchymal disease (based on x-ray and gallium-67 uptake quantitation); Table 5 excludes costophrenic angle obliteration and profusion ≥1/0
Bresnitz et al. (1993) Philadelphia Construction—elevator (union) Mean (SD) age 52.2 (7.9) yr Mean (SD) duration 27.1 (5.8) yr TSFE not reported 36% current smokers Pack-yr not reported 8 out of 91 retired	Screening program in 1988 through local chapter of the International Union of Elevator Constructors for 20+ yr. Eligibility based on membership, regardless of current employment status *n* = 91 (*n* total eligible not available)	P-A view Two independent B Readers (+ 3rd reader for consensus) (moderate agreement between readers) Blinded to exposure, medical history, and other reading ILO (1980) Pleural thickening (15 bilateral, 5 unilateral) DPT: none Interstitial changes: none ≥1/0	ATS (1987) procedures, at least three values. NIOSH certified technician, sitting position 86% of patients had three acceptable curves and all had at least one (none excluded for nonrepeatability) Highest value used Percentage predicted based on Crapo et al. (1981) equations FEV_1, FVC, FEV_1/FVC, FEF_{2575}	Duration (job tenure), not used in analysis Authors noted no association between pleural abnormalities and smoking	Table 2, internal and external comparison

Supplemental Table I-A. Localized pleural thickening (LPT) pulmonary function studies evaluation: cross-sectional studies, internal comparison (alphabetical within x-ray and high resolution computed tomography [HRCT] groups) (continued)

Reference, population[a]	Selection	X-ray or HRCT measures	Spirometry	Consideration of exposure and smoking	Analysis
Di Lorenzo et al. (1996) Italy Asbestos cement factory Mean (SD) age 54.5 (6.5) yr[a] Mean (SD) duration 23.5 (7.4) yr[a] 50% current smokers[a] Pack-yr not reported 100% former workers[a]	Recruited through union, *n* = 30 (out of 35) participated Eligibility criteria not described Referent: *n* = 9 male union members, "never exposed to respiratory irritant dust or fumes"	P-A, lateral and oblique views Two readers (radiologist and occupational physician); 100% concordance Blinded to exposure status and to other reading ILO (1980) Pleural plaques (*n* = 10) Asbestosis (diffuse interstitial fibrosis, ≥ 1/1, *n* = 11) Healthy exposed (no bronchial, parenchymal, or pleural disease, *n* = 9) Nonexposed (*n* = 9)	ATS (1987) procedures, (details not reported) Absolute value and percentage predicted based on reference values from European Community for Coal and Steel (Quanjer and van Zomeren, 1983) FEV_1, FVC, FEV_1/FVC, PEF, FEF_{25}, FEF_{50}, FEF_{75}	Duration, not used in analysis Authors indicated that smoking distribution was similar across groups	Percentage predicted, by group (takes into account age differences) (see Table 3)
Dujić et al. (1993) Croatia Asbestos cement factory Mean (SD) age 58.2 (10.1) yr[a] TSFE not reported Mean (SD) cumulative exposure 39.6 (12.3) f-yr[a] 62% current smokers[a] Mean (SD) 37.7 (29.4) pack-yr[a] 83% current workers	Current and retired workers at asbestos cement factory eligible; *n* = 344 total (284 out of 309 current workers, 92%; 58 out of 112 retired workers, 52%). Excluded (*n* = 37): Further exclusions: isolated parenchymal changes (profusion ≤1/1, *n* = 16) combined pleural and parenchymal disease (*n* = 17) DPT (*n* = 4) Included: isolated pleural plaques (*n* = 55) workers without any radiographic change (*n* = 255)	P-A view Two ILO-trained readers (radiologists) Blinded to exposure, clinical, and pulmonary function data ILO (1980) Plaque-like thickening at the lung pleura interface along the lateral thorax or either hemidiaphragm was 2+ mm	ATS (1987) procedures, best of three acceptable values Percentage predicted based on Cotes (1975) FEV_1, FVC, FEV%, FEF_{25-75}, TLC, RV, DL_{CO} Restriction: FVC <80% and FEV% ≥70% Obstruction: FEV_1 <80%, FEV% <70%	Annual exposure data from approximately 1960 to 1990, PCM fiber counts. These data used to calculate individual level cumulative exposure (1950s exposures assumed to be 3 fibers/mL). Smoking data for pleural plaque and no pleural plaque groups, respectively: 62 and 38% current smokers, mean 37.7 and 29.5 pack-yr; quantitative adjusted results not provided.	Table 2: Mean difference in percentage predicted by group, unadjusted for smoking and exposure; Table 4 and text: adjusted for exposure and smoking (reported as significance level only)

Supplemental Table I-A. Localized pleural thickening (LPT) pulmonary function studies evaluation: cross-sectional studies, internal comparison (alphabetical within x-ray and high resolution computed tomography [HRCT] groups) (continued)

Reference, population[a]	Selection	X-ray or HRCT measures	Spirometry	Consideration of exposure and smoking	Analysis
García-Closas and Christiani (1995) Massachusetts Construction—carpenters (union) Mean (SD) age 51.9 (8.6) yr[a] Mean (SD) duration 28.0 (8.5) yr[a] TSFE not reported 24% current smokers[a] Mean (SD) pack-yr 30.7 (21.6)[a] 98% currently working[a]	Invited to participate by union, 1987−1988 618 out of 3,897 active workers (16%) and 13 out of 375 retired workers (3%) participated *n* = 631	P-A view Two B Readers Blinded to exposure history (mixed with 1,200 other x-rays) ILO (1980) Circumscribed plaque without obliteration of costophrenic angle) (*n* = 64, 10%) Diffuse pleural thickening (*n* = 3, 0.5%) Interstitial fibrosis (small opacities 0/1, 1,0 or higher) (*n* = 43, (7%) Other nonpneumoconiosis abnormalities (*n* = 64, 10%) No abnormalities (*n* = 457, 72%)	ATS (1987) procedures, multiple technicians, at least three values; nonreproducible results and results with only one value excluded Percentage predicted based on Crapo et al. (1981) equations FEV_1, FVC, FEV%	Duration Smoking data for pleural plaque and no pleural plaque groups, respectively: 32 and 24% current smokers, mean 30.7 and 22.3 pack-yr	Tables III unadjusted, Tables IV−V adjusted for yr in trade, smoking status, pack-yr, occupation (carpenter, millwright, other), and interstitial fibrosis
Hilt et al. (1987) Norway Asbestos-exposed workers Mean (SD) age 67.3 (8.4) yr[a] Mean (SD) duration 3.6 (3.8) yr[a] Mean TSFE 37 yr[a] 39% current smokers[a] Pack-yr not reported Percentage currently working not reported **Other refs:** (Hilt et al. (1986b); Hilt et al. (1986a))	County-wide screening of asbestos-exposed workers (*n* = 21,483), referred for reexamination if abnormalities found on x-ray (*n* = 1,431); 1,372 (96%) participated Exclusions: 141 with obstructive lung disease, lung cancer, or sarcoidosis, or other lung diseases as primary diagnosis 591 other (nonasbestos) reasons for lung disease *n* = 634	P-A + lateral views Department radiologist followed by one B Reader Blinding not described Reference for definitions not cited Pleural plaques only (*n* = 363, 57%) Fibrosis with or without plaques (*n* = 83, 13%) No abnormalities, previous exposure reported (*n* = 98, 15%) No abnormalities, no reported exposure (*n* = 90, 14%)	Procedure reference not given; details not provided (other than upright position) Reference values based on asymptomatic men from Oslo, based on study using random sample of Oslo population FEV_1, FVC, FEV%, FVC <90 %pred, FVC <80 %pred, FEV_1 <80 %pred	4-level exposure: uncertain, light moderate heavy (not used in analysis) Smoking data for pleural plaque and no pleural plaque groups, respectively: 39 and 55% current smokers (higher in pleural plaque group)	Table IV (comparison with predicted based on reference values)

Supplemental Table I-A. Localized pleural thickening (LPT) pulmonary function studies evaluation: cross-sectional studies, internal comparison (alphabetical within x-ray and high resolution computed tomography [HRCT] groups) (continued)

Reference, population[a]	Selection	X-ray or HRCT measures	Spirometry	Consideration of exposure and smoking	Analysis
Järvholm and Sandén (1986) Sweden (Gothenburg) Shipping industry Mean (SD) age 54.9 (5.8) yr Mean duration 26 yr 0% current smokers 0 pack-yr Percentage currently working not reported (but likely to be high)	General screening of workers in 1977−1979 (*n* = 3,904 participated; total *n* not reported). Included if: Men Ages 40−65 yr Never smoked No other known or suspected lung disease on chest x-ray No other asbestos exposure before shipyards No change of jobs during employment at shipyards ≥20 yr TSFE Insufficient exposure data (*n* = 1) *N* = 202	P-A + lateral views One reader (from group of three chest physicians) Blinding not described Thiringer et al. (1980) definition: circumscribed thickening not extending to the apices or with connection to costophrenic sinuses, or ≥3 mm thickness on diaphragm if no calcification, or <5 mm thick and no calcifications with a marked edge at top and bottom (*n* = 87)	Procedure reference not given; best of three values; Trained nurses (*n* not reported) Tested before x-ray Percentage predicted based on Berglund et al. (1963) FEV_1, FVC	4-level exposure (very low, low, heavy, very heavy); 7-level exposure time (< once a yr to >2 hr per d). Limited to never smokers	Adjusted for age and height (see Table 1); Table II vs. Table III and Figures 1 and 2 include stratification by exposure (level or time)
Järvholm and Larsson (1988) Sweden (Gothenburg) Asbestos-exposed workers 62% ages 50−59 yr[a] 43% current smokers[a] 89% >5 yr continuous exposure[a] Percentage currently working not reported (but likely to be high)	General screening of asbestos-exposed workers in 1976 (*n* = 4,268). Included if: Men Ages 40−65 yr No other known or suspected lung disease No cardiac disease *n* = 1,233	P-A + lateral views One reader (from a group of readers) Blinding not described Thiringer et al. (1980) definition: calcifications typically localized on the diaphragm or chest wall, or typically localized elevations on the diaphragm, ≥3 mm thick, with a sharp edge, or well-demarcated thickenings on chest wall ≥5 mm wide (*n* = 130) No pleural plaques (*n* = 1,103)	Procedure reference not given; best of two values A trained assistant Percentage predicted based on Berglund et al. (1963) FEV_1	Smoking data for pleural plaque and no pleural plaque groups, respectively: 43 and 39% current smokers; analyses stratified by smoking status	Percentage predicted, stratified by smoking (see Table 5)

Supplemental Table I-A. Localized pleural thickening (LPT) pulmonary function studies evaluation: cross-sectional studies, internal comparison (alphabetical within x-ray and high resolution computed tomography [HRCT] groups) (continued)

Reference, population[a]	Selection	X-ray or HRCT measures	Spirometry	Consideration of exposure and smoking	Analysis
Miller et al. (1992) United States and Canada Insulation workers Mean (SD) age 57 Mean (SD) TSFE 35 80% current and exsmokers Mean (SD) pack-yr 40.6 (26.2) **Other ref:** Lilis et al. (1991b); Lilis et al. (1991c); Lilis et al. (1991a), Lilis et al. (1992), Miller and Zurlo (1996)	Cohort established 1967 (Selikoff and Hammond, 1979); 1981 to 1983 screening Participation rate reported as approximately 40%. No difference in subsequent mortality between participants and nonparticipants. *n* = 2,611 (*n* = 2,270 with duration ≥30 yr, plus 341 who joined with less than this duration)	P-A and lateral views One B Reader Blinded to occupational and medical history ILO (1980) Pleural plaques (circumscribed and diffuse; diffuse = costophrenic angle obliteration) Limited to 0/− or 0/0 profusion score): *n* = 203 no pleural thickening, *n* = 121 circumscribed pleural plaques, *n* = 7 diffuse pleural plaques	ATS (1987) procedures; standing position, ≥3 acceptable readings Percentage predicted based on random sample evaluated in the same laboratory controlling for smoking and age (Miller et al., 1986) FVC	Smoking data by group not reported and not included in analysis	Table 3, 0/0 and 0/− row; circumscribed vs. no pleural thickening
Miller et al. (2013) United States (four states) Mean (SD) age 62.1 (9.5) yr Mean (SD) duration 28.0 (10.6) "vast majority" TSFE >15 yr 21% current smokers	Screening program through unions, 1997−2004 (for medico-legal evaluation) Total *n* = 6,932; excluded women, nonwhites, and those missing smoking information, x-ray, spirometry, or diffusing capacity data. *n* = 4,003	P-A and lateral views One B Reader Blinded to occupational and medical history ILO (1980) Circumscribed only (*n* = 290) Diffuse only (*n* = 10) Circumscribed and diffuse (*n* = 16) Diaphragm only (*n* = 83) Costophrenic angle (*n* = 1)	ATS (1987) procedures (details not reported but equipment, techniques, technicians noted to be same as in teaching hospitals) Percentage predicted based on Crapo et al. (1981) FVC	Smoking data by group not reported and not included in analysis	Table VI, pleural abnormalities only

Supplemental Table I-A. Localized pleural thickening (LPT) pulmonary function studies evaluation: cross-sectional studies, internal comparison (alphabetical within x-ray and high resolution computed tomography [HRCT] groups) (continued)

Reference, population[a]	Selection	X-ray or HRCT measures	Spirometry	Consideration of exposure and smoking	Analysis
Ohlson et al. (1985) and Ohlson et al. (1984): 1985 provides quantitative results, but is smaller *n*; Sweden Asbestos cement plant Mean age 59.1 yr[a] Mean fiber-yr 20.9 (range: 0–48)[a] Mean pack-yr 40.6[a] 100% current workers[a]	Screening offered in 1976 (after plant closed), participation rate 96% Excluded if: Retired Former smokers Female <10 yr employment Comparison group: workers from other plants not using asbestos (fertilizer, cement products, wood products), selected from same health center, no x-ray signs of chest disease Original group *n* = 125 exposed workers and 76 referents. At follow-up: *n* = 75 exposed, 56 referents. 6 cases and 3 referents had died (cause of death for 5 of the 6 cases known, not related to asbestos), 32 cases and 9 referents had changed smoking status and were excluded	P-A, lateral and oblique views One qualified reader (member of National Pneumoconiosis Panel) Blinding not described ILO (1980) Pleural plaques (not defined) (*n* = 42, 34%)	Procedure reference not reported; sitting position; best of three values (within 5%) One trained technician Reference values from Berglund et al. (1963)) FEV_1, FVC	Estimated average 2 fibers/mL in 1950s and 1960s, 1 fiber/mL in 1970s; levels for specific work areas estimated and used for individual-level cumulative exposure Smoking data for pleural plaque and no pleural plaque groups, respectively: mean 40.6 and 33.4 pack-yr.	Table 4 (combining exposure groups)

Supplemental Table I-A. Localized pleural thickening (LPT) pulmonary function studies evaluation: cross-sectional studies, internal comparison (alphabetical within x-ray and high resolution computed tomography [HRCT] groups) (continued)

Reference, population[a]	Selection	X-ray or HRCT measures	Spirometry	Consideration of exposure and smoking	Analysis
Oliver et al. (1988) Pennsylvania Railroad workers Mean age 65 yr[a] Mean duration 35 yr[a] Mean TSFE 45 yr[a] 26% current smokers (among full sample) Mean pack-yr 30.8 **Related reference:** Oliver et al. (1985)	Screening study, *n* = 383 *n* = 377 white men Excluded if: Interstitial fibrosis (≥0/1, *n* = 6) Diffuse pleural thickening (*n* = 10) Unreadable x-rays (*n* = 2) *n* = 359	P-A and lateral views One B Reader + one A or B Reader Blinding not described ILO (1980) Plaque-like thickening at the lung-pleura interface along the lateral chest wall tangentially or along the en face rib margin, ≥2 mm, or typical plaque-like thickening along either hemidiaphragm (*n* = 81, 23%) No plaques(*n* = 278, 77%)	Renzetti (1979) procedures, ≥ three tests Percentage predicted based on Crapo et al. (1981) FEV_1, FVC, DL_{CO}	Duration, used as stratification variable Smoking data for pleural plaque and no pleural plaque groups, respectively: Mean 30.9 and 21.2 pack-yr; adjusts for smoking in the analysis	Percentage predicted adjusts for age and height; also adjusted for smoking status (in text)
Rosenstock et al. (1988) United States (Washington) Plumbers and pipefitters Mean age 42.1 yr Mean duration 1,711 yr TSFE not reported 33% current smokers	Surveillance program through unions, 1982−1984, participation rates about 20 and 7% in Seattle and Tacoma, respectively. *n* = 681	P-A view Two trained readers Blinded to clinical status ILO (1980) Validity test of 50 radiographs read several mo later showed 98% agreement within one category of profusion Pleural thickening: diffuse or circumscribed, in absence of other evident cause Interstitial fibrosis: ≥1/0 profusion	Procedure reference not reported. Best of ≥3 values used; data on reproducibility and impact of nonreproducibility on results given; no exclusions based on nonreproducibility. Percentage predicted based on Crapo et al. (1981) FEV_1, FVC	Smoking data by group not reported and not included in analysis	Figure 4 (group 0/− and 0/0)
Schwartz et al. (1990) Iowa Sheet metal workers union, Mean (SD) age 57.0 (8.0) yr Mean (SD) duration 32.7 (6.7) yr Mean (SD) TSFE 35.7 (6.5) yr 31% current smokers Mean pack-yr 28 72% currently working **Related reference:** Broderick et al. (1992)	12 union locals 1,223 out of 2,646 (46%) participated; Included if: Employed ≥25 yr *n* = 1,211 with x-rays	P-A view One experienced reader (+10% validation study) Blinded to exposure history ILO (1980) Circumscribed plaque, without obliteration of costophrenic angle (*n* = 260, 21.5%); includes 31% with asbestosis ≥1/0 Diffuse (*n* = 74, 6%) Normal (*n* = 877, 72%)	Renzetti (1979) procedures, seated, without repeatability requirement (18% would have been excluded) Average of the two largest values FVC (see Table 9—Schwartz)	Duration, included in adjusted analysis Smoking data for pleural plaque and no pleural plaque groups, respectively: 30.1 and 31.2% current smokers, mean 29.9 and 25.4 pack-yr. (These data presented in table that also includes asbestosis); pack-yr	Adjusted for age, height, interstitial fibrosis (ILO profusion), pack-yr, in sheet metal trade. (see Table 4 in Broderick; Tables 6-9 in Schwartz) Table 9 in Schwartz excludes interstitial changes

Supplemental Table I-A. Localized pleural thickening (LPT) pulmonary function studies evaluation: cross-sectional studies, internal comparison (alphabetical within x-ray and high resolution computed tomography [HRCT] groups) (continued)

Reference, population[a]	Selection	X-ray or HRCT measures	Spirometry	Consideration of exposure and smoking	Analysis
				included in adjusted analysis	
Singh et al. (1999) Australia Asbestos-exposed (various sources) Mean (SD) age 64.1 (2.3) yr[a] Duration not reported TSFE not reported 8% current smokers[a] Pack-yr not reported	Cohort seen in outpatient clinic because of asbestos exposure, 1994−1995 Excluded if: Clinical or x-ray evidence of asbestosis or other interstitial lung disease, asthma, emphysema, lung cancer, pleural effusions, neurologic or myopathic disorder likely to weaken respiratory muscles *n* = 26	Views not reported One experienced reader Blinding not described ILO (1980) **LPT = costal and/or diaphragmatic plaques with no involvement of costophrenic angle (*n* = 12, 46%)** DPT = costophrenic angle obliteration and thickening with or without calcification of the costal and/or diaphragmatic pleura (*n* = 7, 27%) No abnormalities (*n* = 7, 27%)	Reference not reported, details not provided. Percentage predicted based on various references TLC, VC, RV	Smoking data for pleural plaque and no pleural plaque groups, respectively: 8 and 0% current smokers.	Percentage predicted
Weill et al. (2011) Montana (Libby) Community-based Mean (SE) age 60.07 (0.53) yr[a] 64% ever smokers	Community screening, includes former workers at vermiculite mine and mill, family members, and other area residents; *n* = 7,307 Excluded if: No chest x-ray (*n* = 639) Age <25 or >90 yr or missing spirometry (*n* = 817) Other (nonvermiculite) exposure likely (*n* = 1,327) No consensus x-ray reading, missing smoking data or missing exposure pathway data (*n* = 127) *n* = 4,397	P-A view Two out of three B Readers consensus Blinding not described ILO (1980) Pleural abnormality excluding DPT, costophrenic angle obliteration, or interstitial disease (profusion ≥1/0) (*n* = 482, 11%) DPT and costophrenic angle obliteration, no interstitial disease (*n* = 33, 1%) Interstitial disease (profusion ≥1/0) (*n* = 40, 1%) No abnormality (*n* = 4,065; 92%) (total = 4,620, bigger than 4,397)	ATS (1995) procedures, three acceptable (two reproducible) tests or one or two acceptable tests Percentage predicted based on Knudson et al. (1983) FEV_1, FVC, FEV_1/FVC	Stratified by smoking status (ever/never) and men and women	Table 4 (unadjusted) and Table 6 stratified by gender-smoking and adjusted for age and BMI

Supplemental Table I-A. Localized pleural thickening (LPT) pulmonary function studies evaluation: cross-sectional studies, internal comparison (alphabetical within x-ray and high resolution computed tomography [HRCT] groups) (continued)

Reference, population[a]	Selection	X-ray or HRCT measures	Spirometry	Consideration of exposure and smoking	Analysis
Zavalić and Bogadi-Sare (1993) Croatia Shipyard workers Mean (SD) age 45.1 (5.2) yr[a] Mean (SD)duration 21.5 (14.1) yr[a] Mean (SD) TSFE 26.6 (17.2) yr[a] Smoking data not reported	Excluded 51 with other confirmed diseases could affect pulmonary function	P-A and oblique views Agreement based on two out of three readers (independent readings; two occupational health specialists and a radiologist) Blinding not described ILO (1980) No changes (*n* = 101) Pleural plaques only (*n* = 68) Parenchymal fibrosis (*n* = 130; *n* = 42 only parenchymal fibrosis) No DPT, effusion, mesothelioma, or lung cancer. All plaques were bilateral.	Procedure reference not provided. Best of three values Percentage predicted based on Quanjer et al. (1993) FEV_1, FVC, FEV_1/FVC, MEF_{25}, MEF_{50}, MEF_{75}	Authors indicated that smoking distribution was similar across groups	Table 5 (pleural plaques and parenchyma category 0)
HRCT Studies					
Clin et al. (2011) France Exposed workers (retired or inactive) Mean (SD) age 64.6 (5.4) yr[a] 72% duration ≥30 yr[a] TSFE not reported 6.4% current smokers[a] Pack-yr not reported **Related ref:** Paris et al. (2009)	Various recruitment strategies (letters, union, advertisements) for medical surveillance program 4,812 recruited, excluded: 312 missing data; 873 inadequate CT quality, 57 extreme spirometry values, 227 asbestosis or other interstitial abnormalities. *n* = 2,743	Independent reading by two (out of panel of seven) readers Blinded to asbestos exposure and smoking Isolated pleural plaques (*n* = 403, 14.7%) Normal (*n* = 1,802, 65.7%) (excluding 123 with pleural plaques with and other nonspecific abnormalities [e.g., emphysema, bronchiectasis], 41 with diffuse pleural thickening, and 374 with other nonspecific abnormalities)	Procedure reference not reported. Multiple locations. Percentage predicted based on Quanjer et al. (1993) European reference equations. Extreme values excluded (*n* = 57)	Semiquantitative exposure index: lifetime job history questionnaire, industrial hygienist rating on 4-level exposure (passive, 0.01 to high, 10). Cumulative index based on sum for all jobs, divided into quintiles (exposure units-yr), included in adjusted analysis. Smoking data by pleural plaque and no pleural plaque group, respectively: 6.4 and 6.0% current smokers, included in adjusted analysis.	Table 3 Adjusted for age, gender, body mass index, smoking, location of pulmonary function testing, yr asbestos exposure, cumulative exposure index

Supplemental Table I-A. Localized pleural thickening (LPT) pulmonary function studies evaluation: cross-sectional studies, internal comparison (alphabetical within x-ray and high resolution computed tomography [HRCT] groups) (continued)

Reference, population[a]	Selection	X-ray or HRCT measures	Spirometry	Consideration of exposure and smoking	Analysis
Lebedova et al. (2003) Czech Republic Exposed workers (current or former) Mean (SD) age 61.5 (9.2) yr[a] Mean (SD) duration 23.9 (9.9) yr[a] Mean (SD) TSFE 38.0 (10.8) yr[a] 15.5% current smokers, 36.1% exsmokers[a] Mean (SD) pack-yr 21.4 (17.7) Mean (SD) BMI 29.3 (5.7)	Registry of current and former asbestos processing plant employees. 1,199 employees in registry, 2000 follow-up included those (i) with documented occupational exposure to asbestos; (ii) absence of parenchymal fibrosis (profusion scores <0/1); (iii) no history of disease likely to bias chest radiograph; (iv) no bronchial asthma, *n* = 591. Of those followed up in 2000, approximately 30% were randomly selected from profusion score groups defined on the basis of x-rays taken in 2000, *n* = 162.	HRCT: Reading procedures not described. Pleural lesions divided into categories based on size of largest plaque: 0 = none, 1 = small, 2 = medium, 3 = large, 4 = very large. Pleural plaques (*n* = 97, 59.9%) Normal (*n* = 65, 40.1%) X-ray (used to define and exclude those with parenchymal fibrosis): P-A view Evaluated independently by one radiologist and three physicians. Blinding not described ILO (1980) Parenchymal changes recorded were: thickened intralobular and interlobular septal lines, subpleural curvilinear lines, parenchymal bands, ground glass opacities, and honeycombing. Definite asbestosis (*n* = 17, 10.5%) Suspected asbestosis (*n* =58, 35.8%)	European Respiratory Society procedures used. Reference equations for percentage predicted not reported.	Exposure not considered in analysis Smoking data by pleural plaque and no pleural plaque group, respectively: 15.5 and 27.2% current smokers, 36.1 and 23.1% exsmokers, mean (SD) 21.4 (17.7) and 19.8 (14.5) pack-yr; smoking habit included in adjusted analysis	Table 5 Adjusted for smoking, chronic bronchitis, BMI and ischemic heart disease, with an interaction term between fibrosis and pleural lesions

Supplemental Table I-A. Localized pleural thickening (LPT) pulmonary function studies evaluation: cross-sectional studies, internal comparison (alphabetical within x-ray and high resolution computed tomography [HRCT] groups) (continued)

Reference, population[a]	Selection	X-ray or HRCT measures	Spirometry	Consideration of exposure and smoking	Analysis
Neri et al. (1996) Italy Shipyard factory workers (current, but exposure ceased 11−14 yr prior to examination) Mean (SD) age 45.6 (6.5) yr[a] Mean (SD) duration 9.1 (5.5) yr[a] Mean (SD) duration of heavy exposure 3.8 (4.1) yr[a] Mean (SD) TSFE 22.6 (5.2) yr[a] Mean (SD) pack-yr 8.9 (10.1) yr[a] 100% current workers	161 male 'blue-collar' employees; included those who (i) consented to exam; (ii) were employed when asbestos was being used; (iii) were not occupationally exposed to other mineral dusts/welding fumes; (iv) absence of small irregular opacities (profusion score ≥1/0) and/or clinical symptoms of lung disease. *n* = 119	HRCT: by agreement of two thoracic radiologists blinded to exposure status Pleural alterations were quantified applying 1980 ILO criteria to the reading of CT scans Parenchymal abnormalities were interpreted on the basis of previous studies (Akira et al., 1991; Akira et al., 1990; Lynch et al., 1989) Pleural plaques only (*n* = 50, 42.0%) Normal (*n* = 31, 26.1%)	American Thoracic Society guidelines used Reference values from Paoletti et al. (1985); Paoletti et al. (1986) FEV_1,FVC, TLC, FEV_1/FVC%, MEF_{25}, MEF_{50}, MEF_{75}, MEF_{25-75}	Estimated duration of 'heavy exposure' (based on work tasks/location) and total exposure (total yr of employment ant plant). Industrial hygiene sampling performed in 1977 showed averages ranging from 6–18 f/cm^3 at sites near specific pieces of equipment	No quantitative results
Oldenburg et al. (2001) Germany Exposed workers: Mean age not reported Mean duration 30.7 yr TSFE not reported 76.2% of those with pleural plaques, and 68.2% of those without plaques, current or ex-smokers Additional study details provided in personal communication from Xavier Baur to L. Kopylev, 3/13/2014).	Registry of asbestos-exposed workers (*n*~500,000); included highly exposed subjects with no other lung disease, who had pleural plaques or without pleural or pulmonary asbestos-associated changes. Approximately 2/3 in registry undergo periodic exams. This study conducted in Bochum area. *N* = 43	HRCT: reading procedures not described, blinding not reported. Authors stated no subjects showed signs of parenchymal abnormalities. Pleural plaques only (*n* = 21, 48.8%) Normal (*n* = 22, 51.2%)	Spirometry procedures and references not described FEV_1,FVC, FEV_1/VC%, MEF_{25}, MEF_{50}, MEF_{75}	None	Table 1. Results stratified by smoking status (current and former smokers, nonsmokers)

Supplemental Table I-A. Localized pleural thickening (LPT) pulmonary function studies evaluation: cross-sectional studies, internal comparison (alphabetical within x-ray and high resolution computed tomography [HRCT] groups) (continued)

Reference, population[a]	Selection	X-ray or HRCT measures	Spirometry	Consideration of exposure and smoking	Analysis
Rui et al. (2004) Italy Mean (SD) age 53 (7) yr[a] Mean (SD) duration 30 (6) yr[a] TSFE not reported[a] 22% smokers (<15 pack-yr), 42% smokers (≥15 pack-yr), 36% nonsmokers[a] 42% current workers Additional study details provided in personal communication from Francesca Rui to L. Kopylev, 3/15/2014).	Workers referred to an occupational medicine clinic 1991−2000; included those with history of asbestos exposure; had two spirometry tests performed at least 1 yr apart; had radiological examination performed; no signs of interstitial fibrosis, emphysema, bronchiecstasis, pleurisy, TB, or other significant lung, cardiac, skeletal or systemic disease. Included only those workers with pleural plaques on x-ray who were further referred for HRCT. *N* = 103	One reader for x-ray and HRCT, blinding not reported. Pleural plaques described by location (unilateral/bilateral, diaphragmatic) and presence of calcification; defined as "circumscribed areas of thickening of the parietal pleura in thoracic cage and/or diaphragm" Pleural plaques only (*n* = 36, 35%) Normal (*n* = 67, 65%)	Spirometry procedures not referenced. Reference values from CECA71 FEV_1, VC, TLC	Exposure duration data by pleural plaque and no pleural plaque group, respectively: mean (SD) 30 (6) and 22 (6) yr; exposure duration included in adjusted analysis Smoking data by pleural plaque and no pleural plaque group, respectively: 36 and 36% nonsmokers, 22 and 30% smokers (<15 pack-yr), 42 and 34% smokers (≥15) pack-yr; smoking "habit" included in adjusted analysis (<15 or ≥15 pack-yr)	Table 2: unadjusted, cross-sectional analysis.
Soulat et al. (1999) France Nitrate fertilizer plant (asbestos insulation) (former workers) Mean (SE) age 65.2 (0.6) yr Mean (SE) duration 12.9 (0.6) yr Mean (SE) TSFE 38.9 (0.5) yr 19% current smokers Mean (SE) 22.6 (1.6) pack-yr	350 exworkers identified through retirement association; 254 potentially exposed, still living; *n* = 170 participants	One reader, blinded to patient history and x-ray results Pleural changes defined by size and appearance: normal, focalized, and diffuse thickening (*n* = 84 without parenchymal changes). Parenchymal abnormalities were interpreted on the basis of previous studies (Aberle et al., 1988; Yoshimura et al., 1986) *N* = 84 pleural thickening only; No abnormalities (*n* = 51)	Spirometry procedures not referenced. Reference values from Quanjer et al. (1993)	Estimation of exposure intensity (high, 65.9%; moderate, 12.3%; low, 12.3%) but not used in analysis of spirometry results	Table IV (unadjusted)

Supplemental Table I-A. Localized pleural thickening (LPT) pulmonary function studies evaluation: cross-sectional studies, internal comparison (alphabetical within x-ray and high resolution computed tomography [HRCT] groups) (continued)

Reference, population[a]	Selection	X-ray or HRCT measures	Spirometry	Consideration of exposure and smoking	Analysis
Staples et al. (1989) California Mean (SD) age 59 (11) yr Mean (SD) duration 20 (10) yr Mean (SD) TSFE 34 (10) yr 38% current smokers Mean pack-yr not reported Percentage current workers not reported	Selected from 400 exposed workers. Included if: Documented exposure to asbestos Latency >10 yr HRCT (and x-ray within 1 yr of HRCT) Profusion ≤0/1 by x-ray Excluded if: DPT on x-ray or HRCT HRCT indeterminate for asbestosis *n* = 136	X-rays: ILO (1980). By agreement of two readers, one of which NIOSH-certified; disagreement between 0/1 and 1/0 read by 3rd radiologist HRCT: By agreement of two radiologists Blinded to x-ray and clinical data Normal parenchyma (*n* = 76) (divided into with and without plaques; *n* per group not reported) Suggestive of asbestosis (*n* = 57)	Procedure reference not provided (details not reported) Percentage predicted based (Crapo et al., 1981) FEV_1, TLC, VC, RV	Authors noted that smoking distribution was similar across groups.	Text, page 1,507; "normal" group divided into with and without plaques; reported as "not significantly different" but quantitative results not reported
van Cleemput et al. (2001) Belgium Asbestos cement factory Mean (SD) age 43.5 (2.2) yr Mean (SD) duration 25.0 (1.4) yr Mean (SD) cumulative exposure 26.3 (12.2) fiber-yr/mL 85% ever smokers Mean pack-yr 10.9 yr 100% current workers	Included if: Born between 1945 and 1954 Hired between 1965 and 1969 Worked ≥2 yr *n* = 73 (out of 88 identified workers; 3 of 15 nonparticipants had plaques)	X-rays: ILO (1980) three independent readers, blinded to exposure status CT scans (reading protocol not stated) Pleural plaques seen in 26% of exposed workers by x-ray, and in 70% by HRCT. None of the exposed workers had asbestosis or profusion scores above 1/0	European procedures Quanjer et al. (1993) (details not reported) Percentage predicted based on Quanjer et al. (1993) FEV_1, FEV_1/VC, PEF%, MEF_{25}, MEF_{50}, MEF_{75}, TL_{CO} (transfer fraction for carbon monoxide)	Smoking data by group not reported and not included in analysis.	Table 3

NIOSH = National Institute for Occupational Safety and Health; PCM = phase contrast microscopy.
[a]Descriptive data for pleural plaque (or LPT) group; when not noted as such, data is for full study sample.

Supplemental Table I-B. Localized pleural thickening (LPT)—pulmonary function studies evaluation: longitudinal studies (alphabetical)

Reference, population	Selection	X-ray or HRCT measures	Spirometry	Exposure	Analysis
Ohlson et al. (1985) Sweden 4 yr follow up of workers first evaluated in 1976 Mean age 59.1 yr Mean fiber-yr 20.9 (range: 0−48) 62% current smokers Mean pack-yr 40.6 100% current workers **Related reference:** Ohlson et al. (1984)	*n* = 75; male active workers at an asbestos cement plant (production ceased in 1976). Limited to current and never smokers. Referents: *n* = 56 workers from three plants without exposure to asbestos. Original group was *n* = 125 exposed workers and 76 referents. 6 cases and 3 referents had died (cause of death for 5 of the 6 cases known, not related to asbestos), 32 cases and 9 referents had changed smoking status and were excluded.	P-A, lateral and oblique views One qualified reader (member of National Pneumoconiosis Panel) Blinding not described ILO (1980) Exposed subjects had second radiograph in 1980, referents only in 1976. Pleural plaques (*n* = 24)	Procedure reference not reported; sitting position; best of three values (within 5%). One trained technician Reference values from Berglund et al. (1963) FEV_1, FVC	Estimated average 2 fibers/mL in 1950s and 1960s, 1 fiber/mL in 1970s; levels for specific work areas estimated and used for individual-level cumulative exposure	Table 6: Longitudinal decline among those with and w/o pleural plaques, controlling for height, age, tracheal area, f/yr, and smoking
Ostiguy et al. (1995) Canada Copper refinery 7 yr follow up of workers first evaluated in 1983−1984 Mean (SE) age 46.6 (0.5) yr Mean (SE) duration 20.6 (0.5) yr 28.7% current smokers 100% current workers	*n* = 396 original survey (1983−1984) and 1991 follow-up (*n* that did not have follow-up data not reported); 262 included in case-control study of pleural plaques (four to five controls selected per case)	P-A and lateral views Two experienced readers (members of Canadian Pneumoconiosis Reading Panel), independent readings and then consensus discussions Blinded to asbestos exposure ILO (1980) Pleural thickening of the chest wall or diaphragm, without costophrenic angle obliteration; all plaques were circumscribed and all readings of lung parenchyma were in category 0 (*n* = 54 or 50?) Costophrenic angle obliteration (*n* = 4) No pleural thickening (*n* = 440)	Renzetti (1979) procedures, excluded those (<1%) not meeting repeatability criteria Same technician and equipment for baseline and follow-up Percentage predicted based on Quanjer and van Zomeren (1983) FVC, FEV_1, MMEF	Asbestos (used in insulation materials) gradually removed from workplace in the 1980s	Table 7, loss of FVC by presence or absence of pleural plaques

Supplemental Table I-B. Localized pleural thickening (LPT)—pulmonary function studies evaluation: longitudinal studies (alphabetical; all x-ray-based) (continued)

Reference, population	Selection	X-ray measures	Spirometry	Exposure	Analysis
Rui et al. (2004) Italy 3.7 yr follow-up Workers with pleural lesions: Mean (SD) age 53 (7) yr Mean (SD) duration 30 (6) yr TSFE not reported 22% smokers (<15 pack-yr), 42% smokers (≥15 pack-yr), 36% nonsmokers 42% current workers Additional study details provided in personal communication from Francesca Rui to L. Kopylev, 3/15/2014.	Workers referred to an occupational medicine clinic 1991−2000; included those with history of asbestos exposure; had two spirometry tests performed at least 1 yr apart; had radiological examination performed; no signs of interstitial fibrosis, emphysema, bronchiectasis, pleurisy, TB, or other significant lung, cardiac, skeletal or systemic disease. Included only those workers with pleural plaques on x-ray who were further referred for HRCT. *n* = 103	One reader for x-ray and HRCT, blinding not reported. Plaques detected by x-ray, with HRCT used to rule out parenchymal disease. Pleural plaques described by location (unilateral/bilateral, diaphragmatic) and presence of calcification; defined as "circumscribed areas of thickening of the parietal pleura in thoracic cage and/or diaphragm" Pleural plaques only (*n* = 36, 35%) Normal (*n* = 67, 65%)	Spirometry procedures not referenced. Reference values from CECA71 FEV_1, VC, TLC	Exposure duration data by pleural plaque and no pleural plaque group, respectively: mean (SD) 30 (6) and 22 (6) yr; exposure duration included in adjusted analysis Smoking data by pleural plaque and no pleural plaque group, respectively: 36 and 36% nonsmokers, 22 and 30% smokers (<15 pack-yr), 42 and 34% smokers (≥15) pack-yr; smoking "habit" included in adjusted analysis (<15 or ≥15 pack-yr)	Table 3: longitudinal analysis. Generalized estimating equations used to examine changes in pulmonary function over time, adjusting for presence/absence of pleural plaques, smoking habit, and yr of exposure.
Sichletidis et al. (2006) Greece Residential exposure 15 yr follow-up 14 men, 4 women, Mean (SD) age at follow-up 72.7(6.5) yr Smoking data not reported **Related reference:** Sichletidis et al. (1992)	Recruited in seven villages in northern Greece (asbestos used in whitewash). Baseline survey in 1988: 198 > age 40 with pleural plaques (out of 818); 23 of these had pulmonary function testing; Follow-up survey in 2003, 126 survivors (18 with baseline pulmonary function data, 78%) *n* = 18 for longitudinal study	Details not reported Two experience physicians, independent readings ILO (1980) Computer-based comparison of 2003 to 1,988 scans	Procedure reference not reported. Performed at hospital-based pulmonary function laboratory Percentage predicted based on Crapo et al. (1982). FEV_1, FVC, FEV_1/FVC, TLC, RV	Discussion notes exposure had ceased.	Table II (Also information on progression of plaques in *n* = 126)

Supplemental Table I-C. Localized pleural thickening (LPT)—pulmonary function studies evaluation: external comparison (alphabetical within x-ray and high resolution computed tomography [HRCT] groups)

Reference, population	Selection	X-ray or HRCT measures	Spirometry	Exposure	Analysis
X-ray, studies					
Ameille et al. (2004) France (Paris, Normandy) 88% male Mean (SD) age 58 (9.0) yr Mean (SD) duration 25.4 (9.4) yr Mean (SD) TSFE 33.5 (9.4) yr 20% current smokers Pack-yr not reported Percentage currently working not reported	Consecutive patients referred to occupational medicine departments in 1992−1994 for suspected asbestos related pleural fibrosis *n* = 287 out of 365 with evidence of pleural thickening (55 excluded because of no pleural thickening; 18 excluded because of x-ray quality)	P-A view Three independent, experienced readers (chosen from group of four) Blinding not reported ILO (2002) Two definitions of DPT: Definition 1: pleural thickening of the chest wall, Associated and in continuity with costophrenic angle obliteration (11.8%) Definition 2: pleural thickening at least 5 mm wide and extending for more than one quarter of the chest wall (35.5%). Pleural plaques is any pleural thickening not satisfying the DPT definition (88.2 or 64.5%) HRCT scans also used as "gold standard"	ATS (1987) procedures,(details not reported). Expressed as percentage predicted, but reference population not specified FEV_1, FVC, TLC	Cumulative fiber exposure estimated for 152 patients (Normandy group): mean 255 f/cc-yr), not used in analysis	External comparison, (percentage predicted); separate analysis excluding 48 with parenchymal abnormalities
Fridriksson et al. (1981) Sweden Mean (SD) age 62.5 (9.8) yr Mean (SD) duration 22.0 (14.4) yr Mean (SD) TSFE 38.9 (9.95) yr 29% current smokers Pack-yr not reported Percentage current workers not reported	General health survey, Uppsala, Sweden, 1975−1976. Selected if pleural plaques and no other abnormality on x-ray and history of asbestos exposure, no clinical lung disease *n* = 45 (five additional refusals)	X-ray details not specified Total *n* = 45 divided into four groups: Grade 1: pleural plaques only in the flanks or flanks and diaphragm, ≥5 mm thick, noncalcified (*n* = 7) Grade 2: visible in P-A view, noncalcified (*n* = 17) Grade 3: Calcified pleural plaques Grade 1 or 2 (*n* = 15) Grade 4: Pleural plaques with calcification Grade 3 (*n* = 6)	Details not reported Reference values from same laboratory (263 healthy men, equations account for age, height, weight, smoking habits) FEV_1	Duration, 4-level intensity measure (slight or intermittent light, more intense intermittent, continuous exposure at moderate levels, heavy daily exposure) (examined in relation to extent of pleural plaques)	External comparison, Table 3: percentage predicted; also did a matched analysis (gender, age within 4 yr, 3-level smoking status)

Supplemental Table I-C. Localized pleural thickening (LPT)—pulmonary function studies evaluation: external comparison (alphabetical within x-ray and high resolution computed tomography [HRCT] groups) (continued)

Reference, population	Selection	X-ray or HRCT measures	Spirometry	Exposure	Analysis
X-ray, studies					
Hillerdal (1990) Sweden Men with history of asbestos exposure Mean (SD) age 57 (7) yr[a] Mean duration 29 yr[a] TSFE not reported 38% current smokers[a] Pack-yr not reported Percentage currently working not reported	Clinic-based Included if: Age <70 yr No known heart or other systemic disease Bilateral pleural lesions Willing to participate *n* = 23	P-A + lateral views Blinding not described ILO standards (date not given) **Pleural plaques (bilateral), ≥5 mm thick, well demarcated, without obliteration of costophrenic angle and without pulmonary fibrosis or involvement of the visceral pleura (*n* = 13, 57%); plus three unilateral** DPT (unilateral and bilateral fibrosis (*n* = 10, 43%; two with asbestosis)	Procedure reference not given; best of 3 FEV_1 values Percentage predicted based on equations with smoking variable using healthy people not exposed to any fibrosing agent, normal x-ray, same laboratory FEV_1, FEF_{50}		External comparison, Table 1 and Figure 3 (comparison based on reference population)
Hjortsberg et al. (1988) Sweden (Malmö) Railroad workers Median age 57 yr Median duration 30 yr 44% current smokers Pack-yr not reported "mostly" currently working	Initial study 1977−1980 with chest x-rays; *n* = 87 with asbestos induced pleural plaques selected (excluding nine with ILO grading 1/1).	P-A + lateral views (+ oblique if uncertain interpretation) Two readers (trained radiologists) Blinding not described Thiringer et al. (1980) definition: "Distinctly demarcated pleural thickenings not reaching the apices or costophrenic sinuses" (*n* = 87, 100%)	Procedure reference not given; details not provided (other than sitting). Reference equations based on results from 200 nonsmoking men, ages 20−70 (*n* = 40 per decade); healthy, from workplaces without lung health hazards FEV_1		External comparison, conditional logistic regression based on hypothetical matched controls from reference equations, stratified by smoking (see Table III). Table IV: Predictors of spirometry (including exposure)

Supplemental Table I-C. Localized pleural thickening (LPT)—pulmonary function studies evaluation: external comparison (alphabetical within x-ray and high resolution computed tomography [HRCT] groups) (continued)

Reference, population	Selection	X-ray or HRCT measures	Spirometry	Exposure	Analysis
Kilburn and Warshaw (1990) and **Kilburn and Warshaw (1991)** United States (20 sites) Boilermakers and pipefitters Mean (SD) age 63.3 (8.6) yr[a] Duration ≥5 yr TSFE ≥15 yr 76% current smokers	General screening, union members and other tradesmen. Recruitment strategy not described. (total eligible may be 4,572) "Population comparisons" made to group of 370 Michigan men (random stratified population sample) with and without cardiorespiratory disease *n* = 1,298	P-A + lateral views One reader Blinding not described ILO (1980) Four groups: (A and B) Pleural plaques only (*n* = 45 calcified and *n* = 98 noncalcified) (C) DPT without costophrenic angle obliteration (*n* = 129) (D) DPT with costophrenic angle obliteration (*n* = 61) (Groups A, B, and C = pleural plaques)	Renzetti (1979) procedures, standing with nose clip (other details not provided). Percentage predicted based on referent group of 188 Michigan men (random stratified population sample) without cardiorespiratory disease, adjusting for height, age, and yr of smoking.	Duration (not used in analysis)	External comparison
McLoud et al. (1985) United States (Boston) Asbestos paper mill workers and other high risk employees	Screening of high risk workers (*n* = 1,135) plus "clinic patients" (*n* = 238) *n* = 1,373 External controls: 717 university employees (excluding beryllium or asbestos exposure) All men	P-A view Two B Readers (for pleural findings) Blinding not described ILO (1971) Plaques (circumscribed) (*n* = 227, 16.5%) Diffuse pleural thickening (*n* = 185, 13.5%; 58 benign asbestos effusion; 47 confluent plaques	Procedure reference not given; details not provided percentage predicted based on Kory et al. (1961)		External comparison, text
HRCT Studies					
Chow et al. (2009) **Sandrini et al. (2006)** Australia Mean (SD) age 70 (4.23) yr[a] 42% exsmokers[a] (not clear how much overlap there is in participants)	Dust Disease Board (exposed workers) and controls with no asbestos exposure	HRCT, details not provided (referenced ATS, 2004) Pleural plaques and diffuse pleural thickening definition based on Jones et al. (1988). Pleural plaques (*n* = 26) Diffuse pleural thickening (*n* = 16) Asbestosis (*n* = 18) Controls (*n* = 26)	ATS/ERS (2005) (details not reported). Percentage predicted based on Cotes et al. (1993)		External comparison, Table 1

Supplemental Table I-C. Localized pleural thickening (LPT)—pulmonary function studies evaluation: external comparison (alphabetical within x-ray and high resolution computed tomography [HRCT] groups) (continued)

Reference, population	Selection	X-ray or HRCT measures	Spirometry	Exposure	Analysis
Schneider et al. (2012) Germany Workers with asbestos disease Mean (SD) age 55.9 (5.6) yr[a] Duration not reported Cumulative exposure 66.7 (113.1) fiber-yr[a] TSFE not reported 27% current smokers[a] Mean pack-yr 22.1[a]	Selected from clinic treating workers with compensated asbestos diseases; consecutive male patients *n* = 154	HRCT read by single experienced radiologist, blinded to clinical status but aware of asbestos exposure German (Hering et al., 2004) and Japanese (Kusaka et al., 2005) HRCT guidelines Pleural Plaques: "circumscribed and discrete areas of hyaline or calcified fibrosis localized on the parietal pleura of the lateral chest wall, the diaphragm or the mediastinum." Parietal pleural plaques (*n* = 63) Visceral pleural fibrosis (*n* = 10) Asbestosis and parietal pleural plaques (*n* = 39) Asbestosis and visceral pleural fibrosis (*n* = 42)	European Respiratory Society procedures (details not provided), measures with two highest attempts with agreement within 5% included. Adjusted for body temperature and pressure saturated with water vapor. Trained technicians Percentage predicted from various references (all European), including _ENREF_48Quanjer et al. (1993) FEV_1, FVC, FEV_1/FVC, MEF_{50}, DL_{CO}		Table 2, external analysis

[a]Descriptive data for pleural plaque (or LPT) group; when not noted as such, data is for full study sample.

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I.4. REFERENCES

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