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TOXICOLOGICAL REVIEW

OF

LIBBY AMPHIBOLE ASBESTOS

In Support of Summary Information on the Integrated Risk Information System (IRIS)

December 2014

(Note: This document is an assessment of the noncancer and cancer health effects associated with the inhalation route of exposure only)

Integrated Risk Information System
National Center for Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency
Washington, DC

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LIST OF ABBREVIATIONS AND ACRONYMS

AAHAU	Airborne Asbestos Health Assessment Update
AIC	Akaike Information Criterion
ADAF	age-dependent adjustment factor
ANA	antinuclear antibody
APC	antigen-presenting cells
APT	any pleural thickening
ARC	any radiographic change
ATS	American Thoracic Society
ATSDR	Agency for Toxic Substances and Disease Registry
BALF	bronchoalveolar lavage fluid
BGL	β-glucuronidase
BMI	body mass index
BMC	benchmark concentration
BMCL	lower limit of the BMC
BMR	benchmark response
C	mean exposure
CAO	costophrenic angle obliteration
CDF	cumulative distribution frequency
CE	cumulative exposure
CHEEC	cumulative human equivalent exposure concentration
CI	confidence interval
COPD	chronic obstructive pulmonary disease
COX-2	cyclooxygenase-2
CVD	cardiovascular disease
DEF	deferoxamine
d_{eq}	aerodynamic equivalent diameter
DIC	Deviance Information Criterion
DL_{CO}	single-breath carbon monoxide diffusing capacity
DPT	diffuse pleural thickening
dsDNA	double-stranded DNA
EcSOD	extracellular superoxide dismutase
ED	El Dorado tremolite
EDS	energy-dispersive spectroscopy
EPA	U.S. Environmental Protection Agency
EPMA	electron probe microanalysis
FEV	forced expiratory volume
FVC	forced vital capacity
GOF	goodness of fit
GSH	glutathione
GST	glutathione-*S*-transferase
HAEC	human airway epithelial cell
HO	heme oxygenase
HTE	hamster tracheal epithelial
IARC	International Agency for Research on Cancer
ICD	International Classification of Diseases

IFN	interferon
Ig	immunoglobulin
IH	industrial hygiene
IL	interleukin
ILO	International Labour Organization
IQR	interquartile range
IRIS	Integrated Risk Information System
IUR	inhalation unit risk
JEM	job-exposure matrix
KL	lung cancer slope factor
KM	mesothelioma slope factor
LAA	Libby Amphibole asbestos
LDH	lactate dehydrogenase
LEC_{01}	95% lower confidence limit of the exposure concentration associated with 1% increased risk
LPT	localized pleural thickening
MCAA	antimesothelial cell antibodies
MCMC	Monte Carlo Markov Chain
MMP	matrix metalloproteinase
MOA	mode of action
Mppcf	million particles per cubic foot
MSHA	U.S. Mine Safety and Health Administration
NRC	National Research Council
NDI	National Death Index
Nf2	neurofibromatosis 2
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
ON	Ontario ferroactinolite
OR	odds ratio
PBS	phosphate-buffered saline
PCM	phase contrast microscopy
PCMe	phase contrast microscopy equivalent
PG-PS	peptidoglycan-polysaccharide
PLM	polarized light microscopy
$PM_{2.5}$	particulate matter 2.5 μm diameter or less
POD	point of departure
RCF-1	refractory ceramic fibers
RfC	reference concentration
RfD	reference dose
RNP	ribonucleoprotein
RNS	reactive nitrogen species
ROS	reactive oxygen species
RPM	rat pleural mesothelial
RR	relative risk
RTW	residence time-weighted
SAED	selected area electron diffraction

SAID	systemic autoimmune disease
SD	standard deviation
SE	standard error
SH	spontaneously hypertensive
SHE	Syrian hamster embryo
SHHF	spontaneously hypertensive-heart failure
SIR	standardized incidence ratio
SM	Sumas Mountain chrysotile
SMR	standardized mortality ratio
SOD	superoxide dismutase
SRR	standardized rate ratio
SSA/Ro52	autoantibody marker for apoptosis
SSB/La	autoantibody marker
SV40	Simian virus 40
TEM	transmission electron microscopy
TSFE	time since first exposure
TWA	time-weighted average
UCL	upper confidence limit
UF	uncertainty factor
UICC	Union for International Cancer Control
USGS	United States Geological Survey
VAI	vermiculite attic insulation
WDS	wavelength-dispersive x-ray spectroscopy
WKY	Wistar-Kyoto rat
XRCC1	x-ray repair cross-complementing protein 1

FOREWORD

The purpose of this Toxicological Review is to provide scientific support and rationale for the hazard and dose-response assessment in the Integrated Risk Information System (IRIS) pertaining to chronic inhalation exposure to Libby Amphibole asbestos, a mixture of amphibole fibers identified in the Rainy Creek complex and present in ore from the vermiculite mine near Libby, MT. It is not intended to be an assessment of the toxicity of asbestos generally (nor a comprehensive treatise on the agent or toxicological nature of Libby Amphibole asbestos). The purpose of this document is to establish a Libby Amphibole asbestos-specific reference concentration to address noncancer health effects and to characterize the carcinogenic potential and establish an inhalation unit risk for Libby Amphibole asbestos-related lung cancer and mesothelioma mortality.

The intent of Section 6, *Major Conclusions in the Characterization of Hazard and Exposure Response,* is to present the significant conclusions reached in the derivation of the reference dose, reference concentration, and cancer assessment where applicable, and to characterize the overall confidence in the quantitative and qualitative aspects of hazard and dose-response by addressing the quality of data and related uncertainties. The discussion is intended to convey the limitations of the assessment and to aid and guide the risk assessor in the ensuing steps of the risk assessment process.

The intent of Appendix J, *Documentation of Implementation of the 2011 National Research Council Recommendations,* is to present the IRIS Program's implementation of the NRC recommendations. Implementation is following a phased approach that is consistent with the NRC's "Roadmap for Revision" as described in Chapter 7 of the formaldehyde review report.

For other general information about this assessment or other questions relating to IRIS, the reader is referred to U.S. Environmental Protection Agency's (EPA's) IRIS Hotline at (202) 566-1676 (phone), (202) 566-1749 (fax), or hotline.iris@epa.gov (email address).

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1. INTRODUCTION

This document presents background information and justification for the Integrated Risk Information System (IRIS) summary of the hazard and exposure-response assessment of Libby Amphibole asbestos (LAA),[1] a mixture of amphibole fibers identified in the Rainy Creek complex and present in ore from the vermiculite mine near Libby, MT. IRIS summaries may include oral reference dose (RfD) and inhalation reference concentration (RfC) values for chronic exposure durations, and a carcinogenicity assessment. This assessment reviews the potential hazards, both cancer and noncancer health effects, from exposure to LAA and provides quantitative information for use in risk assessments: an RfC for noncancer health effects and an inhalation unit risk (IUR) addressing cancer risk. LAA-specific data are not available to support RfD or cancer slope factor derivations for oral exposures.

An RfC is defined as "an estimate (with uncertainty spanning perhaps an order of magnitude) of an exposure (including sensitive subgroups) that is likely to be without an appreciable risk of adverse health effects over a lifetime." (U.S. EPA, 2002). In the case of LAA, the RfC is expressed in terms of the lifetime exposure in units of fibers per cubic centimeter of air (fibers/cc) in units of the fibers as measured by phase contrast microscopy (PCM). The inhalation RfC for LAA considers toxic effects for both the respiratory system (portal of entry) and for effects peripheral to the respiratory system (extrarespiratory or systemic effects) that may arise after inhalation of LAA.

The carcinogenicity assessment provides information on the carcinogenic hazard potential of the substance in question, and quantitative estimates of risk from inhalation exposures are derived. The information includes a weight-of-evidence judgment of the likelihood that the agent is a human carcinogen and the conditions under which the carcinogenic effects may be expressed. Quantitative risk estimates are derived from the application of a low-dose extrapolation procedure from human data. An inhalation unit risk (IUR) is typically defined as a plausible upper bound on the estimate of cancer risk per $\mu g/m^3$ air breathed for 70 years. For LAA, the RfC is expressed as a lifetime daily exposure in fibers/cc (in units of the fibers as measured by PCM), and the IUR is expressed as cancer risk per fibers/cc (in units of the fibers as measured by PCM).

Development of these hazard identification and exposure-response assessments for LAA has followed the general guidelines for risk assessment as set forth by the National Research Council (NRC, 1983). U.S. Environmental Protection Agency (EPA) Guidelines and Risk Assessment Forum technical panel reports that may have been used in the development of this assessment include the following: *Guidelines for the Health Risk Assessment of Chemical*

[1]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.

Mixtures (U.S. EPA, 1986c), *Guidelines for Mutagenicity Risk Assessment* (U.S. EPA, 1986b), *Recommendations for and Documentation of Biological Values for Use in Risk Assessment* (U.S. EPA, 1988b), *Guidelines for Developmental Toxicity Risk Assessment* (U.S. EPA, 1991a), *Interim Policy for Particle Size and Limit Concentration Issues in Inhalation Toxicity* (U.S. EPA, 1994a), *Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry* (U.S. EPA, 1994b), *Use of the Benchmark Dose Approach in Health Risk Assessment (*U.S. EPA, 1995*)*, *Guidelines for Reproductive Toxicity Risk Assessment* (U.S. EPA, 1996), *Guidelines for Neurotoxicity Risk Assessment* (U.S. EPA, 1998), *Science Policy Council Handbook*: *Risk Characterization* (U.S. EPA, 2000b), *Benchmark Dose Technical Guidance Document* (U.S. EPA, 2012), *Supplementary Guidance for Conducting Health Risk Assessment of Chemical Mixtures* (U.S. EPA, 2000c), *A Review of the Reference Dose and Reference Concentration Processes* (U.S. EPA, 2002), *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a), *Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens* (U.S. EPA, 2005b), *Science Policy Council Handbook: Peer Review* (U.S. EPA, 2006c), and *A Framework for Assessing Health Risks of Environmental Exposures to Children* (U.S. EPA, 2006b).

The literature search strategy employed for this assessment is based on EPA's National Center for Environmental Assessment's Health and Environmental Research Online database tool (which includes PubMed, MEDLINE, Web of Science, JSTOR, and other literature sources). The key search terms included the following: Libby Amphibole, tremolite, asbestos, richterite, winchite, amphibole, and Libby, MT. The relevant literature was reviewed through July 2011. Any pertinent scientific information submitted by the public to the IRIS Submission Desk was also considered in the development of this document. Note that references have been added to the Toxicological Review after the external peer review SAB (2013) in response to peer reviewers' comments and for the sake of completeness.

1.1. RELATED ASSESSMENTS

1.1.1. Integrated Risk Information System (IRIS) Assessment for Asbestos (U.S. EPA, 1988a)

The IRIS assessment for asbestos was posted online in IRIS in 1988 and includes an IUR of 0.23 excess cancers per 1 fiber/cc (U.S. EPA, 1988a); this unit risk is given in units of the fibers as measured by PCM. The IRIS IUR[2] for general asbestos (CAS Number 1332-21-4) is derived by estimating excess cancers for a continuous lifetime exposure and is based on the central tendency—not the upper bound—of the risk estimates (U.S. EPA, 1988a) and is applicable to exposures across a range of exposure environments and types of asbestos. Although other cancers have been associated with asbestos [e.g., laryngeal, stomach, ovarian

[2]For purposes of this document, termed "IRIS IUR."

(Straif et al., 2009)], the IRIS IUR for asbestos accounts for only lung cancer and mesothelioma. Additionally, pleural and pulmonary effects from asbestos exposure (e.g., pleural thickening, asbestosis, and reduced lung function) are well documented, although there is no RfC for these noncancer health effects on the IRIS database (U.S. EPA, 1988a).

The derivation of the unit risk for general asbestos is based on the *Airborne Asbestos Health Assessment Update* [AAHAU (U.S. EPA, 1986a)]. The AAHAU provides various cancer potency factors and mathematical models of lung cancer and mesothelioma mortality based on synthesis of data from occupational studies and presents estimates of lifetime cancer risk for continuous environmental exposures [0.0001 fiber/cc and 0.01 fiber/cc; (see Table 6-3 of (U.S. EPA, 1986a)]. For both lung cancer and mesothelioma, life-table analysis was used to generate risk estimates based on the number of years of exposure and the age at onset of exposure. Although various exposure scenarios were presented, the unit risk is based on a lifetime continuous exposure from birth. The final asbestos IUR is 0.23 excess cancers per 1 fiber/cc continuous exposure[3] and was posted on the IRIS database in 1988 [(U.S. EPA, 1988a) see Table 1-1 below].

Table 1-1. Derivation of the current Integrated Risk Information System (IRIS) inhalation unit risk for asbestos from the lifetime risk tables in the Airborne Asbestos Health Assessment Update (AAHAU) at 0.01 fiber/cc

Gender	Excess deaths per 100,000[a]			Risk	Unit risk (per fiber/cc)
	Mesothelioma	Lung cancer	Total		
Female	183	35	218.5	2.18×10^{-1}	
Male	129	114	242.2	2.42×10^{-1}	
All	156	74	230.3	2.30×10^{-1}	0.23

[a]Data are for exposure at 0.01 fiber/cc for a lifetime.

Source: U.S. EPA (1988a).

The IRIS database has an IUR for asbestos based on 14 epidemiologic studies that included occupational exposure to chrysotile, amosite, or mixed-mineral exposures [chrysotile, amosite, crocidolite (U.S. EPA, 1988a, 1986a)]. Some uncertainty remains in applying the resulting IUR for asbestos to exposure environments and minerals different from those analyzed

[3]An IUR of 0.23 for general asbestos can be interpreted as 0.23 excess risk of death from mesothelioma or lung cancer per person for each 1 fiber/cc increase in continuous lifetime exposure. Thus, as shown in Table 1-1, for 100,000 people exposed at a concentration of 0.01 fiber/cc, 230 excess deaths would be expected [IUR × Concentration × Number of people = (0.23 excess cancer deaths per fiber/cc per person) × (0.01 fiber/cc) × (100,000 people) = 230 excess cancer deaths]. "Fiber/cc" is a commonly used measure; it is equivalent to 1 million fibers per cubic meter of air while 0.01 fiber/cc is 10,000 fibers per cubic meter of air.

in the AAHAU (U.S. EPA, 1986a). No RfC, RfD, or oral slope factor are derived for asbestos on the IRIS database (U.S. EPA, 1988a).

1.1.2. EPA Health Assessment for Vermiculite (U.S. EPA, 1991b)

An EPA health assessment for vermiculite reviewed available health data, including studies on workers who mined and processed ore with no significant amphibole fiber content. The cancer and noncancer health effects observed in the Libby, MT worker cohort were not seen in studies of workers exposed to mines with similar exposure to vermiculite but much lower exposures to asbestos fibers. Therefore, it was concluded that the health effects observed from the materials mined from Zonolite Mountain near Libby, MT, were most likely due to amphibole fibers and not the vermiculite itself (U.S. EPA, 1991b). At the time, EPA recommended the application of the IRIS IUR for asbestos fibers (0.23 per fiber/cc) in addressing potential risk of the amphibole fibers entrained in vermiculite mined in Libby, MT.

1.2. LIBBY AMPHIBOLE ASBESTOS-SPECIFIC HUMAN HEALTH ASSESSMENT

LAA is a complex mixture of amphibole fibers—both mineralogically and morphologically (see Section 2.3). The mixture primarily includes winchite, richterite, and tremolite fibers with trace amounts of magnesio-riebeckite, edenite, and magnesio-arfvedsonite. These fibers exhibit a complete range of morphologies from prismatic crystals to asbestiform fibers (Meeker et al., 2003). Epidemiologic studies of workers exposed to LAA fibers indicate increased lung cancer and mesothelioma, as well as asbestosis and other nonmalignant respiratory diseases (Larson et al., 2010b; Larson et al., 2010a; Moolgavkar et al., 2010; Rohs et al., 2008; Sullivan, 2007; McDonald et al., 2004, 2002; Amandus et al., 1988; Amandus et al., 1987b; Amandus and Wheeler, 1987; Amandus et al., 1987a; McDonald et al., 1986a; McDonald et al., 1986b; Lockey et al., 1984).

2. LIBBY AMPHIBOLE ASBESTOS: GEOLOGY AND EXPOSURE POTENTIAL

2.1. INTRODUCTION

Libby is a community in northwestern Montana that is located near a large open-pit vermiculite mine that operated from the mid 1920s to 1990 (see Figure 2-1). Vermiculite is a silicate mineral that exhibits a sheet-like structure similar to mica (see Figure 2-2, Panel A). When heated to approximately 870°C, water molecules between the sheets change to vapor and cause the vermiculite to expand like popcorn into a light, porous material (see Figure 2-2, Panel B). This process of expanding vermiculite is termed "exfoliation" or "popping." Both unexpanded and expanded vermiculite have found a range of commercial applications, the most common of which include packing material, attic and wall insulation, various garden and agricultural products, and various cement and building products.

Figure 2-1. Vermiculite mining operation on Zonolite Mountain, Libby, MT.

Panel A: Vermiculite ore sample. Vermiculite ore sample, Zonolite Mountain, Rainy Creek complex, Libby, MT.

Source: USGS Field Collection, Meeker (2007)

Panel B: Expanded vermiculite

Figure 2-2. Unexpanded and expanded vermiculite.

The primary product from the mine was vermiculite concentrate, which was produced by milling, screening, and grading the raw ore to enrich for the vermiculite mineral. In general, mining practices sought to exclude nonvermiculite material when harvesting the ore, and subsequent processing steps were designed to eliminate nonvermiculite materials from the

finished product. Nevertheless, small amounts of other minerals from the ore body tended to remain in the vermiculite (Zonolite) product. This included a form of asbestos referred to as Libby Amphibole asbestos (LAA).

This chapter provides a brief description of the mineralogical characteristics of asbestos (see Section 2.2), an overview of methods used to identify and measure asbestos in air and solid materials (see Section 2.3), a review of the mineralogical characteristics of LAA in particular (see Section 2.4), and an overview of the potential for current human exposures to LAA (see Section 2.5).

2.2. GEOLOGY AND MINERALOGY OF AMPHIBOLES

2.2.1. Overview

Asbestos is the generic name for a group of naturally-occurring silicate minerals that crystallize in long thin fibers. The basic chemical unit of asbestos and other silicate minerals is $[SiO_4]^{4-}$. This basic unit consists of four oxygen atoms at the apices of a regular tetrahedron surrounding and coordinated with one silicon ion (Si^{4+}) at the center (see Figure 2-3, Panel A). The silicate tetrahedra can bond to one another through the oxygen atoms, leading to a variety of crystal structures (see Figure 2-3, Panels B, C, and D).

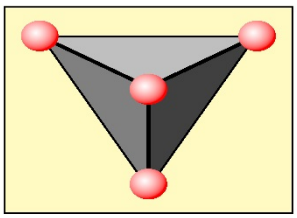
There are two main classes of asbestos: serpentine and amphibole. The only member of the serpentine class is chrysotile, which is the form of asbestos that was most commonly used in the past in various man-made asbestos-containing materials (insulation, brake linings, floor tiles, etc.). Chrysotile is a phyllosilicate (see Figure 2-3, Panel D), occurring in sheets that curl into a fibrous form.

There are many different types of amphibole asbestos. This includes five types that were previously used in commerce (actinolite, tremolite, amosite, crocidolite, and anthophyllite), and these forms of asbestos are now regulated. Numerous other asbestiform amphiboles exist, even though they were never used as commercial products and are not currently named in regulations (Gunter et al., 2007). All forms of amphibole asbestos are inosilicates (see Figure 2-3, Panel C) in which the long axis of the fiber (crystallographically called the c-axis) is parallel to the direction of the chain of silicon tetrahedra.

2.2.2. Mineralogy of Amphibole Asbestos and Related Amphibole Minerals

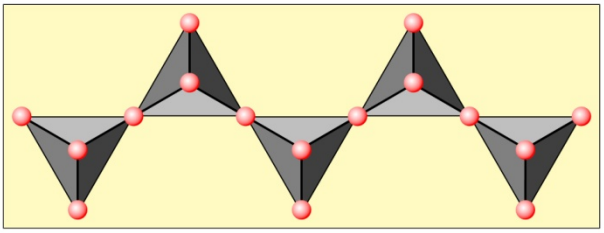
Different types of amphiboles differ from each other primarily in the identity and amounts of monovalent and divalent cations that bind to sites (referred to as A, B, or C sites) along the silicate chains (see Figure 2-4). The specific cations between the two double-chain plates define the elemental composition of the mineral, while the ratio of these cations in each location is used to classify amphiboles within a solid-solution series. The general chemical formula for double-chain inosilicate amphiboles is shown below:

(A) Nesosilicates or single tetrahedron.



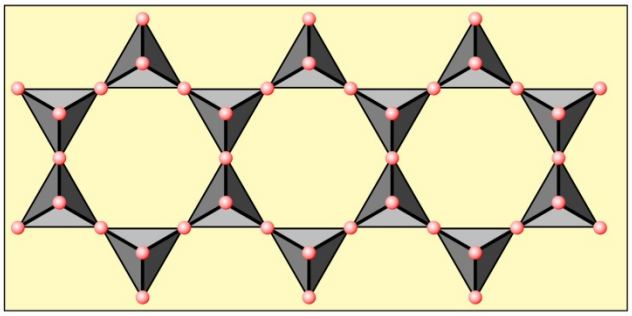
The single tetrahedron comprises four oxygen molecules covalently bound to the silicon, at the center of the $[SiO_4]^{4-}$-tetrahedron.

(B) Inosilicates [*ino* (*gr.*) = thread]—Single-chain silicates.



Chain silicates are realized by linking $[SiO_4]^{4-}$-tetrahedrons in a way to form continuous chains. They can be represented by a composition of $[SiO_3]^{2-}$. A typical example is diopside $CaMg[Si_2O_6]$, in which the "endless" chains are also held together by Ca^{2+} and Mg^{2+} ions.

(C) Inosilicates—Double-chain silicates.



Two silicate chains of the inosilicates are linked at the corners, forming double-chains and yielding $[Si_4O_{11}]_{6-}$ ions, as realized in the tremolite-ferro-actinolite series $Ca_2(Mg,Fe)_5Si_8O_{22}(OH,F,Cl)_2$. Double-chain silicates are commonly grouped with the single-chain inosilicates.

(D) Phyllosilicates [*phyllo* (*gr.*) = sheet] or sheet silicates. These are formed if the double-chain inosilicate $[Si_4O_{11}]^{6-}$ chains are linked to form continuous sheets with the chemical formula $[Si_2O_5]^{2-}$. Examples of sheet silicates include chrysotile $Mg_3Si_2O_5(OH)_4$ and vermiculite $[(Mg, Fe,Al)_3(Al,Si)_4O_{10}(OH)_2 \bullet 4H_2O]$.

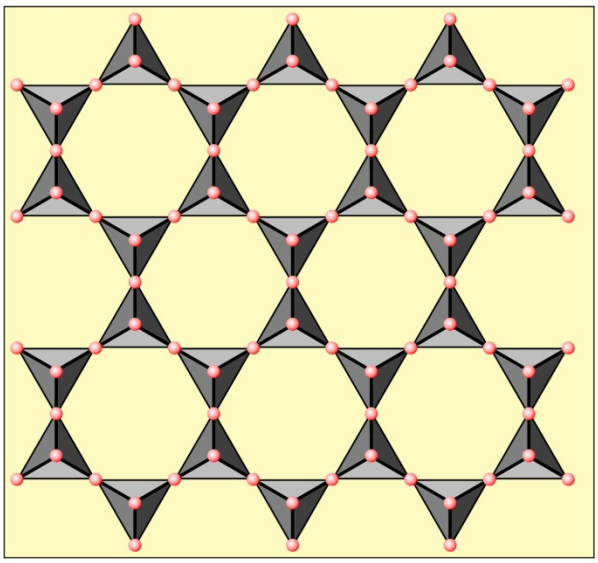


Figure 2-3. Structure of the silicate minerals, illustrating silicate subclasses by the linking of the basic silicon tetrahedron (A) into more complex structures (B, C, or D).

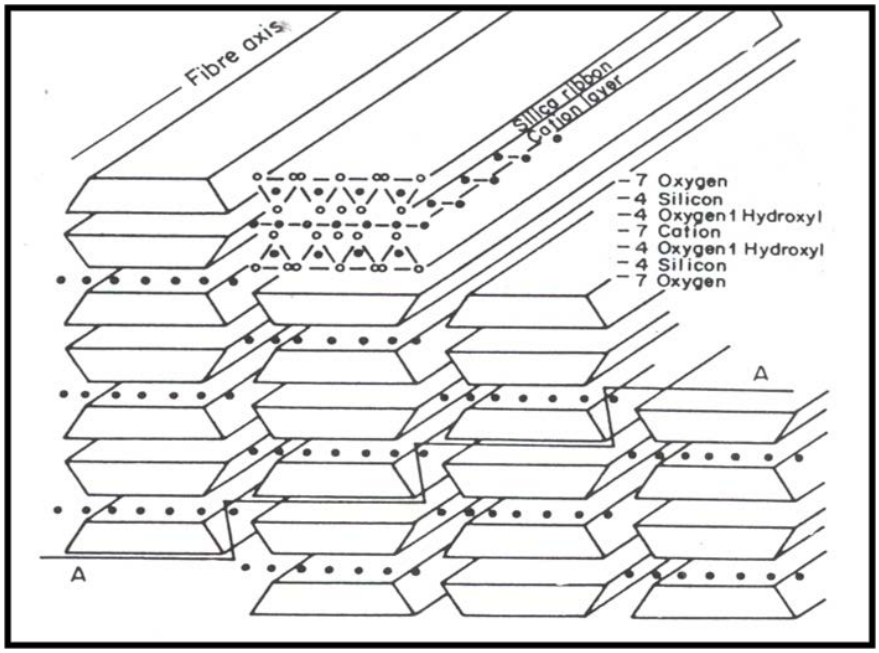


Figure 2-4. Cross section of amphibole fibers showing the silicon tetrahedrons (triangles with open circles at apex) that make up each double-chain plate (shown along the fiber axis). Cations (shown as the darkened dots) occur between the plates forming the basic fiber.

Source: Kroschwitz et al. (2007).

$$A_{0-1}B_2C_5T_8O_{22}(OH, F, Cl)_2 \qquad (2\text{-}1)$$

where:

A = Na, K
B = Na, Li, Ca, Mn, Fe^{2+}, Mg
C = Mg, Fe^{2+}, Mn, Al, Fe^{3+}, Ti
T = Si, Al

The mineral subgroup within amphiboles is determined by the elemental composition.

- Calcic amphiboles (tremolite)
- Sodic-calcic amphiboles (richterite, winchite)
- Sodic amphiboles (riebeckite [also known as "crocidolite"], arfvedsonite)
- Iron-magnesium-manganese-lithium amphiboles (anthophyllite, cummingtonite-grunerite [also known as "amosite"])

Because the stoichiometry of the cations is not fixed, a continuum of compositions may occur. These are referred to as "solid solution series." The series are defined by their end

members. For example, a solid solution series for the cation Site A will have one end member with 100% sodium ions and one end member with 100% potassium ions. This series would include all intervening ratios.

Because each cation site has multiple possibilities, the elemental composition of the amphibole silicates can be quite complex. It is the complexity of the amphiboles that has historically given rise to a proliferation of mineral names with little systematic basis (Hawthorne, 1981). Currently, amphiboles are identified by a clear classification scheme based on crystal chemistry that uses well-established names based on the basic mineralogy, with prefixes and adjective modifiers indicating the presence of substantial substitutions that are not essential constituents of the end members (Leake et al., 1997). As implemented, this mineral classification system does not designate certain amphibole minerals as asbestos. However, some mineral designations have traditionally been considered asbestos (in the asbestiform habit; e.g., tremolite, actinolite). Other commercial forms of asbestos were known by trade names (e.g., Amosite) rather than mineralogical terminology (cummingtonite-grunerite).

2.2.3. Morphology of Amphibole Minerals

Most amphibole minerals occur in a variety of growth habits, depending on the temperature, pressure, local stress field, and solution chemistry conditions during crystallization. The nomenclature used to describe the crystal forms varies between disciplines [field geologist, microscopist; e.g., see Lowers and Meeker (2002)]. Text Box 2-1 provides definitions for common terms used to describe the morphology of asbestos and other related minerals.

Text Box 2-1: Nomenclature

Acicular: The shape showed by and extremely slender crystal with small cross-sectional dimensions (a special case of prismatic form). Acicular crystals may be blunt-ended or pointed. The term "needlelike" refers to an acicular crystal with pointed termination at one of both ends.

Amphibole: A group of silicate minerals that may occur either in massive or fibrous (asbestiform) habits.

Asbestiform (mineralogical): A specific type of mineral fibrosity in which the fibers and fibrils are long, 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 therefore are suitable for uses where incombustible, nonconducting, or chemically resistant materials are required.

Bundle: A group of fibers occurring side by side with parallel orientations.

Cleavage fragment: A fragment produced by breakage of crystal in directions that are related to the crystal structure and are always parallel to possible crystal faces.

Cluster: A group of overlapping fibers oriented at random.

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 length greater than or equal to 5 µm and aspect ratio greater than or equal to 3:1 (by PCM) or 5:1 (by transmission electron microscopy [TEM]).

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.

Fibril: A single fiber which cannot be separated into smaller components without losing its fibrous properties or appearance. 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, needlelike grains or fibers.

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.

Prismatic: Having blocky, pencil-like elongated crystals that are thicker than needles.

Structure: A term used mainly in microscopy, usually including asbestos fibers, bundles, clusters, and matrix particles that contain asbestos.

Asbestiform morphology is present where the conditions of formation allow crystals to form very long individual flexible fibers which are parallel and easily separable and may become visible to the naked eye when crushed (see Figure 2-5). Under the microscope, individual amphibole structures may be described as asbestiform, acicular, prismatic, or fibrous. Typically, a fiber is defined as a highly elongated crystal with parallel sides. The definitions for acicular crystals are "needlelike" in appearance while prismatic crystals may have several parallel faces with a low aspect ratio (ratio of length to width, <3:1).

Panel A **Panel B**

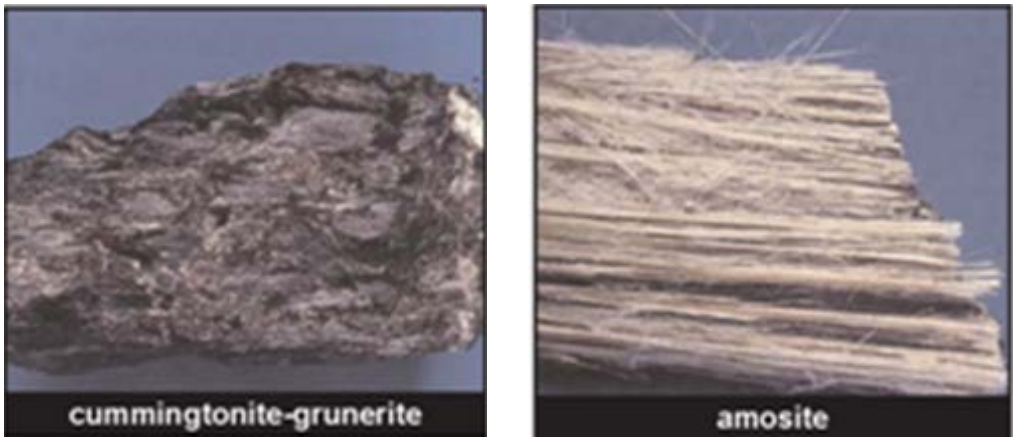


Figure 2-5. Comparison of crystalline forms of amphibole minerals. Panel A shows a specimen identified as an amphibole mineral in the cummingtonite-grunerite solid solution series. Although crystalline in form, the habit of formation did not favor formation of individual particles and fibers, hence its appearance as "massive." Panel B shows an amphibole mineral with very similar elemental composition but formed in a habit where very long fibers were allowed to form—hence the asbestiform appearance.

Source: Adapted from Bailey et al. (2006).

Where conditions are not conducive to the formation of individual fibers and particles, the amphibole is described as massive—appearing as a solid contiguous sample. Mechanical forces that break amphibole crystals along the cleavage planes create smaller pieces or cleavage fragments. These fragments may be elongated and have a morphology that is generally similar to amphibole asbestos, but differ from the regulated minerals in that they did not grow in an asbestiform habit.

2.3. METHODS FOR ANALYSIS OF ASBESTOS

Because asbestos is a solid that does not dissolve in water or other solvents, methods for the analysis of asbestos are somewhat different than for most other chemical substances. This section provides a brief overview of the most common methods for the analysis of asbestos.

2.3.1. Methods for Air Samples

The exposure pathway of primary health concern for humans is inhalation of asbestos. Air is evaluated for the presence of asbestos by drawing a known volume of air through a filter that traps the solid particles in the air on the filter surface, and the number of asbestos particles are then determined. The concentration is generally expressed as fibers[4] per cubic centimeter of air (fibers/cc) and is computed by dividing the number of asbestos fibers on the filter by the volume of air drawn through the filter.

In all cases, the evaluation of the particles that are collected on an air filter is performed using a microscope. All methods begin with the basic shape (morphology) of a particle to classify it as a possible asbestos particle or not. In general, particles that are clearly fibrous (substantially longer than they are thick) are considered to be potential asbestos. However, other minerals besides asbestos may occur in long thin particles, and a number of nonmineral fibers may be present in a sample as well. Consequently, some techniques rely on other physical or optical properties of the particles to help distinguish asbestos from nonasbestos and to classify the type of asbestos. These differences in the ability to visualize and distinguish asbestos particles are the most important differences between the various microscopic techniques.

The most common technique in the past for analyzing asbestos in air samples was PCM, and this method remains the current industrial hygiene (IH) standard methodology, usually using National Institute for Occupational Safety and Health (NIOSH) Method 7400 (http://www.cdc.gov/niosh/docs/2003-154/pdfs/7400.pdf). Under this method, a fiber is defined as any particle greater than 5 μm in length with an aspect ratio greater than or equal to 3:1. Depending on the microscope set-up and refractive index of the mounting medium and fibers, the limit of detection of PCM can be up to a fiber width of 0.25 μm. Fibers thinner than the limit of detection are not observable. A key attribute of PCM is that identification of countable fibers is based only on morphology, and does not consider mineralogy or crystal structure. Because of this, it is not possible to classify asbestos fibers by mineral type, or even to reliably distinguish between asbestos and nonasbestos fibers. This is not usually a significant concern when applied to air samples collected in a workplace where asbestos is present, but can become an issue in

[4]Most techniques for analyzing air samples do not distinguish individual fibers from more complex structures composed of two or more fibers, including bundles, clusters and matrix particles. For simplicity, the term “fiber” is used here to include not only fibers but the more complex structures as well.

nonworkplace settings where asbestos concentrations tend to be lower and other types of fibers are more common.

Transmission electron microscopy (TEM) has also been developed for analysis of air samples for asbestos. TEM uses a high-energy electron beam rather than a beam of light to irradiate the sample, and this allows visualization of structures much smaller than can been seen under light microscopy. In addition, most TEM instruments used for asbestos analysis have equipment that allows a more detailed characterization of a particle than is possible by PCM:

- EDS (energy-dispersive spectroscopy) provides data on the atomic composition of each particle being examined. This makes it possible to distinguish organic fibers from mineral fibers, and also allows for distinguishing between different types of mineral fibers.

- SAED (selected area electron diffraction) provides a diffraction pattern for crystalline particles that is helpful in distinguishing organic from mineral fibers, and in classifying the nature of the crystalline structure (serpentine, amphibole, pyroxene, etc.).

- WDS (wavelength-dispersive x-ray spectroscopy) provides x-ray spectral data from a single wavelength at a time, providing detailed atomic composition of a particle. Generally, WDS is a more precise measure of the atomic composition of a particle than EDS and is often used with an electron microprobe attached to a scanning electron microscope.

Several different standard methods have been developed for TEM analyses of air samples, the most common of which is ISO 10312 (ISO 10312:1995). ISO 10312 defines a fiber as an elongated particle with parallel or stepped sides, an aspect ratio of 5:1, and a minimum length of 0.5 µm, and further defines a PCM-equivalent fiber (PCMe) as having an aspect ratio greater than or equal to 3:1, longer than 5 µm, and a diameter between 0.2 µm and 3.0 µm. The counting rules require both types of fiber to be reported.

2.3.2. Methods for Solid Materials

Measurement of asbestos in solid samples (vermiculite, building materials, soil, etc.) usually employs polarized light microscopy (PLM). There are several standard PLM methods for the analysis of asbestos in bulk materials, including NIOSH 9002, EPA/600/R-93/116, and CARB 435. PLM uses the optical properties of asbestos to identify and classify different types of asbestos fibers. In general, these methods are most reliable for materials that contain relatively high concentrations of asbestos, and results tend to become more variable as concentrations decrease below about 1% by mass. At present, the use of TEM for the analysis of bulk materials is not a well-developed procedure.

2.4. CHARACTERISTICS OF LIBBY AMPHIBOLE ASBESTOS

Amphibole asbestos occurs in the Libby vermiculite ore body both in high concentration veins (>80%), as well as in lower concentrations (0.1 to 3%) within the layers of the vermiculite ore itself (Lowers et al., 2012; U.S. EPA, 2000a; Boettcher, 1967; Pardee and Larsen, 1928). Analysis of historical ore samples from the Harvard and Smithsonian Museums (circa 1920s), the Butte Museum (circa 1960), and recent ore samples from the mine (circa 1999) indicate that the amphibole content of vermiculite ore from the mine has remained approximately constant over the 70-year mining history at the Rainy Creek complex (Sanchez et al., 2008; Meeker et al., 2003).

2.4.1. Mineralogy of Libby Amphibole Asbestos

Historically, the amphibole mineral fibers that occur in the Libby ore body were described as a sodium-rich tremolite (Amandus et al., 1987b; McDonald et al., 1986a; Leake, 1978; Boettcher, 1966; Larsen, 1942), although McDonald et al. (1986a) noted the sodium content was too high to allow classification as tremolite, and suggested that at least some fibers might be better classified as magnesio-riebeckite or richterite.

More recently, various research groups (Gunter and Sanchez, 2009; Sanchez et al., 2008; Meeker et al., 2003; Wylie and Verkouteren, 2000; Ross et al., 1993; Moatamed et al., 1986) have recharacterized the mineralogical composition of amphiboles from the Libby mine using the modern classification scheme developed by Leake et al. (1997).

The most extensive investigation was reported by the U.S. Geological Survey [USGS (Meeker et al., 2003)]. In this investigation, USGS personnel collected amphibole samples from different areas of the mine to identify the range of materials present. The mineral composition of individual fiber structures was determined using EDS and electron probe microanalysis (EPMA). The results, which are presented in Figure 2-6, show that most amphibole structures were classified as winchite (84%), with lesser amounts classified as richterite (11%) and tremolite (6%). Trace amounts of magnesio-riebeckite, magnesio-arfvedsonite, and edenite are also present. Sanchez et al. (2008) found a similar distribution of amphibole mineral types in a sample of ore collected from the mine in 2009. Wylie and Verkouteren (2000) reported the presence of asbestiform winchite and richterite in ore samples from the mine, which was consistent with the alteration of alkali igneous rocks.

The relationship between the cationic compositions of the three primary minerals is illustrated in Figure 2-7. In some fibers, the composition differed within the length of a single fiber (e.g., winchite at one end and richterite at the other end). All of these minerals are within the solid solution series for tremolite-richterite-magnesio-riebeckite. Magnesio-riebeckite and magnesio-arfvedsonite fall within the range of sodic amphiboles, winchite and richterite fall within the range of sodic-calcic amphiboles, and tremolite and edenite are considered calcic

amphiboles. Structural formulae and optical and crystallographic data are presented in Table 2-1.

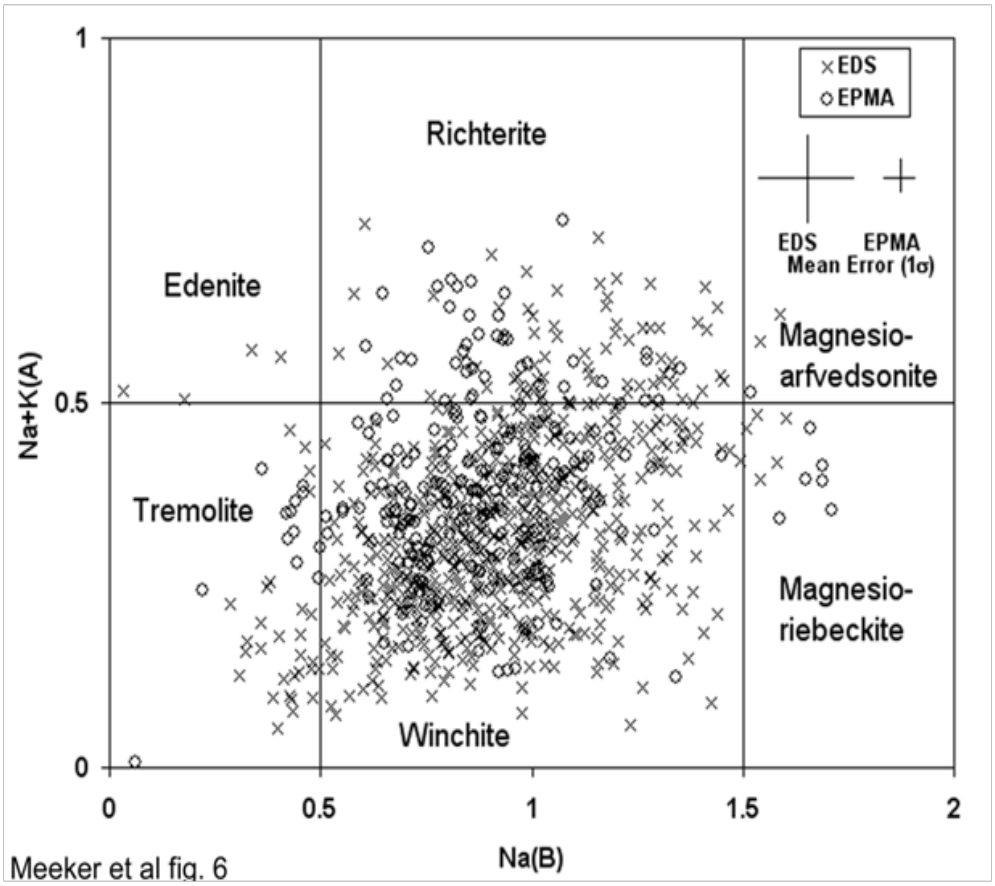


Figure 2-6. Mineralogy of LAA structures from samples taken from the Zonolite Mountain site. An evaluation of the textural characteristics shows the material to include a complete range of morphologies from prismatic crystals to fibers. Each data point represents the cation composition (number of occupied sites) for a single fiber. The *x*-axis shows the number of sites occupied by Na, and the *y*-axis shows the number of sites occupied by Na or K. The data shown are a composite of the analysis of fibers taken from 30 different field samples from various locations within the mine.

Source: Meeker et al. (2003)

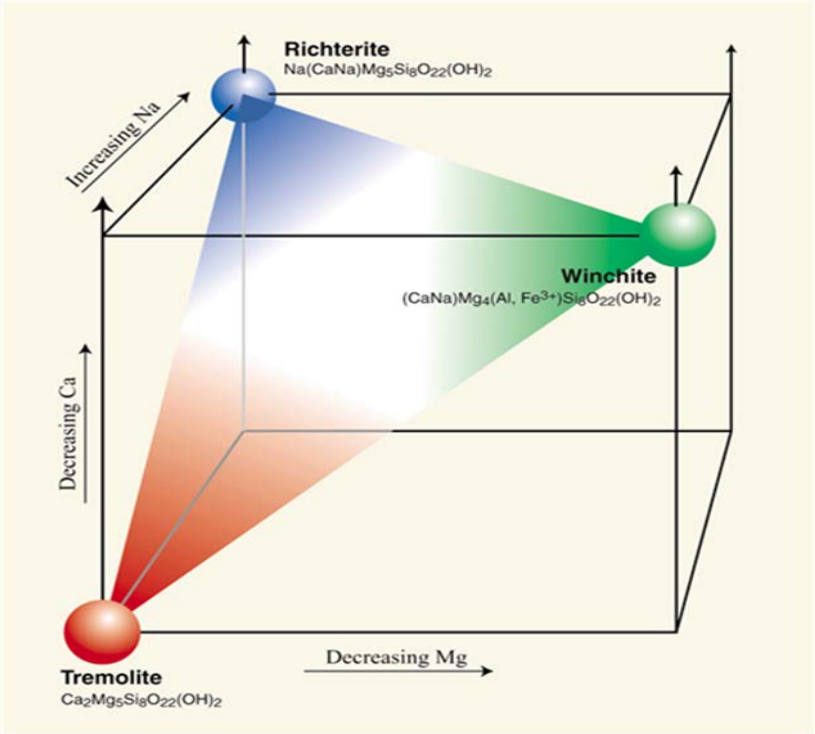


Figure 2-7. Solution series linking tremolite, winchite, and richterite amphibole fibers.

Table 2-1. Optical and crystallographic properties of fibrous amphiboles associated with Libby Amphibole asbestos

Mineral	Habit and color	Refractive indices		Birefringence	Extinction	Elongation sign
		α	γ			
Tremolite[a] $Ca_2Mg_5Si_8O_{22}(OH)_2$	Straight to curved fibers and bundles. Colorless to pale green.	1.600−1.628 1.604−1.612 1.599−1.612 1.6063	1.625−1.655 1.627−1.635 1.625−1.637 1.6343	0.017−0.028	Oblique up to 21°	+ (length slow)
Actinolite $Ca_2(Mg,Fe)_5Si_8O_{22}(OH)_2$		1.600−1.628 1.612−1.668 1.613−1.628 1.6126	1.625−1.655 1.635−1.688 1.638−1.655 1.6393	0.017−0.028		+ (length slow)
Winchite $CaNaMg_4(Al,Fe^{3+})Si_8O_{22}(OH)_2$	Straight to curved fibers or bundles. Colorless to pale blue. Pleochroism weak to moderate: X = colorless, Y = light blue−violet, Z = light blue.[d]	**1.618−1.626**[b] **1.618−1.621**[c] 1.629[d] 1.636[e]	**1.634−1.642**[b] **1.634−1.637**[c] 1.650[d] 1.658[e]	**0.008−0.019**[b] **0.016**[c] 0.021[d] 0.022[e]	**Oblique, 22°**[b] **15.8°**[c] Oblique, 7−29°[h]	+ (length slow)
Richterite $NaCaNa(Mg,Fe)_5Si_8O_{22}(OH)_2$	Straight to curved fibers or bundles. Colorless, pale yellow, brown, pale to dark green, or violet.[h] Pleochroism weak to strong in pale yellow, orange, and red.[f]	**1.622−1.623**[b] 1.605−1.624[f] 1.615[g]	**1.638−1.639**[b] 1.627−1.641[f] 1.636[g]	**0.012−0.017**[b] 0.017−0.022[f]	**Oblique, 21−22°**[b] Oblique, 5−45°[h]	+ (length slow)
Magnesio-riebeckite $Na_2Mg_3Fe_2^{3+}Si_8O_{22}(OH)_2$	Prismatic to fibrous aggregates. Blue, grey-blue, pale blue to yellow. Can be pleochroic.[h]	1.650−1.673[h]	1.662−1.676[h]	Up to 0.015[h]	Oblique, 8−40°[h]	− (length fast)[h]

Table 2-1. Optical and crystallographic properties of fibrous amphiboles associated with Libby Amphibole asbestos (continued)

Mineral	Habit and color	Refractive indices		Birefringence	Extinction	Elongation sign
		α	γ			
Magnesio-arfvedsonite $NaNa_2Mg_4Fe^{3+}Si_8O_{22}(OH)_2$	Prismatic to fibrous aggregates. Yellowish green, brownish green, or grey-blue. Can be pleochroic.[h]	1.623−1.660[h]	1.635−1.680[h]	0.012−0.026[h]	Oblique, 18−45°[h]	− (length fast)
Edenite $NaCa_2Mg_5AlSi_7O_{22}(OH)_2$	Prismatic to fibrous aggregates. White, grey, pale to dark green, also brown and pale pinkish-brown. Can be pleochroic.[i]	1.606−1.649[i]	1. 631−1.672[i]	0.025[i]	Oblique, 12−34°[h]	+ (length slow)

[a]Adapted from: U.S. EPA (1993) Method for the determination of asbestos in bulk building materials. Method EPA/600/R-93/116. July 1993. (NTIS/PB93-218576).
[b]Bandli et al. (2003) Optical, compositional, morphological, and x-ray data on eleven particles of amphibole from Libby, MT, U.S.A. Canadian Mineralogist 41: 1241−1253.
[c]Wylie and Verkouteren (2000) Amphibole asbestos from Libby, MT: Aspects of nomenclature. American Mineralogist, 85: 1540−1542.
[d]www.minsocam.oeg/msa/Handbook/Winchite.PDF.
[e]www.mindat.org/min-4296.html.
[f]www.minsocam.oeg/msa/Handbook/Richterite.PDF.
[g]www.webmineral.com/data/Richterite.shtml.
[h]Deer and Zussman (1997) Rock Forming Minerals Volume 2B: Double Chain Silicates, 2nd Edition. The Geological Society, London.
[i]www.mindat.org/min-1351.html.

2.4.2. Morphology of Libby Amphibole Asbestos

A number of investigators have reported on the morphology of LAA structures in samples from the mine site, as well as in air samples from the former mine and mill or from present-day town of Libby. McDonald et al. (1986a) used TEM to examine particles collected on air filters from the mine and mill in Libby. The authors reported that fibers on the filters included a range of morphologies, including straight with uniform diameter, lath- or needle-shaped, or curved.

Brown and Gunter (2003) used PLM to examine structures obtained from three different mineral samples collected at the mine in Libby. Each of the three samples was crushed and sieved through a 250 μm screen. Based on aspect ratio, 95% of the structures were considered possible asbestos. Based on a more detailed evaluation of crystal structure, about one-third were judged to be asbestos, about one-third were judged to be cleavage fragments, and about one-third could not be classified with confidence.

Meeker et al. (2003) reported that all of the amphiboles found at the mine site, with the possible exception of magnesio-riebeckite, can occur in fibrous habit. It was observed these amphibole materials—even when originally present as massive material—can produce abundant, extremely fine fibers by gentle abrasion or crushing.

Figure 2-8 shows a scanning electron microscope image of amphibole mineral collected from the mine in Libby (Meeker et al., 2003). This image illustrates the broad range of size and morphologies that can occur in this material. As individual structures are viewed under greater magnification, the range of morphologies can be more clearly seen (see Figure 2-9). The USGS has observed structures that are fibrous, acicular, and prismatic, all within the minerals from the mine (Meeker et al., 2003).

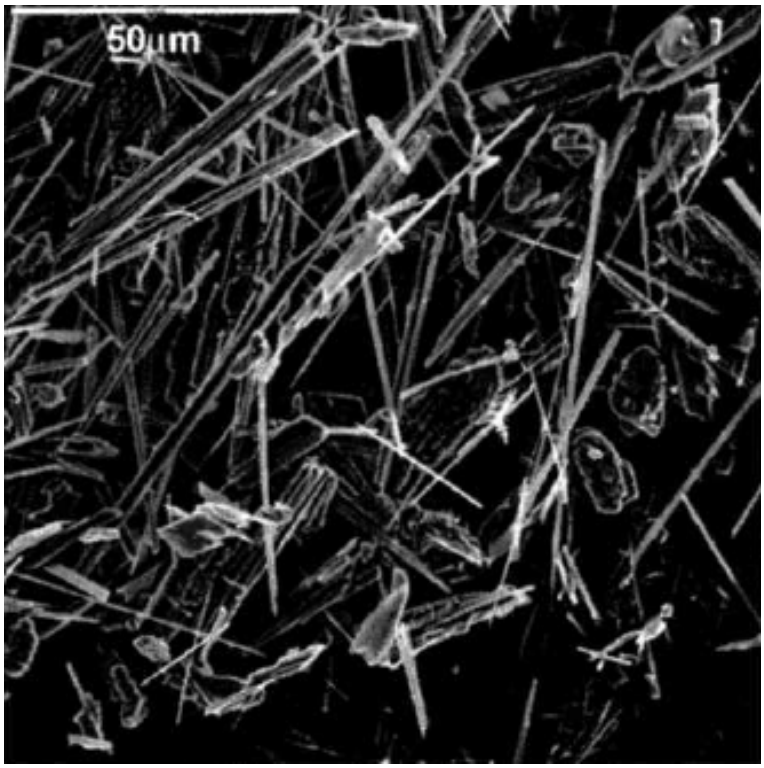


Figure 2-8. Scanning electron microscope image of amphibole mineral structures from the Libby, MT mine. An evaluation of the textural characteristics shows the material to include a range of morphologies from prismatic crystals to fibers. Acicular and prismatic crystals, fibers bundles, and curved fibers are all present.

Source: Meeker et al. (2003).

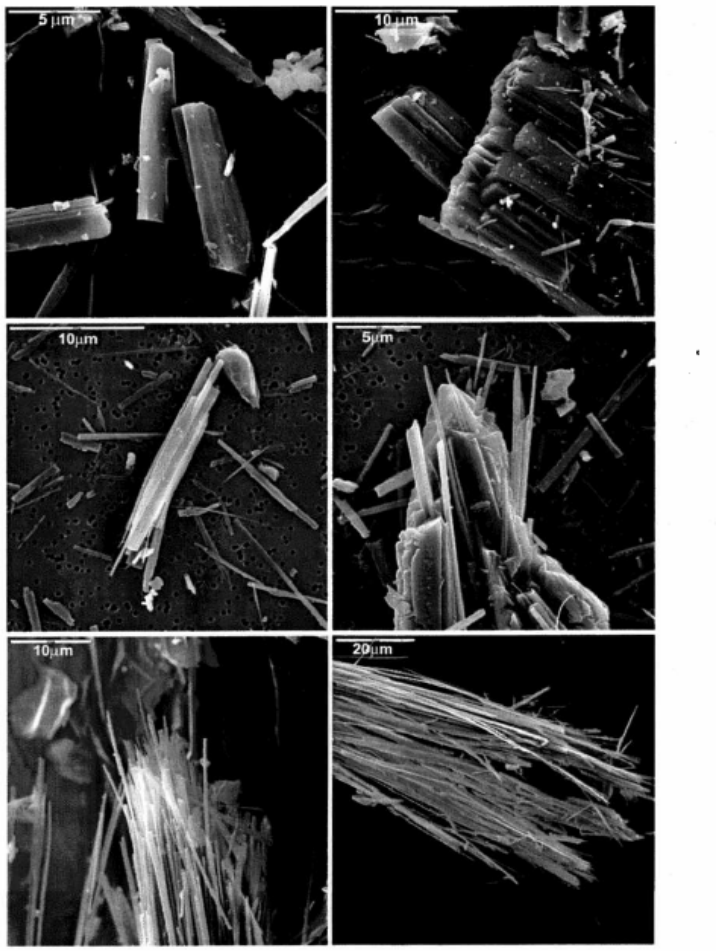


Figure 2-9. Fiber morphology of amphibole asbestos from the Libby, MT mine viewed under a scanning electron microscope.

Source: Meeker et al. (2003).

Sanchez et al. (2008) evaluated fiber morphology using an electron microscopy and EMPA and reported that most structures could be classified as either prismatic or fibrous. There was no difference in the mineralogy between the two morphologies, and the authors concluded the different habits were formed at the same time.

Figure 2-10 shows cumulative particle-size-distribution frequencies (CDFs) for LAA fibers (aspect ratio ≥3:1) observed using TEM in Libby ore Grade 3, expanded Libby ore Grade 3, and ambient air samples collected in Libby. The data used to construct this plot are described in Appendices B and C. In general, most fibers identified as LAA have widths that range from about 0.1 μm to 1 μm, with an average of about 0.6 μm. Fiber lengths vary greatly, ranging from <1 μm to ≥100 μm. Aspect ratios also range widely, from 3:1 to ≥100:1.

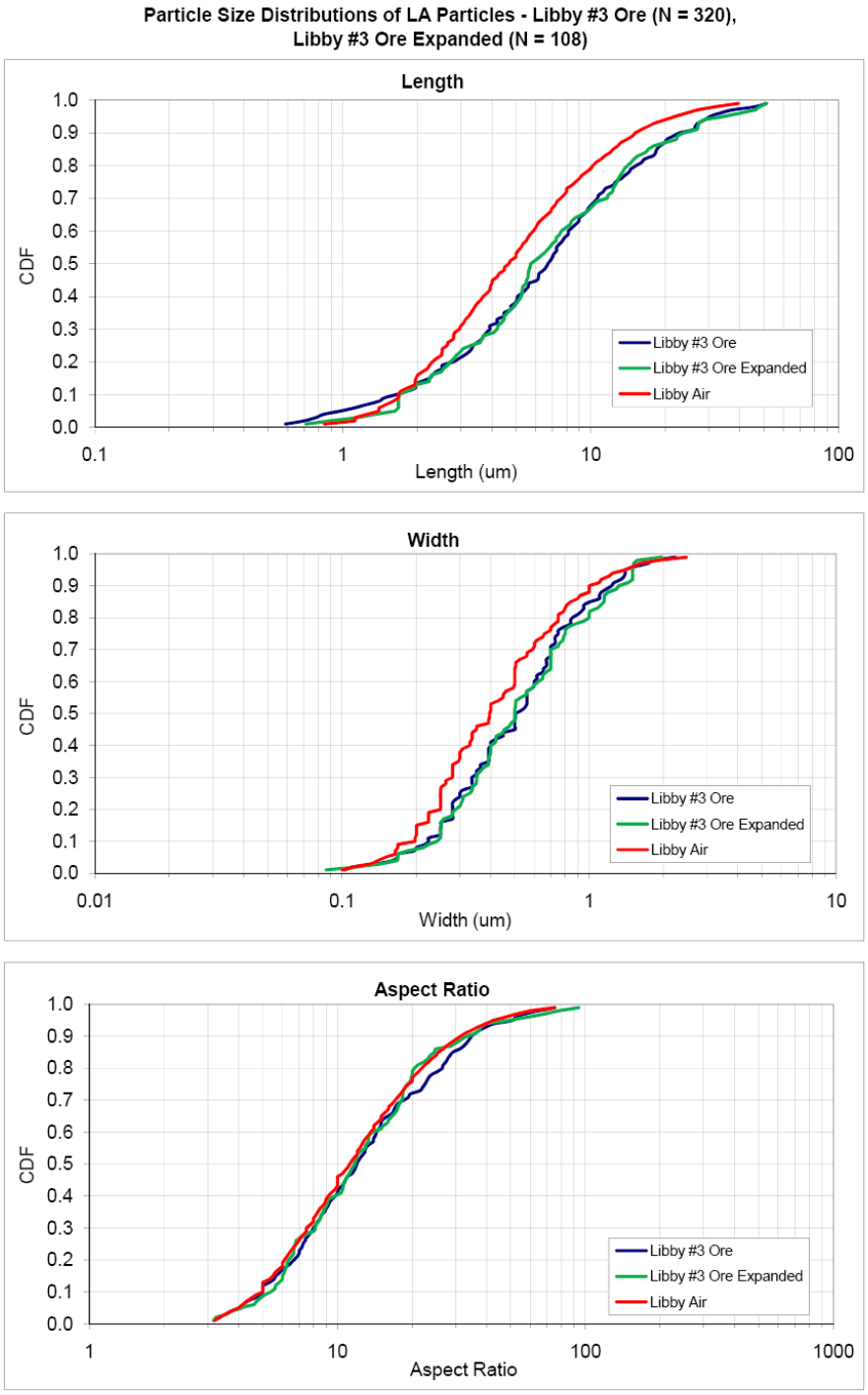


Figure 2-10. Particle size (length, width, aspect ratio) of fibers in Libby ore and Libby air.

CDF = cumulative distribution frequency; LA = Libby Amphibole.

Source: U.S. EPA (2010b); provided as Appendix B.

An important question is whether the mineralogy and morphology of LAA fibers observed in geological samples of amphibole material collected at the mine are similar to that observed for airborne fibers collected on filters in Libby or other locations where vermiculite was used or processed. As shown in Figure 2-10, the size distributions for fibers observed in the unexpanded and expanded Libby Grade 3 ores are very similar to each other, while the LAA fibers observed in air monitoring samples from Libby tend to be slightly thinner and shorter than in the ore samples. However, the differences are relatively minor. Mineralogical characterization by EDS and SAED of the fibers from the Libby ore Grade 3 and the expanded product provided additional confirmation of the similarity between the fibers from the Libby Grade 3 ore and Libby air samples (methodology described in Section 2.3; see also Appendix B). EDS spectra yielded an elemental fingerprint with sodium and potassium peaks that were highly consistent with values reported for the winchite-richterite solution series described for the Libby ores (Meeker et al., 2003).

2.5. HUMAN EXPOSURE POTENTIAL

Several different populations have the potential for exposure to vermiculite (Zonolite) from the mine in Libby, MT, and hence the potential for exposure to the LAA associated with this material. This includes not only the former workers at the mine and mill site, but also residents in the community of Libby, MT, as well as workers at other locations who processed the vermiculite product. A brief description of these potentially exposed populations is presented below.

2.5.1. Exposures Pathways in the Libby Community

When the mine in Libby, MT was active, miners, mill workers, and those working in the processing plants were exposed to vermiculite, silica dust, and amphibole structures released to air from the ore during the mining and processing operations (Meeker et al., 2003; Amandus et al., 1987b; McDonald et al., 1986a). In some cases, workers may have inadvertently transported, typically on their clothing, shoes, and hair, contaminated materials from the workplace to vehicles, homes, and other establishments. This transported material may have resulted in "take-home exposure" for the workers, their families, and other coresidents. The magnitude of these historic take-home exposures was not measured, so the levels to which individuals in the home might have been exposed are not known.

The Agency for Toxic Substances and Disease Registry (ATSDR) performed an exposure survey in Libby to identify activities that may have led to the exposure of residents to vermiculite and LAA. Based on the responses of survey participants, it was found that men were more likely than women to have had both occupational and nonoccupational exposures, while women were more likely to have had only household contact with exposed workers (Peipins et al., 2003; ATSDR, 2001b). Expanded vermiculite, as a finished product (Zonolite), was used for

insulation in attics and walls in homes in Libby, and was also used as a soil amendment in home gardens and recreational areas. Community members may have been exposed, and are possibly still exposed, to these consumer (Zonolite) products. In a survey of Libby residents conducted by ATSDR in 2000−2001, almost 52% reported using vermiculite for gardening, 8.8% used vermiculite around the home, and 51% reported handling vermiculite attic insulation [VAI; (Peipins et al., 2003)]. Because vermiculite ore, vermiculite product, and waste stoner rock (the waste material from exfoliation) were present in the community, numerous other activities may also have resulted in exposure. Individuals also reported exposures from the following activities: participating in recreational activities along Rainy Creek Road, which is the road leading to the mine (67%); playing at the ball field near the expansion plant (66%); playing in vermiculite piles (34%); heating the vermiculite to make it expand/pop (38%); or other activities in which contact with vermiculite occurred [31%; (Peipins et al., 2003)].

Because a number of different activities may be associated with exposure to LAA in Libby, it is important to recognize that the overall health hazard to an individual is related to the sum of the exposures across all scenarios that apply to that individual.

2.5.2. Exposure Pathways in Communities with Vermiculite Expansion and Processing Plants

While some vermiculite concentrate was exfoliated and used in Libby, MT, most of the concentrate was transported to expansion plants at other locations across the country where it was exfoliated and distributed. A review of company records from 1964−1990 indicates that more than 6 million tons of vermiculite concentrate was shipped to over 200 facilities outside of Libby (ATSDR, 2008). Figure 2-11 shows the locations of facilities that received and processed vermiculite from the mine in Libby.

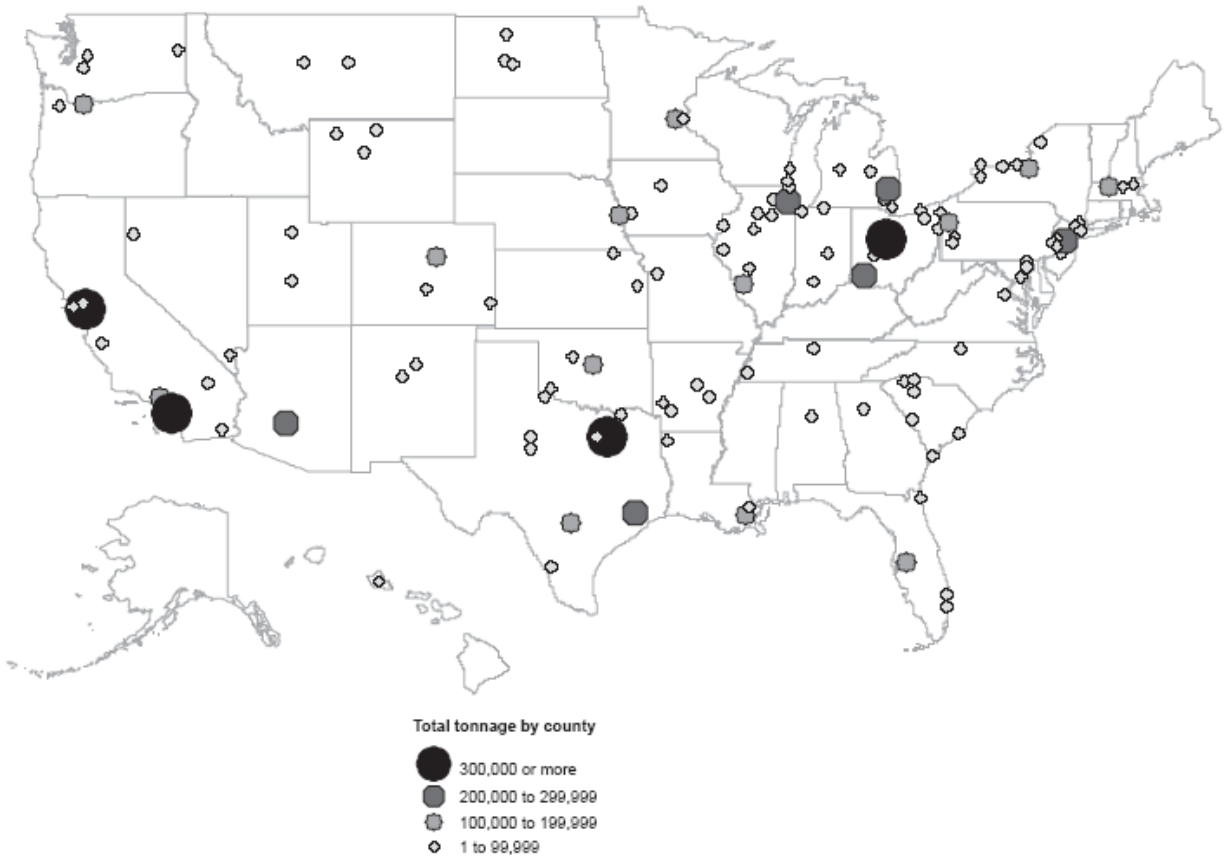


Figure 2-11. Nationwide distribution of Libby ore by county (in tons). Data on the distribution of ore are based on approximately 80,000 invoices that EPA obtained from W.R. Grace that document shipments of vermiculite ore made from the Libby mine between 1964 and 1990. EPA tabulated this shipping information in a database.

Source: U.S. GAO (2007).

Workers in these expansion and processing facilities likely were exposed to LAA released during processing operations. The 2008 ATSDR Summary Report (ATSDR, 2008) on28 Libby vermiculite expansion and processing facilities stated that in some cases household residents may also have been exposed by contact with vermiculite from the workers' clothes, shoes, and hair. Workers' personal vehicles likely contained vermiculite dust from facility emissions and from vermiculite that fell from their clothing and hair on the drive home after work.

Other residents living in communities near the expansion plants may also have been subjected to some of the same LAA exposure pathways as for the Libby community. The 2008 ATSDR Summary Report observed that individuals in a community with a vermiculite expansion and processing plant could have been exposed to LAA by breathing airborne

emissions from the facility or by inhalation exposure to contaminants brought into the home on workers' clothing or from outdoor sources (ATSDR, 2008).

2.5.3. Libby Amphibole Asbestos Exposure Pathways in Other Communities

Because expanded vermiculite from Libby was widely used in numerous consumer and construction products throughout the United States, even people not associated with Libby or other communities with expansion plants may also have the potential for exposure to LAA (see Table 2-2). Vermiculite was most notably used as attic insulation [VAI; (Versar, 2003)], as a soil amendment for gardening, fireproofing agent, and in the manufacturing of gypsum wallboard.

Table 2-2. Air sampling results for asbestos from Zonolite vermiculite attic insulation (VAI) in three homes

Activity	Personal samples		Area samples
	PCM[a] fibers/cc	TEM[b] PCMe, s/cc	TEM PCMe, s/cc
No activity	NS[c]	NS	<0.003
Cleaning items in the attic	1.54	<0.42	0.07
Cleaning storage area in the attic	2.87	2.58	0.47
Cutting a hole in the ceiling below the VAI	5.80	1.32	0.52
VAI removal (various methods)	2.9−2.5[d]	0.98−10.3	0.53−1.47

[a]Air sampling results reported as fibers analyzed by PCM.
[b]Air sampling results reported as structures; PCMe as analyzed by TEM.
[c]NS—not sampled; personal samples were not taken for background levels.
[d]Range of results for three different removal methods (shop vacuum, homeowner method, and manufacturer-recommended method).

Source: Ewing et al. (2010).

3. FIBER TOXICOKINETICS

There are no published data on the toxicokinetics of Libby Amphibole asbestos (LAA).[5] However, to help inform the reader as to the expected toxicokinetics of LAA, this section contains a general summary description of the toxicokinetics of inhaled particles, with specific discussion of dosimetry differences for fibers. A more detailed discussion of fiber dosimetry is beyond the scope of this document and is reviewed elsewhere (NIOSH, 2011; ICRP, 1994).

LAA includes fibers with a range of mineral compositions, including amphibole fibers primarily identified as winchite, richterite, and tremolite, along with magnesio-riebeckite, magnesio-arfvedsonite, and edenite (see Section 2.2). Although the fiber size varies somewhat from sample to sample for LAA, a large percentage (~45%) is less than 5 μm long in bulk samples examined from the Libby mine site (Meeker et al., 2003). Limited data from air samples taken in the mill and screening plant at the Libby mine site also document a large percentage of fibers (including both respirable[6] fibers as well as fibers >3 μm long; see Section 4.1.1.2 and Table 4-3). Laboratory animal studies have examined the biologic response to LAA fibers from both raw samples (Blake et al., 2007; Pfau et al., 2005) and samples of particles respirable by rats (<2.5 μm) following water elutriation [(Cyphert et al., 2012b; Cyphert et al., 2012a; Shannahan et al., 2012a; Shannahan et al., 2012c; Shannahan et al., 2012b; Shannahan et al., 2012d; Padilla-Carlin et al., 2011; Shannahan et al., 2011a; Shannahan et al., 2011b; Shannahan et al., 2010); see Section 4.2; Appendix D]. The mean fiber dimensions in the rat-respirable fractions are in the range of length = 4.99 μm; width = 0.26 μm; aspect ratio ≥5:1 (as measured by TEM)[7]. The importance of the dimensions and density of fibers to their inhalation dosimetry—how they deposit and are subsequently cleared—is described below. Due to a lack of toxicokinetic data specific to LAA, these dosimetry mechanisms are discussed for inhaled fibers in general, with a specific focus on amphibole asbestos.

The main route of human exposure to mineral fibers is through inhalation. Inhaled dose of fibers to the respiratory tract tissue depends on the fiber concentration in the breathing zone, the physical (aerodynamic) characteristics of the fibers, the breathing mode (nose only or also oronasal), anatomical and physiological features of the respiratory tract (e.g., airway branching pattern and ventilation rate), and clearance mechanisms (Oberdorster et al., 2002; U.S. EPA, 1994a; Oberdorster, 1991). Ingestion is another pathway of human exposure and occurs mainly through the swallowing of material removed from the respiratory tract via mucociliary clearance or drinking water contaminated with asbestos, or eating, drinking, or smoking in

[5]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.

[6]Respirable fibers are those that can reach the alveolar regions when inhaled and are defined by their aerodynamic diameter [$d_a \leq 3$ μm;(NIOSH, 2011)].

[7]When available, detailed fiber dimension information for each study can be found in Appendix D.

asbestos-contaminated work environments (Condie, 1983). Handling asbestos can result in heavy dermal contact and exposure. Asbestos fibers can become lodged in the skin, producing a callus or corn—but generally with no serious health effects (Lockey et al., 1984). Because few studies have examined the deposition and clearance of fibers following ingestion or dermal exposure to fibers, the focus of this section is on the main route of exposure: inhalation.

Studies useful for assessing the relationship between airborne fiber concentrations and respiratory disease must involve meaningful measurements of environmental exposure and an understanding of how to apply these measurements to the target tissue dose. Tissue dose is a more specific measure associated with disease development than is external dose. Many studies have examined the role of the physical and chemical characteristics of fibers in asbestos-induced disease in the lung and are reviewed in more depth elsewhere (NIOSH, 2011; ATSDR, 2001a; Myojo and Takaya, 2001; Witschi and Last, 1996; Lippmann, 1990; Merchant, 1990; Yu et al., 1986; Griffis et al., 1983; Harris and Fraser, 1976; Harris and Timbrell, 1975). Factors influencing dose to other tissues in the body (e.g., pleura, peritoneum, stomach, and ovaries) are not as well known, but they are discussed below where data are available.

The principal components of inhaled fiber dosimetry in mammalian respiratory tract systems are (1) inhalability, (2) deposition on the epithelial surface, (3) clearance from the lung due to both physical (e.g., dissolution) and biological mechanisms (including mucociliary transport, phagocytosis, and translocation from the lung to other tissues [including the pleura]), and (4) elimination from the body (see Figure 3-1).

3.1. DEPOSITION OF FIBERS IN THE RESPIRATORY TRACT

The respiratory tract encompasses the extrathoracic region (nasal passages, pharynx, and larynx), tracheobronchial region (the conducting airways [trachea, bronchi, bronchioles]), and the gas-exchange or pulmonary region of the lung (respiratory bronchioles, alveolar ducts, and alveoli). Each region has unique anatomic and functional features, including dramatically different architecture, cell types, and defense mechanisms, that determine the dosimetry of inhaled agents in each region (U.S. EPA, 1994a). A full review of the anatomy and architecture of the respiratory tract is beyond the scope of this document but has been reviewed by the International Commission on Radiological Protection for its reference human respiratory tract model (ICRP, 1994). Figure 3-2 illustrates the major anatomical features of the human respiratory tract and mechanisms of fiber deposition.

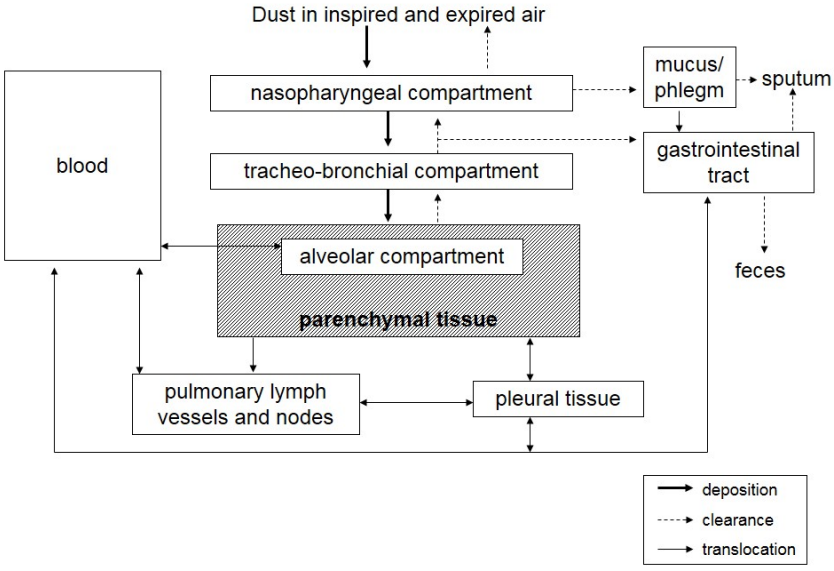


Figure 3-1. General scheme for fiber deposition, clearance, and translocation of fibers from the lung and gastrointestinal tract. General scheme for fiber inhalation and deposition (heavy arrows), clearance (light dotted arrows), and translocation (light arrows). Diagram of Bignon et al. (1978) derived from International Commission on Radiological Protection lung model by the Task Group on Lung Dynamics (Bates et al., 1966), as cited in ICRP (1994).

Source: ICRP (1994).

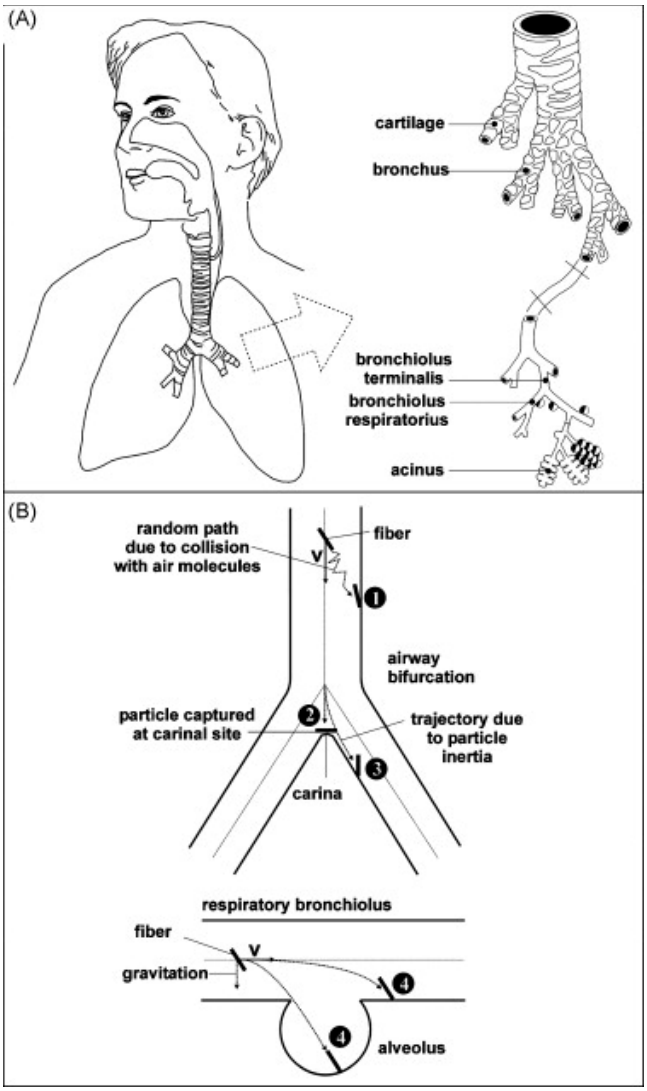


Figure 3-2. Architecture of the human respiratory tract and schematic of major mechanisms of fiber deposition. Mechanisms of fiber deposition illustrated in panel (B) are as follows: (1) diffusion, (2) interception, (3) impaction, and (4) sedimentation.

Source: Sturm and Hofmann (2009).

Four major mechanisms determine fiber deposition: impaction, interception, sedimentation, and diffusion. Some authors also suggest electrostatic precipitation plays a role in fiber deposition, but no experimental data exist to verify this (Sturm and Hofmann, 2009). The relative contribution to deposition in each region of the respiratory tract depends on fiber dimension and density, breathing mode and ventilation rate, and the airway architecture of the species in question (e.g., rat vs. human). The deposition mechanisms and where these mechanisms are typically dominant in the human respiratory tract are described below (see Table 3-1).

Table 3-1. Factors influencing fiber deposition and clearance in the respiratory system

Size of fiber (aerodynamic diameter)	Area of deposition in respiratory system	Predominant method of deposition	Mechanisms for fiber retention	Physical clearance	Dissolution	Target tissue for translocation
5−30 µm	Extrathoracic region (nasopharyngeal region, nasal passages, pharynx, larynx)	Impaction	Epithelial cell uptake	Mucous flow (mucociliary apparatus into gastrointestinal tract) Macrophage: phagocytosis and transport	Not measured, although dissolution can occur; removal from mucous flow is fairly quick and likely predominant	Gastrointestinal tract Nasal-associated lymphoid tissue, lymph system
1−5 µm	Thoracic Region (trachea, bronchial, and bronchiolar region)	Sedimentation, impaction, interception	Epithelial cell uptake	Mucociliary apparatus Macrophage: phagocytosis and transport	Mucous Macrophage	Gastrointestinal tract Mucosa-associated lymphoid tissue, lymph system Pleura
2 µm or less	Gas-Exchange Region (respiratory bronchioles, alveolar ducts, alveoli)	Diffusion	Epithelial cell uptake Translocation to other target tissues	Macrophage: phagocytosis and transport	Lung surfactant Macrophage Asbestos bodies	Gastrointestinal tract Mucosa-associated lymphoid tissue, lymph system Pleura

Source: Adapted from Witschi and Last (2001) in Casarett and Doull's Toxicology: The Basic Science of Poisons, 6th edition, p. 515.

1. **Impaction:** The momentum of the fiber causes it to directly impact the airway surface as the airflow changes direction. This is the predominant method of deposition in the nasopharyngeal region where airflow is turbulent and in the larger conducting and bronchial airways at bifurcations where airflow is swift and directional changes are dramatic.

2. **Interception:** A special case of impaction where the edge of the fiber touches the airway wall and is prevented from continuing along the airway. The longer a fiber, the higher its deposition by interception. This mechanism is important in the conducting airways (trachea and bronchi).

3. **Sedimentation:** Gravitational forces and air resistance cause fibers to settle out of the convective air stream onto the airway surface. For sedimentation to occur, air flow velocities must be low to allow the fiber to settle, so this is **a predominant** mechanism in the smaller conducting airways.

4. **Diffusion:** This method of deposition is predominant in the alveolar region where air movement is negligible. Diffusion occurs from interactions of the fibers with the movement of air molecules, and becomes important for particles <0.5 μm in physical diameter.

The aerodynamic properties of particulate aerosols, including fibers, are characterized by the particle's aerodynamic diameter and its distribution, usually as the mass median aerodynamic diameter and geometric standard deviation (GSD) because aerosols tend to be log normally distributed. The aerodynamic diameter is the diameter of a unit density (1 g/cm^3) sphere that has the same gravitational settling velocity as the fiber of interest and the aerodynamic diameter derivation is based on fundamental laws governing fluid dynamics. However, characterizing a fiber by its aerodynamic diameter is dubious due to the multiple factors that define a fiber's aerodynamic properties [e.g., density, length, width, and its orientation with respect to the convective airflow (Asgharian and Anjilvel, 1998; Cheng, 1986)]. Vincent (2005) has proposed that fibers should be described by criteria that address both the aerodynamic properties that govern their regional deposition after inhalation and the biological effects and responses following deposition.

Computational models or algorithms to address fiber dosimetry typically derive an aerodynamic equivalent diameter (d_{eq}) to remain consistent with the concept of aerodynamic diameter and provide some comparative context, and are based as well on fundamental fluid dynamics. Such formulae are mechanism specific (e.g., for impaction or sedimentation) and describe fibers as cylinders characterized by their density and length-to-width aspect ratio (beta), although the explicit bivariate distribution for a fiber aerosol can be described by the means and variances of the natural logarithms for length and width with correlations for their joint distribution (Moss et al., 1994; Cheng, 1986). The latter is unfortunately not often done due to the lack of bivariate data when aerosols are sized in various experiments. The formulae to derive d_{eq} must additionally account for the orientation of the fibers with respect to the convective airflow in the Stokes flow regime where it is necessary to describe the frictional forces encountered by an object (i.e., fiber or particle) in a fluid (i.e., air). For example, dynamic shape factors (χ) that relate the drag force of the cylindrical object to a sphere are derived for either perpendicular or parallel orientation with respect to the flow. Likewise, adjustments in these formulae are made for fiber orientation to the Cunningham slip correction factor which accounts for the relative velocity (or "slip") of gas molecules in air at the surface of objects entrained in that airflow. Additional assumptions regarding the orientation are typically used for each region of the respiratory tract, for example, random orientation for fibers in the upper airway subject to

impaction or parallel orientation in the peripheral airways. Fibers enter the respiratory tract through the nasal and oral passages.

Deposition in the nasal and oral passages is mainly by impaction. The nasal passage, from the nostril to the pharynx, serves as a filter for some fibers with diameters 5−30 μm. Clumps of fibers could deposit in these regions. Many animal species, including rats and mice, are obligate nose breathers so fibers pass only through the nasal passages and are always subject to nasopharyngeal filtering. Humans, monkeys, and dogs breathe both orally and nasally (oronasal). During oral respiration, larger fibers and clumps of fibers can bypass the filtering of the upper respiratory tract and be inhaled directly into the larynx/trachea, especially during exertion (e.g., exercise or work), thereby altering deposition. This distinction is important when comparing results of inhalation studies conducted in different species.

Fibers in the lower respiratory tract deposit by combined mechanisms of impaction, interception, sedimentation, and diffusion. The relative contribution of each mechanism depends on the fiber characteristics and region-specific airway anatomy, and respiratory flow rates (air velocities). Interception is heavily influenced by fiber length. Where the physical length of the fiber greatly exceeds the aerodynamic diameter, interception can be underpredicted by modeling the center of gravity of the fiber because the length of the fiber will determine its propensity to intersect with the airway. Sedimentation is related to the mass of the fiber, as well as the aerodynamic diameter, but generally occurs at lower velocities in smaller airways. Diffusion occurs from interactions of the fibers with the movement of air molecules; this Brownian motion increases with decreasing fiber size (<0.5 μm diameter).

The conducting airways beyond the nasopharyngeal region serially bifurcate into airways of decreasing internal diameters that restrict the size of fibers deposited in these regions. Fiber length enhances bronchial deposition via interception, especially fibers exceeding lengths of 10 μm (Sussman et al., 1991a, b). The aerodynamic diameter of fibers that are more likely to deposit in the tracheobronchial region is in the range of 1−5 μm. Fibers with an aerodynamic diameter of <1 μm are more likely to deposit in the bronchioles and the alveoli (ICRP, 1994). As reviewed in Aust et al. (2011), some studies have demonstrated that short fibers (<5 μm) are present in substantially greater numbers than long fibers (>5 μm) when examining the whole lung (Churg, 1982). Whether this is due directly to deposition of smaller fibers or the breakage of larger fibers over time is not known (Bernstein et al., 1994; Davis, 1994). Although information is limited on how fibers get to the pleura, fibers observed in pleural tissue from mesothelioma cases are more likely to be short [<5 μm; (Suzuki et al., 2005)].

Fibers with aerodynamic characteristics conducive to depositing in the respiratory bronchioles and alveoli may cause pulmonary fibrosis and other associated diseases. Regardless of shape, mineralogy, or concentration, the majority of fibers that are small enough to reach the alveoli are deposited at the alveolar duct bifurcations (Brody and Roe, 1983). Deposition is controlled by air flow characteristics and is greatest at the bifurcations that are closest to the

terminal bronchioles (Brody et al., 1981). Furthermore, deposition in the bifurcations is consistent across laboratory animal species (Warheit and Hartsky, 1990). Alveolar deposition is limited when fiber length approaches 40 μm (Morgan et al., 1978). However, alveolar deposition of fibers can occur with high aspect ratios and lengths ranging from <1 μm to >200 μm long (Morgan et al., 1978). All fibers having an aerodynamic diameter less than approximately 2 μm, which includes LAA, meet the physical criteria necessary for deposition in the deeper regions of the respiratory tract at the level of the terminal bronchioles or alveoli.

3.2. CLEARANCE MECHANISMS

Once fibers deposit on the surface of the respiratory tract, they may be removed (cleared) in several ways—including physical clearance, dissolution, phagocytosis, encapsulation, or transcytosis. Some of these mechanisms, such as dissolution of the fibers or removal via the mucociliary apparatus, can result in the fibers being cleared from the body (see Figure 3-1). Other clearance mechanisms may remove fibers from the surface of the respiratory tract but result in transport of the fibers to different locations or tissues by translocation. Translocation of fibers from the terminal bronchioles and alveoli into the peribronchiolar space, lymph nodes, and pleura has been implicated in disease causation (e.g., pleural plaques, mesothelioma) (Dodson et al., 2001). In human studies, the translocation of asbestos fibers following inhalation has been observed to varying degrees throughout the pulmonary and extrapulmonary tissues of the respiratory system (Dodson et al., 2005; Dodson et al., 2001; Kohyama and Suzuki, 1991; Suzuki and Kohyama, 1991; Armstrong et al., 1988), as well as to other organs, including the brain, kidney, liver (Miserocchi et al., 2008), and ovaries (Langseth et al., 2007). In many cases, the type of fiber is not defined, and the individual exposure information not available. Fibers that are not cleared can remain at the epithelial surface or enter the parenchymal tissue of the lung. Retention of fibers in the human thoracic region generally shows two distinct phases. The first, on the order of 24 hours, is considered to represent mucociliary clearance to the gastrointestinal tract from the conducting airways and bronchioles; the second represents clearance from the alveolar region (ICRP, 1994).

Berry (1999) provided a review of the animal toxicity literature specifically for fiber clearance. There are limited data on clearance patterns based on autopsy studies in humans. Two studies estimated clearance half-life for amphibole asbestos (~20 years) as compared with chrysotile asbestos [~10 years (Finkelstein and Dufresne, 1999; Churg and Vedal, 1994)]; in evaluating the data on lung fiber burden, Berry et al. (2009) estimated the range of the half-life for crocidolite to be between 5 and 10 years. Generally, studies have focused on determining the size and type of asbestos retained in specific tissues (Suzuki et al., 2005; McDonald et al., 2001; Suzuki and Yuen, 2001; Dumortier et al., 1998; Gibbs et al., 1991; Dodson et al., 1990) and do not discuss changes in fiber content since exposure due to possible clearance. Sebastien et al.

(1980) concluded that lung fiber burden could not be used as an accurate reflection of pleural fiber burden.

3.2.1. Physical and Physicochemical Clearance of Fibers

Mechanisms of physical and physicochemical clearance of fibers depend on the fiber size, physicochemical characteristics, and site of deposition (IOM, 2006). Physical clearance includes mechanical mechanisms, including transport via the mucociliary apparatus, macrophage uptake, and translocation. Fibers can also translocate due to physical forces associated with the mechanics of respiration [e.g., expansion, contraction of the rib cage (Davis, 1989)]. Physicochemical clearance of fibers includes dissolution and breakage of fibers.

3.2.1.1. *Mechanical Reflex Mechanisms*

Fibers deposited in the nasal passages can be removed by all clearance mechanisms. When breathing occurs through the nose, many fibers are filtered by the turbulent airflow in the nasal passages, impacting against the hairs and nasal turbinates, as well as becoming entrained in mucus in the upper respiratory tract where they can be subsequently removed by mucociliary action (described below) or reflexive mechanical actions such as coughing or sneezing. Dissolution can also occur in this region, especially for soluble fibers.

3.2.1.2. *Mucociliary Clearance*

Physiological mechanisms include mucociliary escalator movement and how specific cells or mechanisms in various regions of the respiratory tract respond and attempt to detoxify or remove deposited fibers.

The mucociliary escalator removes fibers through ciliary movement of the sticky mucus lining much of the respiratory tract (Wanner et al., 1996; Churg et al., 1989). Fibers removed from the conducting airways through this mechanism are coughed out or swallowed and enter the digestive tract where they may adversely affect the gastrointestinal tissue, enter the blood stream, or be excreted. Clearance of fibers via mucociliary action is usually complete within hours or days (Albert et al., 1969).

The mucociliary escalator extends only down to the level of the terminal bronchioles and not to the alveoli. Thus, the particles deposited in the alveolar region of the lung cannot be cleared through this process. Particles can reach the mucociliary escalator from the alveoli either by way of surface fluids that are drawn onto the mucociliary escalator by surface tension or by travelling through lymphatic channels that empty onto the escalator at bronchial bifurcations.

Although ingestion is a potential route of exposure due to swallowing of material from the mucociliary escalator, limited research has examined clearance (e.g., translocation) of fibers following ingestion, and no clearance studies are available specific to LAA. An early study to examine gastrointestinal tissue response to asbestos fibers is not truly representative of a natural

ingestion exposure, as the researchers directly injected a suspension of amosite fibers into the duodenal wall (Meek and Grasso, 1983). This study, however, also examined oral ingestion of amosite in healthy animals and those with gastrointestinal ulcers to determine whether translocation of fibers occurs through ulcers. Following injection of amosite, granulomatous lesions were observed. Ingestion of the same material resulted in no such lesions or in any other histopathological changes in either healthy or rats compromised with ulcers. Thus, no translocation was observed from either the healthy or the compromised rat gastrointestinal tracts in this study. Truhaut and Chouroulinkov (1989) examined the effects of chrysotile and crocidolite ingestion in Wistar rats. No translocation was observed. No further studies have been found on clearance or translocation of fibers from the gastrointestinal tract.

Some fibers are not cleared via the mucociliary escalator from the respiratory tract, leading to an accumulation with time (Case et al., 2000; Finkelstein and Dufresne, 1999; Jones et al., 1988). The fibers that remain in the conducting airways and alveolar regions may undergo a number of processes including translocation, dissolution, fragmentation, splitting along the longitudinal axis, or encapsulation with protein and iron. Available data indicate prolonged clearance from the thoracic region of long (>5 μm) or short amphibole fibers (Coin et al., 1994; Tossavainen et al., 1994).

The prolonged clearance times for long amphibole fibers have led some investigators to conclude that long fibers (>5 μm) rather than short amphibole fibers (i.e., LAA) are predominant in the cause of disease due to their persistence in the lung (Mossman et al., 2011; ATSDR, 2003). However, others argue that fibers of all lengths induce pathological responses and urge caution in excluding, based on length, any population of fibers from consideration as possibly contributing to the disease process (Aust et al., 2011; Dodson et al., 2003). Respirable-sized fibers of LAA have been identified in air samples from Libby, MT and in airborne fibers suspended from both Libby vermiculite ore and in the exfoliated product from that ore (length range from 1 μm to 20−30 μm, with average length of 7 μm; width range from 0.1−2 μm, with average of 0.5 μm; see for details Appendix B and Appendix C). Based on fibers counted by the TEM analytical method (ISO 10312), the majority of counted fibers are respirable (see Figure 2-10).

3.2.1.3. *Phagocytosis by Alveolar Macrophages*

The principal clearance pathway for short, insoluble fibers deposited in the alveoli is through phagocytosis by macrophages. Impaction of durable fibers in the deeper region of the respiratory tract stimulates activation of alveolar macrophages. In vitro and in vivo studies clearly indicate that macrophage cells play a role in the translocation of fibers (Dodson et al., 2000a; Castranova et al., 1996; Brody et al., 1981; Bignon et al., 1979). These studies demonstrated the presence of asbestos fibers in cell cytoplasm where the fibers can be transported in association with cytoskeletal elements to the proximity of the cell nucleus.

Alveolar macrophages that have phagocytized insoluble fibers migrate to the bronchoalveolar junctions along epithelial surfaces to ciliate bronchioles where they are removed (Green, 1973). Alternatively, alveolar macrophages that have phagocytized insoluble fibers can also migrate through the epithelial wall into the interstitial space and enter the lymphatic system (Green, 1973).

A number of processes can disrupt the normal phagocytic function of alveolar macrophages, such as the overwhelming of phagocytosis and the mucociliary escalator by an excessive number of particles (often termed "overload"), or the attempted phagocytosis of fibers with lengths that exceed the dimensional capacity of the macrophage [>15−20 μm depending on species; often termed "frustrated phagocytosis"; (NIOSH, 2011)]. Any of these processes can induce inflammatory and fibrogenic responses. Limited inhalational laboratory animal studies exist at concentrations of fibers insufficient to induce overload; therefore information is insufficient to determine mechanisms of inflammation at lower doses (Mossman et al., 2011).

Fibers that are too long to be easily engulfed by the alveolar macrophage can stimulate the formation of "asbestos bodies." Asbestos bodies are fibers that become coated with proteins, iron, and calcium oxalate as a result of prolonged residence in the lung where they can remain throughout an individual's lifetime. Due to their iron content, histological stains for iron have long been used to identify them in tissue; thus, they are sometimes called "ferruginous bodies." The mechanisms that result in the formation of asbestos bodies are poorly understood, although most appear to be formed around amosite fibers (Dodson et al., 1996). The iron in the coating is derived from the asbestos fiber, cells, or medium surrounding the fiber and can remain highly reactive (Lund et al., 1994; Ghio et al., 1992). Asbestos bodies comprise a minor portion of the overall fiber burden of the lung. Once fully coated, fibers within asbestos bodies may or may not participate directly in asbestos disease. The presence of iron in the coating could provide a source for catalysis of reactive oxygen species (ROS).

3.2.1.4. *Epithelial Transcytosis*

In addition to phagocytosis by alveolar macrophages, fibers deposited on type I alveolar epithelial cells may also be subjected to transcytosis with subsequent sequestration to the alveolar interstitium (Sturm, 2011). Fiber length may play a key role in this aspect of clearance.

3.2.1.5. *Translocation*

Translocation represents the movement of intact fibers along the alveolar epithelial surface towards the terminal bronchiole, or into and through the epithelium. Translocation typically occurs via drainage of the alveolar macrophages to the lymphatics, but transcytosis of fibers by type I alveolar epithelial cells can also result in transport to the interstitium. The relative contribution of a specific mechanism and translocation route depends both on fiber characteristics and the tissue upon which the fibers deposit. Fiber translocation depends on the

physicochemical characteristics of the deposited fibers, including two-dimensional size (length and width), durability, solubility, and reactivity. This translocation is aided by high durability and an inflammation-induced increase in permeability, but could be hindered by fibrosis.

Translocation of fibers to extrapulmonary tissues has been reported in multiple studies; however, the precise mechanism is still unknown. This process was recently reviewed by Miserocchi et al. (2008). Fibers have been identified in all of the analyzed locations, including pleural plaques and mesothelial tissue (i.e., pleural or peritoneal) in miners, brake workers, insulation workers, and shipyard workers (Roggli et al., 2002; Dodson et al., 2000b; Churg, 1994; Kohyama and Suzuki, 1991). However, amphibole fibers were less prevalent than chrysotile fibers in the pleura and mesothelial tissues (Kohyama and Suzuki, 1991; Sebastien et al., 1989; Armstrong et al., 1988; Churg, 1988; Bignon et al., 1979). Confocal microscopic observations of rats inhalationally exposed to amosite fibers showed that fibers were present on the parietal pleural surface 7 days postexposure and more than twofold thickening of the pleura was noted (Bernstein et al., 2011). Bignon et al. (1979) also reported increased amphibole fibers in the thoracic lymph nodes. Conflicting results from another inhalational rat study do not indicate any evidence of fiber translocation from the central to peripheral compartments, although this could be due to the short duration of the study [29 days postexposure; (Coin et al., 1992)].

Few studies have examined the size distribution of fibers translocated to specific tissues. For example, one early study suggested that longer amphibole fibers predominate in the lung (Sebastien et al., 1980); other studies showed that the fiber-length distribution was the same by fiber type regardless of location (Kohyama and Suzuki, 1991; Bignon et al., 1979). Dodson et al. (1990) observed that the average length of fibers found in the lung (regardless of type) was longer than that of fibers found in the lymph nodes or plaques. Most fibers at all three sites were short (<5 μm). Similar results were observed in a later study by this group [i.e., Dodson et al. (2000b)] which examined tissue from 20 individuals with mesotheliomas, most with known nonoccupational asbestos exposures.

Transplacental transfer of both asbestos (tremolite, actinolite, and anthophyllite) and nonasbestos fibers occurs in humans, as measured in the placenta and in the lungs of stillborn infants (Haque et al., 1998; Haque et al., 1996; Haque et al., 1992; Haque and Kanz, 1988). It is hypothesized that maternal health might influence the translocation of fibers, as some of the mothers had preexisting health conditions [e.g., hypertension, diabetes, or asthma; (Haque et al., 1992)]. This group also measured transplacental translocation in a mouse study and observed early translocation of crocidolite fibers through the placenta in animals exposed via tail-vein injection (Haque et al., 1998). These transplacental migration studies did not evaluate the source or levels of exposure, only the presence of fibers in the body during early life stages in mice and humans.

3.2.1.6. *Dissolution and Fiber Breakage*

Dissolution, or the chemical breakdown of fibers, is another method of physical removal of fibers from the respiratory tract. This process varies, depending on the solubility and chemical composition of the fibers, as well as the physiological environment. Dissolution can occur in the extracellular lung fluids or in the macrophage phagolysosome; the former can make the breakdown products available for uptake into the blood. Studies performed in vitro to determine dissolution rate of fibers attempt to mimic the extracellular lung fluids and macrophage-phagolysosome system to understand the length of time that fibers remain in the system (Rendall and Du Toit, 1994). Fibers can also be physically degraded through splitting or breakage. These smaller fragments are then more easily removed by phagocytosis or translocation.

3.3. DETERMINANTS OF TOXICITY

Multiple determinants of fiber toxicity, including dimension (length, width, aspect ratio, and surface area), chemical characteristics (solubility, charge, and surface chemistry) and durability (dissolution, breakage) have been studied relative to specific biological responses to fibers and recently reviewed (Aust et al., 2011; Broaddus et al., 2011; Bunderson-Schelvan et al., 2011; Case et al., 2011; Huang et al., 2011; Mossman et al., 2011).

3.3.1. Dosimetry and Biopersistence

The dosimetry factors discussed in the previous sections are major factors influencing toxicity, as the initial deposition sites in the respiratory tract determine the subsequent clearance mechanisms (Brain and Mensah, 1983); solubility and composition also influence the biopersistence of deposited fibers (Maxim et al., 2006; Bernstein et al., 2005a). Thus, fiber toxicity has been associated with dose, density, dimensions, and durability, and likely involves a combination of these and other factors. To the extent that a fiber is resistant to the clearance mechanisms described in Section 3.1., biopersistence becomes a determinant of toxic response. Fiber durability is a determinant of retained dose at the site of deposition and likely plays a role in chronic inflammation, fibrosis, and lung burden following chronic exposure to fibers. Biopersistence is influenced by fiber characteristics such as size (length, width) and chemistry. Hesterberg et al. (1998a) and Hesterberg et al. (1998b) observed that, in general, increased in vitro solubility decreases in vivo biopersistence. Several supporting studies reported increased levels of crocidolite, tremolite, and amosite in respiratory diseases (asbestosis, mesothelioma) compared to chrysotile and controls (Churg and Vedal, 1994; Churg et al., 1993) and found that chrysotile has a lower biopersistence than amphibole fibers (Churg and Vedal, 1994; Wagner et al., 1974). The role of fiber size in biopersistence was examined by Bernstein et al. (2004) who found that the clearance half-time of longer fibers (>20 μm; 1.3 days) was less than that of shorter fibers (<5 μm; 23 days) for one form of chrysotile. Biopersistence is the basis of

short-term in vitro testing required for new fibers introduced to the market (Maxim et al., 2006; Bernstein et al., 2005a).

Fiber burden analysis of human tissues is frequently employed to determine the presence of specific fiber type and size in disease (Aust et al., 2011; Case et al., 2011). The majority of these studies have focused on lung tissue, but studies have also examined fiber burden in other tissues of interest, including lymph nodes and pleural tissues (Bunderson-Schelvan et al., 2011; Dodson and Atkinson, 2006; Dodson et al., 2001; Dodson et al., 2000b; Boutin et al., 1996). While informative, analysis of tissue fiber burden has some limitations, including differences in methodologies that hinder comparisons between laboratories, as well as potential cross contamination with other tissues. A further limitation of fiber burden analysis is that it is generally performed on tissue digests, making it difficult to show fiber dimensions at specific tissue locations. The use of TEM analysis can determine length and width of fibers found in tissues from exposed individuals.

3.3.2. Biological Response Mechanisms

Although numerous studies have examined specific mechanisms of toxicity for many different fiber types, the results often are contradictory or do not account for dosimetry, and thus, only limited conclusions can be made for fibers in general. Research has focused mainly on the role of length, width, and durability in fiber toxicity. The relative contribution of fiber dimensions and composition that drive the toxicity of fibers remains poorly understood due to the difficulty in experimentally evaluating each determinant independently. Further, as can be appreciated from an evaluation of Table 3-2, the determinants of toxicity induce various toxic responses that represent interrelated biological activities (e.g., chronic inflammation, oxidative stress, and genotoxicity), making a clear causal relationship or relative contribution of any individual endpoint difficult to determine. The information described below focuses on in vivo studies that have examined determinants of amphibole fiber toxicity for some major specific biological responses. A more detailed discussion of potential tissue response mechanisms can be found in the mode of action (MOA) section (see Section 4). Table 3-2 summarizes the major determinants of toxicity as fiber-host interactions along the continuum of source-exposure-dose-response used for risk assessment.

Table 3-2. Determinants of fiber toxicity

Biological activity	Length	Width	Mineralogy	Biopersistence	Morphology	Density	Surface area	Surface chemistry (charge, metal ions)
ROS production	+++	++	+++	+++				+++
Genotoxicity (direct or indirect)	+++	++	++	++	++		+	++
Inflammation	++	++	++	+++		++	+++	+++
Carcinogenesis	+++	++		++			+	+

Note: This table describes the potential role for various fiber determinants in biological activity. Level of confidence is based on available literature for all fiber types. (+++, suggested role with substantial data support; ++, suggested role but data not conclusive; +, suggested role but insufficient data). Level of confidence based on recent literature reviews (Aust et al., 2011; Case et al., 2011; Mossman et al., 2011; ATSDR, 2003).

Limited studies have examined the role of specific fiber determinants in autoimmune disease or pulmonary function, and therefore these endpoints are not discussed in this section.

3.3.2.1. *Inflammation and Reactive Oxygen Species (ROS) Production*

Inflammation is an important biologic response to fibers and is related to multiple pathways following exposure. Fiber exposure leads to ROS production, which in turn has been shown to increase the activation of inflammatory and immune signaling pathways (Mossman et al., 2011). Inflammation often occurs at the site of fiber deposition; therefore those fiber characteristics that play a role in fiber deposition (e.g., length and width) will also play a role in chronic inflammation. Further, those additional characteristics that lead to ROS production (e.g., surface chemistry) may also contribute to induction of chronic inflammation. Acute inflammation in response to asbestos further contributes to chronic inflammation with the activation of signaling pathways (e.g., mitogen-activated protein kinase [MAPK]) that lead to the release of proinflammatory cytokines.

Increased ROS production is hypothesized to result from frustrated phagocytosis and activation of signaling pathways in various cell types or through iron catalysis, which may account for the differential induction of ROS due to variable intrinsic or acquired iron by different fibers (Aust et al., 2011). Either indirect or direct ROS release following exposure to fibers may in turn lead to increased damage to DNA or other biological molecules.

3.3.2.2. *Genotoxicity*

Genotoxicity (including mutagenicity) from exposure to fibers likely involves multiple pathways, and the role of specific fiber determinants is not completely understood. This genotoxicity is generally described as direct (e.g., fiber interference with spindle formation) or indirect (e.g., ROS production). A recent review by Huang et al. (2011) examines the role of fiber determinants in genotoxicity and mutagenicity in detail. Briefly, research studies designed to examine the role of fiber dimensions or surface characteristics in genotoxicity are limited, and are mainly in vitro work. In general, fiber dimensions are expected to play a role in genotoxicity. Long thin fibers are associated with interference with the spindle apparatus during mitosis, as well as increased ROS/reactive nitrogen species (RNS) production through frustrated phagocytosis, which in turn may lead to increased genotoxicity. Similarly, increased iron associated with fibers may also lead to increased ROS/RNS production and increased genotoxicity.

3.3.2.3. *Carcinogenicity*

The work by Stanton et al. (1981) examined fiber type and dimension in relation to carcinogenicity in an animal model resulting in the “Stanton Hypothesis” that identifies fiber size as a major determinant of toxicity. This study focused on amphibole asbestos due to difficulties

in measurements of chrysotile (Stanton et al., 1981). However, this hypothesis was formulated from the results of studies where fibers were imbedded in agar and implanted against the pleura, thereby inducing sarcomas in rats (Stanton et al., 1981; Stanton and Wrench, 1972). The results of these studies led Stanton and colleagues to state that "carcinogenicity of fibers depended on dimension and durability rather than on physicochemical properties" (Stanton et al., 1981). However, the study design did not allow for the influence of pulmonary clearance mechanism, as the implant was made to the outer pleural tissue. Additionally, it is unknown how the dissolution of fibers in the agar influenced findings. All fibers tested (including mineral wool and fiber glass) induced sarcomas. While these studies showed high correlation between disease and longer (>8 μm), thinner (<0.25 μm) fibers, high correlations were noted in other size categories as well. The ability of these studies to define the dimensional aspects of fibers (length and width cutoffs) that determine toxicity is clearly limited because major aspects of toxicokinetics and biological activity in the lung tissue are not included in the experimental design. Additionally, these studies do not rule out the potential role of shorter (<4 μm) and wider (>1.5 μm) fibers (Stanton et al., 1981). This latter point was further confirmed by Pott et al. (1987) and Pott et al. (1974) who showed that shorter fibers (<10 μm in length) could also induce tumors in rats following intraperitoneal injection. Although informative, both of these study designs bypass normal physiological deposition and clearance mechanisms that would be observed following inhalation of fibers, an important consideration when comparing these types of studies.

Suzuki et al. (2005) also examined the role of fiber dimensions in mesothelioma, but through fiber burden analysis of human mesothelioma tissue. Fibers were identified by high-resolution analytical electron microscopy from digested or ashed lung and mesothelial tissues samples taken from 168 cases of malignant mesothelioma. Their results were that the majority of fibers (89%) were shorter than or equal to 5 μm in length, and generally (92.7%) smaller than or equal to 0.25 μm in width, which on initial consideration might seem contrary to the "Stanton Hypothesis." However, this study is also not without interpretation challenges, as, longer fibers that had been translocated to the mesothelial tissue may have broken down by dissolution or fiber breakage during life, or the digestion and ashing process may itself have degraded longer fibers to shorter fibers.

Analyses of fiber dimensions in exposed humans have not led to any clear determinants of toxicity for fibers in general. Lippmann (1990) correlated fiber length with disease status in exposed humans and concluded that asbestosis was associated with shorter (>2 μm), thicker (>0.15 μm) fibers; mesothelioma with longer (>5 μm), thinner (<0.1 μm) fibers; and lung cancer with longer (>10 μm), thicker (>0.15 μm) fibers. Throughout the years, some laboratory animal studies have demonstrated a role for longer (>20 μm) and thinner (<0.3 μm) fibers in lung cancer (Berman et al., 1995) or mesothelioma (Miller et al., 1999), while yet other laboratory animal studies have suggested a role for shorter structures (<0.5−5 μm) in disease based in part on increased numbers in dust clouds and in lung retention (Dodson et al., 2003). Some human

epidemiology studies have supported the role of longer (>20 μm), thinner (<0.3 μm) fibers in lung cancer (Loomis et al., 2010; Berman and Crump, 2008; Dement et al., 2003). However, these results have not been confirmed in other studies and are in some cases contradicted. For instance, Churg and Vedal (1994) did not find an association between fiber length and cancer. However, McDonald et al. (2001) observed that shorter fibers (<6 μm) were more abundant in diseased tissues than longer fibers (>10 μm), and Dodson et al. (1997) concluded that fibers of all sizes are associated with increased mesothelioma risk. More recently, Berman (2011) performed a quantitative analysis of previous studies and demonstrated that differences in biological potency among various amphibole fiber types may be due to differences in their dimensions, particularly fiber length. In all cases, the analytical methods used need to be carefully described in order to draw any conclusions across studies.

3.4. FIBER DOSIMETRY MODELS

Modeling of fiber deposition has been examined for various fiber types [e.g., refractory ceramic fibers, chrysotile asbestos (Sturm, 2009; Zhou et al., 2007; Lentz et al., 2003; Dai and Yu, 1998; Yu et al., 1997; Coin et al., 1992)], but not for LAA. In general, the pattern of deposition for fibers is expected to have some similarities to the well-studied deposition pattern for particles that are essentially spherical [reviewed in (ICRP, 1994)]. For example, the multipath particle dosimetry model (Brown et al., 2005; Jarabek et al., 2005) uses information on the physical properties of the particles (length, width [also called bivariate distribution] and density), the anatomy and architectural features of the airways, airflow patterns that influence the amount and the location of the deposition of the particles, and the dissolution and clearance mechanisms that are operative to estimate the retained dose in the target tissue. The site of fiber deposition within the respiratory tract has implications related to lung retention and surface dose of fibers. It should be noted that differences in airway structure and breathing patterns across life stages (i.e., children, adults) change the depositional pattern of differently sized fibers, possibly altering the site of action and causing differential clearance and health effects (see Section 4.7).

3.5. SUMMARY

Although oral and dermal exposure to fibers does occur, inhalation is considered the main route of human exposure to mineral fibers, and therefore, it has been the focus of more fiber toxicokinetic analyses in the literature. Similar to other forms of asbestos, exposure to LAA is presumed to be through all three routes of exposure; however, this assessment specifically focuses on the inhalation pathway of exposure. Generally, fiber deposition in the respiratory tract is fairly well defined based on fiber dimensions and density, although the same cannot be said for fiber translocation to extrapulmonary sites (e.g., pleura). The deposition location within the pulmonary and extrapulmonary tissues plays a role in the clearance of the fibers from the organism.

Fiber clearance from the respiratory tract can occur through physical and biological mechanisms. Limited mechanistic information is available on fiber clearance mechanisms in general, and no information specific to clearance of LAA fibers is available. Fibers have been observed in various pulmonary and extrapulmonary tissues following exposure, suggesting translocation occurs to a variety of tissues. Studies have also demonstrated fibers may be cleared through physical mechanisms (coughing, sneezing) or through dissolution of fibers.

Multiple fiber characteristics (e.g., dimensions, density, and durability) play a role in the toxicokinetics and toxicity of fibers. There is extensive literature examining a variety of fiber determinants and their role in disease, with a focus on fiber length, width, and durability; however, these studies are often contradictory, making conclusions difficult for fibers in general. This is in part due to the variety of fibers analyzed, inadequate study design, and/or lack of information on fiber dimensions in earlier studies. However, due to the importance in understanding the role of these fiber determinants in the biological response, careful attention has been paid to these fiber characteristics when analyzing research studies on LAA and asbestiform tremolite, an amphibole fiber that comprises part of LAA (see Appendix D). No toxicokinetic data are currently available specific to LAA, winchite, richterite, or tremolite. When available, fiber characteristic data are presented in the discussion of each study in relation to the toxic endpoints described.

4. HAZARD IDENTIFICATION OF LIBBY AMPHIBOLE ASBESTOS

This section discusses the available data derived from studies of people exposed to Libby Amphibole asbestos (LAA),[8] either at work or in the community, and from various laboratory studies. The effects in humans (e.g., parenchymal damage and pleural thickening, lung cancer, and mesothelioma) are supported by the available LAA experimental animal in vivo and laboratory in vitro studies. The health effects from asbestiform tremolite exposure, one of the constituent minerals of LAA, reported in both human communities and laboratory animals, are consistent with the human health effects reported for LAA. Studies examining the health effects of exposure to winchite or richterite alone were not available in the published literature. The review presents noncancer and cancer health effects observed from exposures to LAA.

4.1. STUDIES IN HUMANS—EPIDEMIOLOGY

The LAA epidemiologic database includes studies based in occupational settings and community-based studies of workers, family members of workers, and others in the general population. Occupational epidemiology studies have been conducted at two worksites where workers were exposed to LAA: the vermiculite mine and mill at the Zonolite Mountain operations near Libby, MT, and a manufacturing plant using the vermiculite ore in Marysville, OH. Community-based studies have also been conducted among residents around Libby, MT, (ATSDR, 2001b, 2000) and in an area around a manufacturing plant producing vermiculite insulation in Minneapolis, MN (Alexander et al., 2012).

The epidemiology studies of people exposed to LAA were primarily identified through EPA's specific knowledge of the research endeavors that have taken place since recognition in the 1970s of the asbestos contamination from the vermiculite mined around Libby, MT. These studies were conducted by NIOSH, McGill University, University of Cincinnati, and the ATSDR. Analyses by other researchers using the data collected through these studies as well as other studies of people exposed to LAA were also identified through contacts with these research groups and through "forward searching" through Web of Science for references citing the key publications describing the initial studies [i.e., Amandus et al. (1987a), Amandus et al. (1987b), McDonald et al. (1986a), Lockey et al. (1984), and Peipins et al. (2003)].

Figure 4-1 depicts the sets of studies conducted by different groups of researchers in Libby, MT and in two areas with plants that used Libby vermiculite in various production processes (fertilizer and other lawn products in Marysville, OH and insulation materials in Minneapolis, MN). These studies have examined cancer and noncancer mortality, pulmonary

[8]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.

effects detected through x-ray examinations, pulmonary function tests or respiratory symptoms, autoimmune diseases, and prevalence of autoantibodies.

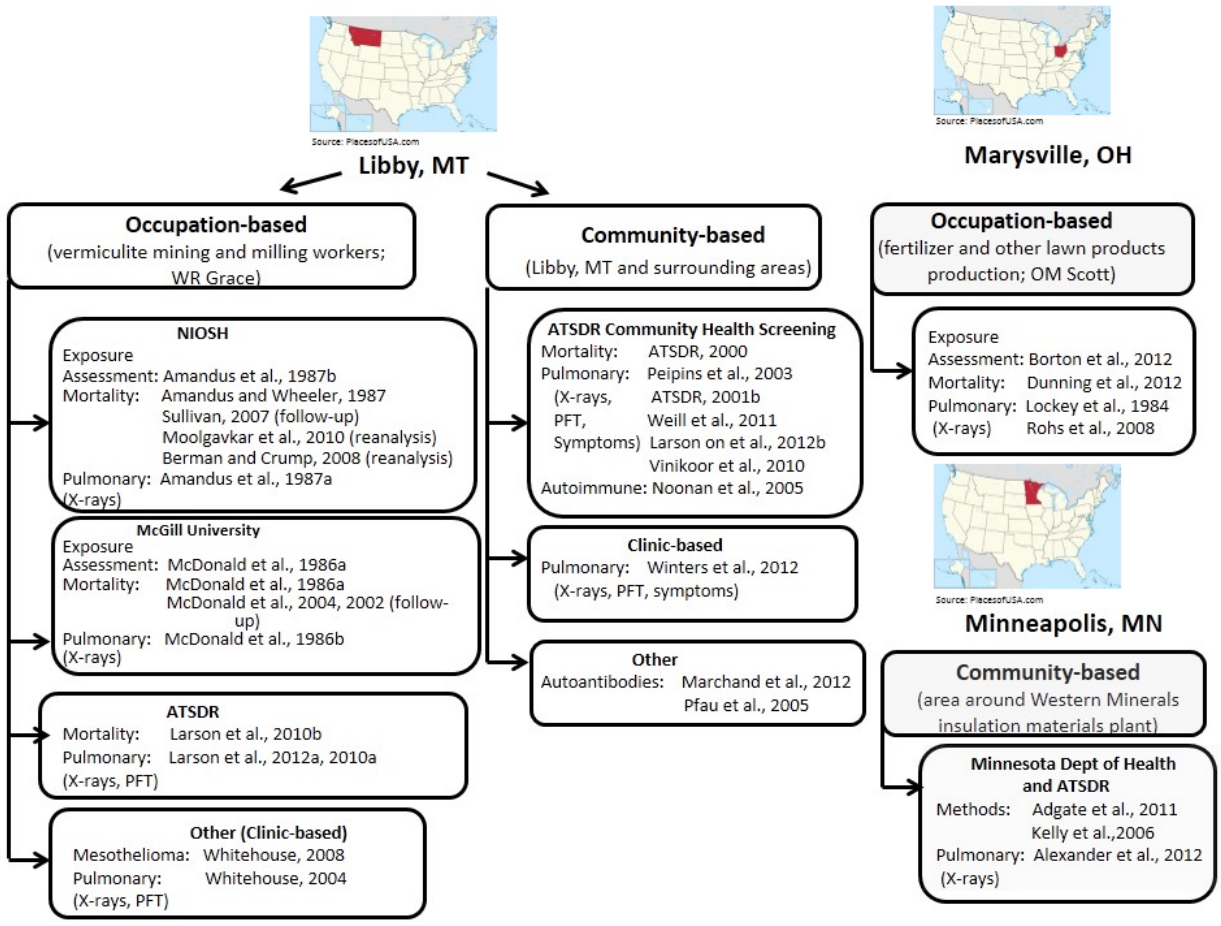


Figure 4-1. Investigations of populations exposed to LAA. Moolgavkar et al. (2010) and Berman and Crump (2008) used the Libby worker cohort assembled by Sullivan (2007) to estimate cancer potency factors; these analyses are summarized in Section 5.4.5.3.1.

PFT = pulmonary function testing.

The various populations and study designs are summarized in Section 4.1.1, and the results of these studies are presented in subsequent sections: respiratory effects other than cancer (see Section 4.1.2), other noncancer effects (see Section 4.1.3), and cancer (see Section 4.1.4). A brief summary of the epidemiology studies of environmental or residential exposure to asbestiform tremolite or asbestiform tremolite-chrysotile mixtures and to crocidolite is presented in Section 4.1.5.

4.1.1. Overview of Primary Studies

4.1.1.1. *Studies of Libby, MT Vermiculite Mining and Milling Operations Workers*

4.1.1.1.1. ***Description of vermiculite mining and milling operations in Libby, MT.*** The vermiculite mining and milling operations have been described in considerable detail (ATSDR, 2000; Amandus et al., 1987b). Briefly, an open-pit vermiculite mine, located several miles east of Libby, began limited operations in 1923, and production increased rapidly between 1940 and 1950. The mining and milling operations continued until 1990 (ATSDR, 2008, 2000). Some of the important features of the operations that affected exposure to workers or community members are described below.

The drilling and blasting procedures used in the open-pit mining operations generated considerable dust exposures, including silica dust, although the mining operations were associated with lower intensity exposures compared to the milling operations. Amandus et al. (1987b) noted that in 1970, a new drill with a dust-control bagging system aimed at limiting workplace exposure was introduced to the mining operations.

Another aspect of the operations was the loading of ore for railroad shipment. From 1935−1950, railroad box cars were loaded at a station in Libby. In 1950, the loading station was moved to a loading dock on the Kootenai River, 7 miles east of town. Tank cars were used from 1950−1959 and then switched to enclosed hopper cars in 1960.

The milling operations used a screening or sifting procedure to separate vermiculite flakes from other particles and increase the concentration of vermiculite ore from approximately 20% in the bulk ore to 80−95% in the resulting product. A dry mill began operating in 1935, and a wet mill began operating in the 1950s in the same building as the dry mill. One of the primary changes in the conditions in the dry mill was the installation of a ventilation fan in 1964. Exposure to LAA inside the mill was estimated to be 4.6 times higher preceding this installation (McDonald et al., 1986a). This ventilation fan resulted in higher amphibole fiber exposures in the mill yard until 1968, when the exhaust stack for the fan was moved to route the exhaust away from the mill area (Amandus et al., 1987b); although these changes reduced the exposure potential within the mill operations, they also resulted in spreading the LAA through the surrounding areas. Other changes to the milling operations in the 1970s included replacement of hand bagging and sewing with an automatic bagging machine (1972), pressurization of the skipper control room used for transferring the ore concentrate from the mill to a storage site (1972), and construction of a new wet mill (1974). Closing of the old dry and wet mills in 1976 had a substantial impact on exposures at the worksite. In 1974, a new screening plant used to size-sort the ore concentrate was constructed at the loading dock near the river.

Two processing plants operated within the town of Libby (ATSDR, 2001b). These expansion or exfoliation plants heated the ore concentrate, resulting in additional release of the LAA fibers in the area.

4.1.1.1.2. ***Descriptions of cohorts of Libby, MT vermiculite mining and milling operations workers.*** The two cohort studies conducted in the 1980s (by NIOSH and McGill University) were similar in terms of populations and study design. For example, both studies included workers who had worked for at least 1 year. Amandus and Wheeler (1987) included men hired before 1970 (n = 575), with follow-up through December 31, 1981, while McDonald et al. (1986a) included men hired before 1963 (n = 406) with follow-up through 1983. A subsequent analysis extended this follow-up through 1999 (McDonald et al., 2004). Another analysis of the Libby, MT workers expanded the NIOSH cohort to include all workers, regardless of duration of employment (Sullivan, 2007). The total sample (n = 1,672 white men) included 808 workers who had worked for less than 1 year. These short-term workers had been excluded from the previous studies. Analyses presented in the report were based on follow-up from 1960−2001. Larson et al. (2010b) reconstructed a worker cohort based on company records and analyzed mortality risks through 2006. This study included 1,862 workers (including a small number of women). Other differences between these two most recent studies include a lower cumulative exposure estimate in Larson et al. (2010b) (median 4.3 fibers/cc-yrs) compared with Sullivan (2007) (median 8.7 fibers/cc-yrs). Part of this difference could reflect the increase of approximately 12% in the total sample size, most of whom are likely to have had low exposures, in Larson et al. (2010b), as well as the use of a higher estimated exposure intensity for the workers with "common laborer" or unknown job categories in Sullivan (2007). A more in depth examination of the reasons for this difference is not possible based on the available information in these publications.

4.1.1.1.3. ***Fiber exposure estimation in Libby, MT mining and milling operations.*** The exposure assessment procedures used in the NIOSH and McGill University investigations of the Libby, MT mining and milling operations relied on the same exposure measurements and used similar assumptions in creating exposure estimates for specific job activities and time periods (see Table 4-1). In brief, available air sampling data were used to construct a job-exposure matrix assigning daily exposures (8-hour time-weighted average) for identified job codes based on sampling data for specific locations and activities. Various job codes and air exposures were used for different time periods as appropriate to describe plant operations. Individual exposure metrics (e.g., cumulative exposure [CE]) were calculated using the work history of each individual in conjunction with the mine and mill job-exposure matrix.

Table 4-1. Population and exposure assessment methodologies used in studies of Libby, MT vermiculite workers

Operation, study cohort, reference describing exposure methods	Asbestos fiber quantification	Job-exposure classification	Primary outcomes examined in studies using methodology
Libby, MT mining and milling operations; NIOSH investigation. *N* = 575 men, hired before 1970, worked at least 1 yr Amandus et al. (1987a)	1962−1967 (and a few earlier yr): midget impinger data (*n* samples = 336). 1967−1982: PCM of fibers >5 µm long and aspect ratio >3:1 (*n* samples = 4,116).	Samples assigned to 25 "occupation locations" to estimate exposures for specific jobs and time periods 1945−1982. Membrane-filter measurement to impinger conversion ratio: 4.0 fibers/cc per mppcf. Average (arithmetic mean) exposure used for >one sample per location or job task and time period.[a]	Mortality: Amandus and Wheeler (1987) Pulmonary (x-rays): Amandus et al. (1987b) Amandus and Wheeler (1987)
Libby, MT mining and milling operations; NIOSH investigation. *N* = 1,672 men, no exclusion based on length of employment Sullivan (2007)	Based on Amandus et al. (1987a)	Modification to Amandus et al. (1987a) job classification: laborers and "unknown" jobs estimated using weighted-average exposure for all unskilled jobs in work area (if known) during calendar time period, rather than lower mill yard exposure. Weights based on the number of workers assigned to unskilled jobs during same calendar time period.	Mortality: Moolgavkar et al. (2010) Berman and Crump (2008) Sullivan (2007)
Libby, MT mining and milling operations; McGill University investigation. *N* = 406 men, hired before 1963, worked at least 1 yr McDonald et al. (1986a)	Similar to Amandus et al. (1987a), but midget impinger data was said to be available through 1969.	Similar to Amandus et al. (1987a). Samples assigned to 28 "occupation locations". Conversion ratio = 4.6 used for dry mill pre- and post-1964. Mean of log-normal distributions used for >one sample per location or job task and time period.[a]	Mortality: McDonald et al. (2004) McDonald et al. (2002) McDonald et al. (1986a) Pulmonary (x-rays): McDonald et al. (1986b)
Libby, MT mining and milling operations; ATSDR investigation. *N* = 1,862 men and women, no exclusion based on length of employment Larson et al. (2010b)	Based on Amandus et al. (1987a)	Extension of Amandus et al. (1987a) exposure data (without the modification used by Sullivan (2007), with additional application of exposure estimates to job titles from early 1980s through 1993 (the time of the demolition of the facilities).	Mortality: Larson et al. (2010b) Pulmonary: Larson et al. (2010a) Larson et al. (2012a)

[a]Cumulative exposure reported in units of fibers-yr (equivalent to the unit of fibers/cc-yr EPA is using for all studies).
Mppcf = million particles per cubic foot.

4.1.1.1.3.1. *Asbestos fiber quantification and development of job-exposure matrices.*

Before 1970, exposure estimates were based on midget impinger samples taken primarily in the dry mill by state and federal inspectors (n = 336). Total dust samples were measured as million particles per cubic foot (mppcf); these samples included mineral dust and vermiculite particles as well as asbestos fibers. Membrane-filter air samples for fibers, taken at various locations within the operations, began in 1967, and data are available from company records as well as state and federal agencies (see Table 4-2). Stationary and short-term (i.e., 20-minute to less than 4-hour) measurements were primarily used before 1974. Air samples collected through membrane filters (n = 4,116) were analyzed by PCM to visually count fibers greater than 5-µm long and having an aspect ratio >3:1 (Amandus et al., 1987b).[9] PCM methods from the 1960s allowed reliable characterization of fibers with widths greater than approximately 0.4 µm (Amandus et al., 1987b; Rendall and Skikne, 1980). Further standardization of the PCM method and improved quality of microscopes provided better visualization of thinner fibers; a 0.25-µm width was considered the limit of resolution for fiber width in the 1980s (IPCS, 1986), with subsequent improvements in resolution to 0.20 µm in width.

Table 4-2. Source of primary samples for fiber measurements at the Libby vermiculite mining and milling operations

Source	Unit of measurement	Yr	Number of samples
State of Montana	mppcf[a]	1956−1969	336
NIOSH	fibers/cc[b]	1967−1968	48
MESA/MSHA[c,d]	fibers/cc	1971−1981	789
Company records	fibers/cc	1970−1982	3,279

[a]Million particles per cubic foot of air, sampled by a midget impinger apparatus and examined by light microscopy.
[b]Fibers per cc of air drawn through a filter and examined under a phased contrast light microscope. Objects >5 µm and with an aspect ratio >3:1 were reported as fibers (see Section 2 for details).
[c]MESA: U.S. Mining Enforcement and Safety Administration; in 1977, MSHA took over MESA's membrane filter collection activities.
[d]MSHA: U.S. Mine Safety and Health Administration.

Source: Amandus et al. (1987b)

[9]Amandus et al. (1987b) indicate (page 12, 4th full paragraph) that fibers >5-µm long and with an aspect ratio >3:1 were measured. The actual value of the aspect ratio used by Amandus et al. could have been ≥3:1 because the criterion for the NIOSH recommended exposure limit is based on an aspect ratio of ≥3:1, but EPA is reporting here the information that was in the Amandus et al. (1987b) publication.

The samples taken from specific work locations within the operations were used to estimate exposures in specific jobs and time periods based on industrial hygienist consideration of temporal changes in facilities, equipment, and job activities. These were defined to categorize tasks and locations across the mining, milling, and shipping operations to group like tasks with respect to exposure potential. Both research groups established similar location operations for the Libby cohort. Because measures from sample filters were not available before 1967, different procedures had to be used to estimate exposures at the various locations for this earlier period. Amandus et al. (1987b) and McDonald et al. (1986a) provide high and low estimates for several locations to address the uncertainties in assumptions used in these estimates. Both researchers also applied a conversion factor to estimate asbestos exposures at the dry mill before 1967: the conversion factor was 4.0 in Amandus et al. (1987b) and 4.6 in McDonald et al. (1986a).[10]

Jobs were mapped to operation/location based on estimated time spent in different job tasks, thus estimating an 8-hour time-weighted average exposure for each job during several calendar time periods. Job histories from date of first employment to 1982 were used with the job-exposure matrix to develop cumulative exposure estimates for each worker.

Additional considerations

The resulting exposure estimates presented by both research groups, and the job-exposure matrices used in calculating cumulative exposure for the cohort, were based on fiber counts by PCM analysis of air filters. As discussed in Section 2 (see Section 2.4.4), PCM analysis does not distinguish fiber mineralogy or morphology, and all fibers >5 μm in length with an aspect ratio of 3:1 or greater are included. Both researcher groups analyzed fibers available at the facility in order to identify the mineral fibers in the air samples.

TEM[11] analysis of airborne asbestos fibers indicated a range of fiber morphologies—including long fibers with parallel sides, needlelike fibers, and curved fibers (McDonald et al.,

[10]The conversion ratio used by Amandus et al. (1987b) was based on a comparison of 336 impinger samples taken in 1965−1969 and 81 filter samples taken in 1967−1971; both sets of air samples were taken in the dry mill. The ratio based on the average fiber counts from air samples in 1967−1971 to the average total dust measurements in 1965−1969 was 4.0 fibers/cc:1.0 mppcf. This ratio was selected because it allowed for the use of the greatest amount of data from overlapping time periods, while controlling for the reduced exposure levels after 1971 where fiber counts based on PCM—but not midget impinger data—were available. The resulting exposure concentrations in the dry mill were estimated as 168 fibers/cc in 1963 and all prior years and 35.9 fibers/cc in 1964−1967. McDonald et al. (1986a) used a different procedure, based on the estimated reduction in dust exposure with the installation of the ventilation system in the dry mill 1964. They observed that total dust levels dropped approximately 4.6-fold after the installation of this equipment. Exposures in the dry mill were thus calculated as 4.6 times the fiber exposures measured by PCM between 1970 and 1974 (22.1 fibers/cc), resulting in estimated dry mill exposures of 101.5 fibers/cc prior to 1965 McDonald et al. (1986a).

[11]TEM utilizes a high-energy electron beam to irradiate the sample. This allows visualization of structures much smaller than can been seen under light microscopy. TEM instruments may be fitted with two supplemental instruments that allow for a more complete characterization of structure than is possible under light microscopy: EDS and SAED.

1986a). Of the fibers examined by TEM, >62% were >5 μm in length and a wide range of dimensional characteristics were noted: length (1−70 μm), width (0.1−2 μm), and aspect ratios from 3:1−100:1. Energy dispersive spectroscopy used to determine the mineral analysis indicated that the fibers were in the actinolite-tremolite solid solution series, but sodium-rich; some fibers could be classified as magnesio-riebeckite and some as richterite (McDonald et al., 1986a). This analysis is consistent with the current understanding of amphibole asbestos found in the Libby mine (see Section 2.2.3).

At the time of their study, when exposure concentrations were reduced to generally less than 1 fiber/cc, Amandus et al. (1987b) obtained eight air filters from area air samples collected in the new wet mill and screening plant (provided by the mining company). These samples were analyzed by PCM using the appropriate analytical method for the time (NIOSH Physical and Chemical Analytical Method No. 239). From early method development through current PCM analytical techniques, the Public Health Service, Occupational Safety and Health Administration, and NIOSH methods have defined a fiber by PCM analysis as having an aspect ratio ≥3:1 (NIOSH, 1994; Edwards and Lynch, 1968). Amandus et al. (1987b) reported the dimensional characteristics of the fibers from these filters including aspect ratio, width, and length (see Table 4-3). Data for 599 fibers from the eight area air samples collected in the wet mill and screening plant are provided. These data are limited in one sense by the minimum width and length cutoffs (>4.98-μm long, >0.44-μm wide, aspect ratio >3:1);[12] 16% had an aspect ratio ≥50:1. Only 7% of the fibers had a width greater than 0.88 μm, with one fiber reported of the 559 with a width greater than 1.76 μm. Note that these data do not give the full fiber-size distribution of LAA fibers because NIOSH was examining only PCM-visible fibers (see Section 2.3.1).

[12]See footnote 9, page 4−6.

Table 4-3. Dimensional characteristics of fibers from air samples collected in the vermiculite mill and screening plant, Libby, MT[a]

Fiber length (µm)			Fiber width (µm)			Aspect ratio		
Range	Total counted	Percentage	Range	Total counted	Percentage	Range	Total counted	Percentage
4.98−7.04	54	9	0.44−0.62	406	68	5:1−10:1	24	4
7.04−9.96	109	18	0.62−0.88	151	25	10:1−20:1	176	29
9.96−14.08	107	18	0.88−1.24	27	5	20:1−50:1	305	51
14.08−19.91	111	19	1.24−1.76	14	2	50:1−100:1	84	14
19.91−28.16	90	15	1.76−2.49	0	0	>100:1	10	2
28.16−39.82	65	11	>2.49	1	0			
39.82−66	46	8						
66−88	10	2						
>88	7	1						

[a]Fibers were viewed and counted by PCM.

Source: Amandus et al. (1987b).

4.1.1.2. *Studies of O.M. Scott, Marysville, OH Plant Workers*

4.1.1.2.1. ***Descriptions of cohorts of O.M. Scott, Marysville, OH plant workers.*** The first study of pulmonary effects in the Ohio plant workers was conducted in 1980 and involved 512 workers (97% of the 530 workers previously identified with past vermiculite exposure; (Lockey et al., 1984); see Tables 4-4 and 4-6). The Rohs et al. (2008) study is a follow-up of respiratory effects in this cohort conducted approximately 25 years later; chest x-rays and interview data were collected from 280 of the 431 workers known to be alive at this time. Dunning et al. (2012) examined mortality rates in the cohort, using an updated exposure analysis described by Borton et al. (2012). In this analysis, vital status through June 2011 was ascertained.

Table 4-4. Population and methods used in studies of O.M. Scott, Marysville, OH plant workers

<table>
<tr><th>Reference(s)</th><th>Population</th><th>Data collection</th><th>Outcomes examined</th></tr>
<tr><td rowspan="5">Lockey (1985)
Lockey et al. (1984)[a]</td><td colspan="3">1980, n = 512 (from 530 identified employees with past vermiculite exposure; nonparticipants included 9 refusals and 9 unavailable due to illness or vacation).
Mean age: 37.5 yr
Mean duration: 10.2 yr[b]
Ever smoked: 64.7%</td><td rowspan="5">Exposure estimates based on air samples taken beginning in 1972; methods described below in Section 4.1.1.2.2.
Interviews: smoking history, work history at the plant, and other asbestos and fiber mineral work history data.</td><td rowspan="5">Respiratory effects, noncancer, based on clinical exam (listening for rales and evaluation of nail clubbing), pulmonary function (spirometry and DL_{CO}) and chest x-rays; two B Readers, 1971 ILO classification guidelines modified with additional grading criteria (e.g., costophrenic angle blunting separated from other pleural lesions)</td></tr>
<tr><td colspan="3">Mean cumulative exposure by group (based on jobs and areas):</td></tr>
<tr><td>Group</td><td>Fibers/cc-yr</td><td>(n)</td></tr>
<tr><td>I</td><td>0.45[c]</td><td>(112)</td></tr>
<tr><td>II</td><td>1.13</td><td>(206)</td></tr>
<tr><td>III</td><td>6.16</td><td>(294)</td></tr>
<tr><td>Rohs et al. (2008)</td><td colspan="3">n = 280 with interviews (2004) and readable chest x-rays (2002−2005) (from 513 workers in the 1980 study group, 431 were alive in 2004[d]; 151 living nonparticipants included 49 refusals, 76 located but did not respond, 8 not located but presumed alive, and 18 missing either x-ray or interview).
Mean age: 59.1 yr
Ever smoked: 58.6%
Mean (range) cumulative exposure: 2.48 (0.01−19.03) fibers/cc-yr</td><td>Exposure estimates based on Lockey et al. (1984).
Interviews: pulmonary medical history and job history since 1980 included information on other asbestos exposure.</td><td>Respiratory effects, noncancer, based on chest x-rays; 3 B Readers, 2000 ILO classification guidelines</td></tr>
<tr><td>Dunning et al. (2012)</td><td colspan="3">Follow-up of workers identified in [Lockey et al. (1984); see first row of this table]. Limited to n = 465 white men.
Follow-up through June 2011; 136 deaths
Mean duration: 11.0 yr
Mean (range) cumulative exposure: 9.0 (<0.01−106.31)</td><td>Exposure estimates updated based on Borton et al. (2012).</td><td>Mortality (cancer and noncancer), based on National Death Index</td></tr>
</table>

[a]Lockey et al. (1984) is the published paper based on the unpublished thesis (Lockey, 1985).
[b]Calculated based on stratified data presented in Table 2 of Lockey et al. (1984).
[c]Characterized as similar to background levels in the community, based on an 8-hr time-weighted average estimated as 0.049 fiber/cc from a single stationary sample taken outside the main facility.
[d]Rohs et al. (2008) identified one additional eligible worker from the original 512 employees identified in Lockey et al. (1984).
DL_{CO} = single-breath carbon monoxide diffusing capacity; ILO = International Labour Organization.

4.1.1.2.1.1. ***Exposure estimation: O.M. Scott, Marysville, OH plant.*** The plant that processed vermiculite ore in Marysville, OH had eight main departments in the processing facility, employing approximately 530 workers, with 232 employed in production and packaging of the commercial products and 99 in maintenance; other divisions included research, the front office, and the polyform plant (Lockey, 1985). Six departments were located at the main facility

(trionizing, packaging, warehouse, plant maintenance, central maintenance, and front offices). Research and development and a polyform plant were located separately, approximately one-quarter mile from the main facility. In the trionizing section of the plant, the vermiculite ore was received by rail or truck, unloaded into a hopper, and transported to the expansion furnaces. After expansion, the vermiculite was blended with other materials (e.g., urea, potash, herbicides), packaged, and stored. Changes to the expander type and dust-control measures began in 1967, with substantial improvement in dust control occurring throughout the 1970s.

Industrial hygiene monitoring at the plant began in 1972, with measurements based on fibers >5-μm long, diameter <3 μm, aspect ratio ≥3:1. Lockey et al. (1984) noted that the limited availability of data that would allow for extrapolation of exposures for earlier time periods possibly resulted in the underestimation of exposures before 1974.[13] Breathing-zone samples were used after 1976, with fiber analysis by PCM.

Cumulative fiber exposure indexes, expressed as fibers/cc-yr, were derived for each worker from available industrial hygiene data and individual work histories; three categories of exposure levels were defined for the 512 workers previously identified with past vermiculite exposure [see Table 4-4 (Lockey et al., 1984)]. Group I was considered to be the nonexposed group and consisted of the chemical processing, research, and front office workers, as well as other workers with an estimated cumulative exposure <1 fiber/cc-yr. Group II was the low-exposure category and included central maintenance, packing, and warehouse workers. The 8-hour time-weighted average fiber exposure in this group was estimated at approximately 0.1−0.4 fiber/cc before 1974 and 0.03−0.13 fiber/cc in and after 1974. Group III was the high-exposure category and included expander, plant maintenance, and pilot plant workers. The 8-hour time-weighted average fiber exposures in this group were approximately 1.2−1.5 fibers/cc before 1974 and 0.2−0.375 fiber/cc in and after 1974. The estimated cumulative exposure for the work force, including Group I workers, ranged from 0.01 to 28.1 fibers/cc-yr using an 8-hour workday and an assumed 365 days of exposure per year.[14] Exposure was assumed to occur from 1957 to 1980 in this study. Exposure outside of work hours was assumed to be zero.

Additional exposure information was identified in 2009, and exposure estimates were updated and refined to reflect information (including fiber measurements) from company reports and other written materials (Borton et al., 2012). In addition, worker focus groups provided insight into plant processes—including industrial hygiene measures—and work patterns and organizations. Further details on the updated exposure assessment are included in Appendix F.

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[13]Subsequent exposure assessment efforts by this team of investigators are described in Borton et al. (2012) and in Appendix F.

[14]Lockey et al. (1984) reported the maximum value for this group as 39.9 fibers/cc-yr, but this estimate was later corrected to exclude work from 1947 to 1956, before the use of vermiculite at the plant. Information provided in Benson (2014).

4.1.1.3. *Community-Based Studies Around Libby, MT Conducted by Agency for Toxic Substances and Disease Registry (ATSDR)*

Analyses using data from community-based studies in Libby, MT conducted by ATSDR are summarized in Table 4-5. ATSDR (2000) includes a mortality analysis based on death certificate data from 1979−1998, with residence at time of death geocoded to areas corresponding to Libby, MT and its surroundings. The estimated population size in 1991 for the areas used in the standardized mortality ratio (SMR) calculations ranged from 2,531 in the Libby city limits to 9,512 for the central Lincoln County area (based on a 10-mile radius around downtown Libby). Cause-specific standardized mortality ratios were computed based on Montana and United States comparison rates; asbestosis SMRs were somewhat higher using the U.S. referent group, but the choice of referent group had little difference on SMRs for most diseases.

ATSDR also conducted a community health screening from July−November 2000 and July−September 2001, with 7,307 total participants (ATSDR, 2001b). Eligibility was based on residence, work, or other presence in Libby for at least 6 months before 1991. The total population eligible for screening is not known, although the population of Libby, MT in 2000 was approximately 10,000. Other studies (Larson et al., 2012b; Weill et al., 2011; Vinikoor et al., 2010; Noonan et al., 2006) used data collected during this community health screening.

Two additional community-based studies, using data sources other than the ATSDR community health screening (Marchand et al., 2012; Pfau et al., 2005) are discussed in Section 4.1.3.2. (Autoimmune disease and autoantibodies), and two clinic-based studies from Libby, MT (Winters et al., 2012) are discussed in Section 4.1.2.2.4 (Clinic-based reports and case reports of respiratory disease [noncancer]).

Table 4-5. Summary of methods used in community-based studies of Libby, MT residents conducted by Agency for Toxic Substances and Disease Registry (ATSDR)

Reference(s)	Methods	Data collection	Outcomes examined
ATSDR (2000)	1979−1998 mortality analysis, underlying cause of death from death certificates: 419 decedents identified, 418 death certificates obtained, 413 geocoded; 16 of 91 residents of elderly care facilities reclassified to nonresident.	Geocoding of street locations (residence at time of death) within six geographic boundaries (ranging from 2,532 residents in Libby city limits to 9,521 in central Lincoln County in 1990)	Mortality (cancer and noncancer); underlying cause of death
Vinikoor et al. (2010) Peipins et al. (2003) ATSDR (2001b)	ATSDR community health screening, July−November 2000 (Peipins et al. (2003); ATSDR, 2001b) also included July−September 2001 participants) Eligibility: resided, worked, attended school, or participated in other activities in Libby for at least 6 mo before 1991 (including vermiculite mine and mill workers). *N* = 7,307 interviews and *n* = 6,668 chest x-rays.	Standardized interview: medical history, symptoms, work history, and other potential exposures. Exposure based on information on "exposure pathways" (e.g., worked at vermiculite mining or milling operations, other asbestos-related work history, lived with worker at the vermiculite mining or milling operations, use of vermiculite products, played in vermiculite piles)	Chest x-rays (posterior-anterior, oblique), 1980 ILO classification guidelines; pulmonary function, respiratory symptoms
Weill et al. (2011)	ATSDR community health screening [see (ATSDR, 2001b)]. *n* = 4,397, ages 25 to 90 yr, excluding individuals with history of other asbestos-related work exposures.	Analysis based on five exposure categories: - Worked at vermiculite mining or milling operations - Other vermiculite occupation - Other dusty (asbestos-related) occupations - Lived with vermiculite/dusty/asbestos worker - Environmental (did not work or live with dusty/asbestos worker)	Chest x-rays (posterior-anterior), 1980 ILO classification guidelines; pulmonary function in relation to chest x-ray findings
Larson et al. (2012b)	ATSDR community health screening [see (ATSDR, 2001b)]. *n* = 6,476, ages ≥18 yr, excluding individuals without interpretable spirometry and chest x-ray data.	Exposure pathways as described in Peipins et al. (2003)	Chest x-rays (posterior−anterior), 1980 ILO classification guidelines; pulmonary function in relation to chest x-ray findings
Noonan et al. (2006)	ATSDR community health screening [see (ATSDR, 2001b)]. Nested case-control study of rheumatoid arthritis, scleroderma, and systemic lupus erythematosus cases (*n* = 161 cases, 1,482 controls); initial self-report confirmed in second interview.	Exposure pathways as described in Peipins et al. (2003)	Systemic autoimmune diseases

4.1.2. Respiratory Effects, Noncancer

4.1.2.1. *Asbestosis and Other Nonmalignant Respiratory Disease Mortality*

Several studies described previously reported noncancer respiratory disease mortality data. Nonmalignant respiratory disease is a broad category (International Classification of Diseases [ICD]-9 codes 460−519) that includes chronic obstructive pulmonary disease, asthma, pneumonia and respiratory infections, asbestosis (ICD-9 code 501), and various forms of pneumoconiosis. A greater specificity of effects due to asbestos would be expected using the narrower category of asbestosis compared with nonmalignant respiratory disease.

The initial studies of the Libby, MT vermiculite mining and milling worker cohorts were based on a relatively small number of nonmalignant respiratory-related deaths (<25); more than 50 deaths in this category were seen in later studies (see Table 4-6). The analytic strategy (e.g., use of a latency period to exclude cases that occurred before the effect of exposure would be expected to be manifested, or use of a lag period to exclude exposures that occurred after the onset of disease) and the cutpoints for exposure categories varied among the studies, but a pattern of increasing risk with increasing cumulative exposure is seen, with more than a 10-fold increased risk of death due to asbestosis and a 1.5- to 3-fold increased risk of nonmalignant respiratory disease in the analyses using an internal referent group (Larson et al., 2010b; Sullivan, 2007; McDonald et al., 2004). Larson et al. (2010b) used a Monte Carlo simulation to estimate the potential bias in nonmalignant respiratory disease risk that could have been introduced by differences in smoking patterns between exposed and unexposed workers in the cohort. The bias-adjustment factor (relative risk $[RR]_{unadjusted}/RR_{adjusted} = 1.2$) reduced the overall RR estimate for nonmalignant respiratory mortality from 2.1 to 1.8. Asbestosis risk was also increased in the ATSDR geographic-based analysis, with SMRs of approximately 40 based on Montana rates and 65 based on U.S. comparison rates (ATSDR, 2000). Only one asbestosis-related death was observed in the Marysville, OH worker cohort, resulting in a very imprecise risk estimate (Dunning et al., 2012).

Table 4-6. Nonmalignant respiratory mortality studies of populations exposed to Libby Amphibole asbestos[a]

Reference(s)	Respiratory disease (SMR, 95% CI)	Dose-response analyses: nonmalignant respiratory diseases and asbestosis			
Occupational studies of Libby, MT mining and milling operations workers					
Amandus and Wheeler (1987) (NIOSH)	No exclusions: nonmalignant respiratory diseases (n = 20) SMR: 2.4 (1.5, 3.8) 20-yr latency: nonmalignant respiratory diseases (n = 12) SMR: 2.5 (p < 0.05)	No exclusions: nonmalignant respiratory diseases			
		Cumulative exposure	n	SMR (95% CI)[b]	
		0.0−49 fibers/cc-yr	8	2.2 (not reported)	
		50−99 fibers/cc-yr	2	1.7 (not reported)	
		100−399 fibers/cc-yr	3	1.8 (not reported)	
		≥400 fibers/cc-yr	10	4.0 (not reported, but p <0.01)	
		20 or more yr since first hire (latency): nonmalignant respiratory diseases			
		Cumulative exposure	n	SMR (95% CI)[b]	
		0.0−49 fibers/cc-yr	7	3.3 (not reported, but p < 0.05)	
		50−99 fibers/cc-yr	2	2.8 (not reported)	
		100−399 fibers/cc-yr	0	0 (not reported)	
		≥400 fibers/cc-yr	3	2.8 (not reported)	
McDonald et al. (2004) McDonald et al. (1986a) (McGill)	Nonmalignant respiratory diseases (n = 51) SMR: 3.1 (2.3, 4.1)	Excluding first 10 yr of follow-up: nonmalignant respiratory diseases			
		Cumulative exposure	n	RR (95% CI)[d]	
		0.0−11.6 fibers/cc-yr	5	1.0 (referent)	
		11.7−25.1 fibers/cc-yr	13	2.5 (0.88, 7.2)	
		25.2−113.7 fibers/cc-yr	14	2.6 (0.93, 7.3)	
		≥113.8 fibers/cc-yr	19	3.1 (1.2, 8.4)	
		per 100 fibers/cc-yr	-	0.38 (0.12, 0.96) (p = 0.0001)	
Sullivan (2007) (NIOSH)	15-yr exposure lag: Asbestosis (n = 22) SMR: 166 (104, 251) Nonmalignant respiratory diseases (n = 111) SMR: 2.4 (2.0, 2.9) Chronic obstructive pulmonary disease (n = 53) SMR: 2.2 (1.7, 2.9) Other nonmalignant respiratory diseases (n = 19) SMR: 2.7 (1.6, 4.2)	15-yr exposure lag: asbestosis			
		Cumulative exposure	n	SMR (95% CI)[b]	SRR (95% CI)[c]
		0.0−49.9 fibers/cc-yr	3	37 (7.5, 122)	1.0 (referent)
		50.0−249.9 fibers/cc-yr	8	213 (91.6, 433)	7.3 (1.9, 28.5)
		≥250 fibers/cc-yr	11	749 (373, 1,368)	25.3 (6.6, 96.3)
		linear trend test			(p <0.001)
		15-yr exposure lag: nonmalignant respiratory diseases			
		Cumulative Exposure	n	SMR (95%CI)[b]	SRR (95% CI)[c]
		0.0−4.49 fibers/cc-yr	18	1.8 (1.1, 2.8)	1.0 (referent)
		4.5−19.9 fibers/cc-yr	24	2.0 (1.3, 3.0)	1.2 (0.6, 2.3)
		20.0−84.9 fibers/cc-yr	26	2.2 (1.5, 3.3)	1.5 (0.8, 2.9)
		85.0−299.9 fibers/cc-yr	20	2.6 (1.6, 4.0)	1.4 (0.7, 2.7)
		≥300 fibers/cc-yr	23	4.8 (3.1, 7.3)	2.8 (1.3, 5.7)
		linear trend test			(p <0.01)

Table 4-6. Nonmalignant respiratory mortality studies of populations exposed to Libby Amphibole asbestos[a] (continued)

Reference(s)	Respiratory disease (SMR, 95% CI)	Dose-response analyses: nonmalignant respiratory diseases and asbestosis			
Larson et al. (2010b)	Asbestosis (*n* = 69) SMR: 143 (111, 181) Nonmalignant respiratory diseases (*n* = 425) SMR: 2.4 (2.2, 2.6) Chronic obstructive pulmonary disease (*n* = 152) SMR: 2.2 (1.9, 2.6) Other nonmalignant respiratory (*n* = 120) SMR: 2.8 (2.3, 3.4)	20-yr exposure lag: asbestosis			
		Cumulative exposure	*n*	SMR (95% CI)[b]	RR (95% CI)[e]
		<1.4 fibers/cc-yr	4	(not reported)	1.0 (referent)
		1.4–<8.6 fibers/cc-yr	8	(not reported)	2.8 (1.0, 7.6)
		86–<44.0 fibers/cc-yr	25	(not reported)	8.0 (3.2, 19.5)
		≥44.0 fibers/cc-yr	32	(not reported)	11.8 (4.9, 28.7)
		Per 100 fibers/cc-yr increase			1.18 (1.12, 1.23)
					(*p* <0.0001)
		20-yr exposure lag: nonmalignant respiratory diseases			
		Cumulative exposure	*n*	SMR (95% CI)[b]	RR (95% CI)[e]
		<1.4 fibers/cc-yr	43	(not reported)	1.0 (referent)
		1.4–<8.6 fibers/cc-yr	46	(not reported)	1.4 (0.9, 2.1)
		86–<44.0 fibers/cc-yr	56	(not reported)	1.8 (1.3, 2.7)
		≥44.0 fibers/cc-yr	58	(not reported)	2.5 (1.7, 3.6)
		Per 100 fibers/cc-yr increase			1.08 (1.03, 1.13)
					(*p* = 0.0028)
Community-based studies in Libby, MT					
ATSDR (2000)	Asbestosis (*n* = 11)	SMR	(95% CI)	SMR	(95% CI)
		Comparison area (Montana reference rates):		Comparison area (U.S. reference rates):	
	Libby city limits	40.8	(13.2, 95.3)	63.5	(20.5, 148)
	Extended Libby boundary	47.3	(18.9, 97.5)	74.9	(30.0, 154)
	Air modeling	44.3	(19.1, 87.2)	71.0	(30.6, 140)
	Medical screening	40.6	(18.5, 77.1)	66.1	(30.2, 125)
	Libby valley	38.7	(19.3, 69.2)	63.7	(31.7, 114)
	Central Lincoln County	36.3	(18.1, 64.9)	59.8	(29.8, 107)

Table 4-6. Nonmalignant respiratory mortality studies of populations exposed to Libby Amphibole asbestos[a] (continued)

Occupational studies of O.M. Scott, Marysville, OH plant workers	
Dunning et al. (2012)	Asbestosis (n = 1) SMR: 15.4 (0.4, 86)

CI = confidence interval; SRR = standardized rate ratio.
[a]Libby, MT mining and milling operations includes miners, millers, and processors; workers in the screening plant, loading docks, and expansion plants; and office workers.
[b]SMR based on external referent group.
[c]In Sullivan (2007), the SRR is a ratio of sums of weighted rates in which the weight for each stratum-specific rate is the combined person-yr for the observed cohort across all duration (or cumulative level of exposure) categories. The Life Table Analysis System provides the SRR for each duration (or cumulative level of exposure) group compared to the referent group. The cutoff points for the categories are specified by the user. Taylor-series-based confidence intervals (Rothman, 1986) are given for each specific SRR.
[d]In McDonald et al. (2004), the RR is based on Poisson analysis using an internal referent group.
[e]In Larson et al. (2010b), the RR is based on Cox proportional hazards modeling using an internal referent group.

4.1.2.1.1. *Pathological alterations of the lung parenchyma and pleura, pulmonary function, and respiratory symptoms*

4.1.2.1.1.1. ***Definition of outcomes***

Text Box 4-1. Pathological Alterations of the Lung Parenchyma and Pleura According to ILO (2002)

Parenchymal changes in the lung (small opacities): The small opacities viewed within the lung (interstitial changes) are indicative of pneumoconiosis and are associated with exposure to not only mineral fibers, but also mineral dust and silica. The radiographic signs of pneumoconiosis begin as small localized areas of scarring in the lung tissue and can progress to significant scarring and lung function deficits. The ILO classification guidelines provide a scheme for grading the severity of the small opacities; the size, shape, and profusion of the small opacities are recorded, as well as the affected zone(s) of the lung.

Obliteration of the costophrenic angle: The costophrenic angle is the angle between the ribcage and the diaphragm on a standard posterior-anterior radiograph (the costophrenic recess). When blunting or obliteration is noted on a radiograph, it is recorded as present or absent. Obliteration of the costophrenic angle may occur in the absence of other radiographic signs.

Pleural thickening: The pleural lining around the lungs (visceral pleura) and along the chest wall and diaphragm (parietal pleura) may thicken due to fibrosis and collagen deposits. Pleural thickening (all sites) is reported as either localized pleural thickening (LPT) or diffuse pleural thickening (DPT). DPT of the chest wall may be reported as in-profile or face-on, and is recorded on the lateral chest wall "only in the presence of and in continuity with, an obliterated costophrenic angle." LPT may also be viewed in-profile or face-on and is generally a pleural plaque (parietal). Calcification is noted where present.

Respiratory disease risk can be evidenced by pleural and parenchymal abnormalities (pathological, structural alterations) detected through radiographic or other types of imaging (see Text Box 4-1). These types of effects are usually classified using criteria developed by the International Labour Organization (ILO) of the United Nations to standardize descriptions of effects and improve inter-rater agreement and accuracy for reading chest radiographs in pneumoconiosis. The guidelines were initially developed in 1950 with several subsequent revisions. A key component of the guidelines is the use of a set of standard films illustrating different types of findings; these films are used by "B Readers" as a reference for comparison to films collected in a research or clinical setting. Findings that were considered to be definitely or probably not pneumoconiosis were to be noted by the readers to allow resolution of discrepancies (ILO, 1980). The B Reader program was initiated in 1974 to reduce variability in readings; B Readers are physicians who pass an examination, recertifying every 4 years, in the adherence to detailed criteria when reading radiographs in individuals with pneumoconiosis.

Parenchymal (the inner structure of the lungs) abnormalities include opacities; these abnormalities are defined as small (≤10 mm diameter) or large (>10 mm diameter). Small opacities are assigned a score based on the concentration of opacities in a given area (profusion), zone(s) of the lung(s) affected, shape, and size. Small opacity profusion is graded on a 4-point scale (0 = absence of small opacities or the presence of small opacities less profuse than Category 1; 3 = highest level of profusion). Two ratings are given (e.g., 0/1 or 2/2), with the second number allowing an indication of a category that was seriously considered as an alternative to the first grade. Large opacities are scored based on their (aggregate) dimension(s). The scarring of the parenchymal tissue of the lung contributes to measurable decrements in pulmonary function, including obstructive pulmonary deficits from narrowing and/or distortion of airways, restrictive pulmonary deficits from the decreased elasticity of the lung or displacement of lung tissue by mass lesions, and decrements in gas exchange (ATS, 2004). According to 2000 ILO guidelines (ILO, 2002), pleural abnormalities are classified as (a) localized pleural thickening (LPT) or (b) diffuse pleural thickening (DPT). LPT can be present on the pleural membrane of the chest wall, diaphragm, and other sites (medinstinal pleura, para-spinal pleura, and para-cardiac pleura). Plaques on the chest wall can be viewed either face-on or in profile. A minimum width of about 3 mm is required for an in-profile plaque to be recorded as present according to the 2000 ILO guidance. This requirement was added to reduce the number of false positives. The terms "LPT" and "pleural plaque" are the same in the 2000 ILO guidelines, and are different from the definition of pleural plaques used prior to 2000 ILO guidelines. Different researchers implementing the earlier ILO guidelines variously used terms such as "discrete pleural thickening," "circumscribed pleural thickening," or "pleural plaques" to describe what is currently called LPT. DPT is now defined as diffuse pleural thickening on the chest wall that is present "only in the presence and in continuity with an obliterated costophrenic angle." The previous ILO guideline (ILO, 1980) did not include the

requirement for involvement of the costophrenic angle. The definition of DPT now also includes a requirement that the thickening on the chest wall have a minimum width of 3 mm when viewed in profile. The changes in the definition of DPT were added to reduce the number of false positives. Both LPT and DPT are scored based on their location, extent, and whether calcification is seen and are recorded separately for the left and right side. LPT is a change in tissue structure and is not known to be an adaptive response to toxicity generally or to asbestos specifically. Examples of what is now called LPT visualized on autopsy are shown in Figures 4-2A and 4-2B (ATS, 2004). Additional discussion of the adversity of LPT is included in Section 5.2.2.3 (*Selection of Critical Effect*) and Appendix I.

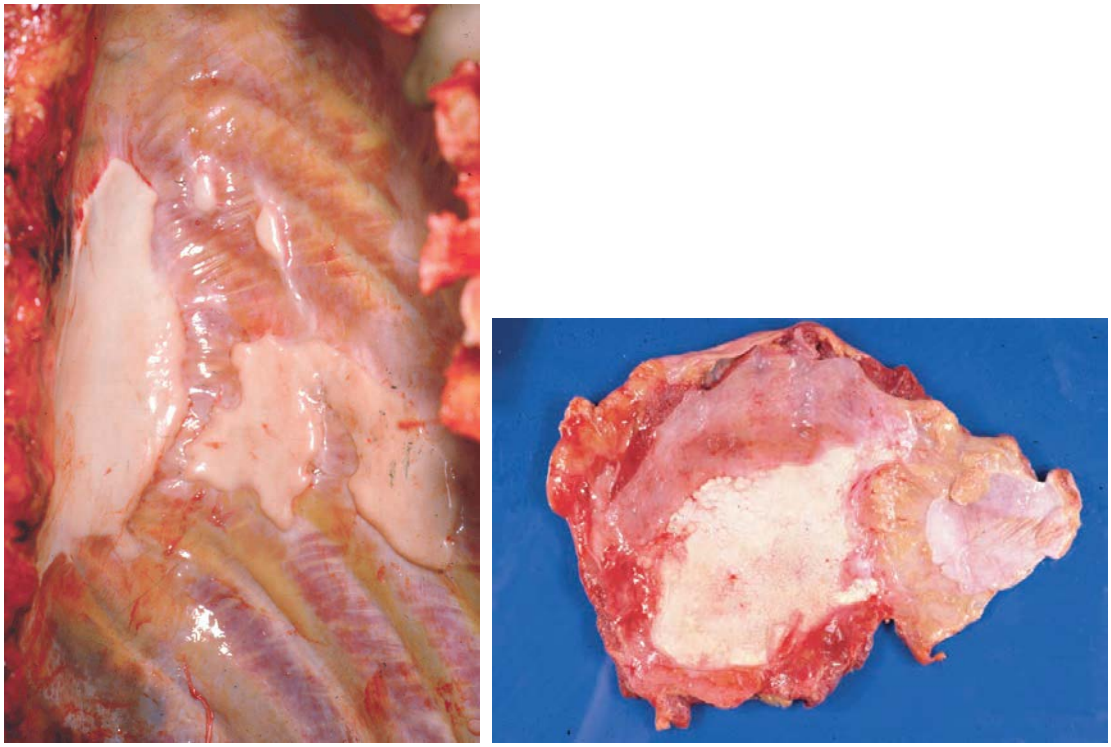

Figure 4-2. A (left). Gross appearance at autopsy of asbestos-associated pleural plaques overlying the lateral thoracic wall [(ATS, 2004) Figure 12]. Figure 4-2. B (right). Gross appearance of large asbestos-related pleural plaque over the dome of the diaphragm [(ATS, 2004) Figure 13].

Source: ATS (2004). Reprinted with permission of the American Thoracic Society. Copyright © 2014 American Thoracic Society.

The latency period for the initial detection of pleural or parenchymal abnormalities varies by type of lesion. Larson et al. (2010a) examined x-rays of 84 workers from the Libby, MT mining and milling operations for whom pleural and/or parenchymal abnormalities were seen and who had one or more previous x-rays covering a span of at least 4 years available for comparison. Circumscribed pleural plaques [a term that corresponds to the term “circumscribed

pleural thickening" in ILO (1980)] was seen in 83 of these 84 workers at a median latency of 8.6 years. Any pleural calcification was seen in 37 workers, with a median latency of 17.5 years, and DPT was seen in 12 workers (median latency: 27.0 years). The latency period for small opacities indicating parenchymal changes (e.g., asbestosis) increased with increasing profusion categories, from a median of 18.9 years for ≥1/0, 33.3 years for progression to ≥2/1, and 36.9 years for progression to ≥3/2.

Pulmonary function

Pulmonary function, commonly measured by spirometry, is used as an indicator of respiratory health and lung disease. Spirometric measurements involve assessment of lung volume and air flow (Pellegrino et al., 2005). Forced vital capacity (FVC) is a measure of the maximum amount of air that can be exhaled forcefully after a full inspiration. Forced expiratory volume (FEV) is the maximum amount of air exhaled forcefully after a full inspiration in a given time period; for example, FEV_1 refers to the amount of air exhaled in the first second of the test procedure. Standardization of test procedures is very important in these tests, and measurements of multiple forced expiration (≥3) are typically needed. Values are compared to "reference values" based on age, gender, height (and sometimes race).

Combinations of various functional measurements may be indicative of specific types of abnormalities affecting lung function. For example, restrictive lung function (or restrictive ventilatory defect) refers to reduced lung volume. Both FEV_1 and FVC would be reduced, but the reduction in FVC would typically be greater than that for FEV_1 (e.g., FEV_1/FVC ratio >0.8). Restrictive lung function can result from interstitial lung disease (including inflammatory or fibrotic disease) or other conditions that restrict the ability of the lungs to expand. Obstructive lung function (or obstructive ventilatory defect) refers to reduced airflow, and is most commonly characterized by narrowing of the airways. It is indicated by a reduction in FEV_1 without a proportionate reduction in FVC (e.g., the ratio of FEV_1/FVC <0.7, or FEV_1/FVC <5th percentile). Both restrictive and obstructive conditions can result in dyspnea (shortness of breath), and many of the various underlying diseases that are associated with restrictive and obstructive lung function cause cough, and chest pain.

4.1.2.1.1.2. ***Results: pathological alterations of lung parenchyma and pleura: occupational studies***

Libby, MT vermiculite mine and mill workers

Studies examining pleural and parenchymal abnormalities in the Libby, MT worker cohorts are shown in Table 4-7. In the McDonald et al. (1986b) and Amandus et al. (1987a) studies, x-ray films for each worker, which NIOSH obtained from the Libby hospital that performed the screening, were independently read by three qualified readers using the 1980 ILO classification system. For the analysis, classification indicating pleural abnormalities by at least

two of the three readers was used to determine the presence of pleural abnormalities, while the median reading was used to determine the profusion category of small opacities. Although both research groups used the ILO 1980 guidelines, McDonald et al. (1986b) reported pleural thickening on the chest wall (both pleural plaques and diffuse) but not in other sites. Amandus et al. (1987a) examined "any unilateral or bilateral pleural change", which included "…pleural plaque, diffuse pleural thickening of the chest wall, diaphragm or other site, but excluded costophrenic angle obliteration."

Amandus et al. (1987a) reported pleural thickening of the chest wall in 13% and small opacities (≥1/0) in 9.8% of employees. The analysis reported by McDonald et al. (1986b) was stratified by employment status. Among current workers, pleural thickening of the chest wall and small opacities were observed in 15.9% and 9.1%, respectively; corresponding figures among former workers were 52.5% and 37.5%, respectively. In both studies, prevalence of these abnormalities increased with increasing cumulative exposure. McDonald et al. (1986b) also included 80 former employees in their study. The prevalence of pleural thickening of the chest wall (52.5%) and small opacities (37.5%) was higher in former employees compared with current workers. These groups differed by age, with only one of the 80 former workers being less than 40 years of age while 80 of 164 current workers were under 40 years of age. Both overall and within age categories, however, the prevalence is higher among former employees, and this is attributed to higher cumulative exposure in this group.

Both Amandus et al. (1987a) and McDonald et al. (1986b) provided categorical exposure-response data as well as logistic models for various endpoints (e.g., small opacities, pleural calcification, pleural thickening of the chest wall, and "any pleural change"). In McDonald et al. (1986b), exposure and age were both predictive of pleural thickening along the chest wall; the regression coefficient for cumulative exposure (fibers/cc-yr) was 0.0024 per unit increase in cumulative exposure for the log odds of the presence of pleural thickening, adjusting for age and smoking. Cumulative exposure, age, and smoking status were all predictive of small opacities; the parameter for cumulative exposure had a regression coefficient of 0.0035 per unit increase in cumulative exposure. In contrast, although the categorical analysis reported by Amandus et al. (1987a) indicated a positive exposure response relationship for both "any pleural change" and pleural thickening along the chest wall, cumulative exposure was not a significant predictor in regression analysis adjusting for age (regardless of smoking status). The lack of statistical significance in these models may reflect a nonlinearity reflected in the observation of the lowest prevalence in the second of four exposure categories rather than in the lowest category. The estimated relationship between exposure and prevalence of small opacities in Amandus et al. (1987a) was similar to that reported by McDonald et al. (1986b).

Table 4-7. Chest radiographic studies of the Libby, MT vermiculite mine workers

Reference(s)	Inclusion criteria and design details	Results
McDonald et al. (1986b)	Men employed July 1, 1983 (n = 164). Former employees living within 200 miles; hired before 1963 (n = 80), worked at least 1 yr (80 participants from 110 eligible). Comparison group—men without known occupational dust exposure (n = 47); x-rays taken for other reasons (mostly employment related) at same place during study period.	Prevalence (%) / Current workers / Former workers / Comparison group Pleural thickening: 15.9 / 52.5 / 8.5 Small opacities (≥1/0): 9.1 / 37.5 / 2.1 Both abnormalities increased with age, and with increasing cumulative exposure in age-adjusted and stratified (>60 yr old) analyses.
Amandus et al. (1987a)	Men, employed 1975−1982 for ≥5 yr (n = 191); 184 with previous chest x-rays; 121 with smoking questionnaires. Annual radiographs since 1964; most recent radiograph evaluated. Duration: mean 14 yr Cumulative exposure: mean 123 (all workers), 119 (with radiographs) fiber-yr.	Pleural thickening of the chest wall observed in 13%. Small opacities (≥1/0) observed in 10%. Beta (p-value), cumulative exposure in relation to: Small opacities: 0.0026 ($p < 0.05$) Any pleural change: 0.0008 ($p \geq 0.05$) Pleural calcification: −0.0010 ($p \geq 0.05$) Pleural change on wall: 0.0008 ($p \geq 0.05$) Effect of age was significant in all models, controlling for exposure.
Larson et al. (2012a)	N = 336 participants in community screening (see Table 4-5 for more details) who reported working at facility, confirmed by company records. Mean age 55.6 yr, 93.6% male. Duration: median 1.5 yr Cumulative exposure: median 3.6 fibers/cc-yr Restrictive spirometry defined as FVC < lower limit of normal and FEV_1/FVC > lower limit of normal.	Association with cumulative exposure (cc/fiber-yr)[a] n / (%) / Starting at / Statistically significant at DPT, CAO: 18 / (5) / 5 / >200 Profusion ≥1/0: 18 / (5) / 1 / 108 Localized pleural thickening: 117 / (35) / 0.5 / 1.0 Restrictive spirometry: 45 / (16) / 26 / 166 [a]Logistic regression with continuous cumulative exposure; restricted cubic spline functions used to assess shape of exposure-response. "Starting at" refers to the cumulative exposure level reflecting the beginning of the increasing risk pattern; "statistically significant at" refers to the cumulative exposure level at which the relative risk estimate was statistically significant.

Larson et al. (2012a) used data collected as part of the community screening program conducted in 2001 [(ATSDR, 2001b); see Section 4.1.1.3] to examine the pleural and pulmonary outcomes based on chest radiographs, spirometry results, and self-reported symptoms in relation to cumulative exposure among 336 workers. Diffuse pleural thickening (in the presence of

costophrenic angle obliteration) and parenchymal small opacities (profusion ≥1/0) were each detected in 5% of the workers. Risk increased monotonically with increasing cumulative exposure for each of these outcomes; however, the slope was shallower for diffuse pleural thickening and was not statistically significant. LPT (only) was found in 35% of the workers with an elevated risk associated with cumulative exposures as low as 1 fiber/cc-yr. For a diagnosis of restrictive spirometry (excluding mixed restrictive and obstructive spirometry; prevalence = 16%), risk began to increase at 26 fibers/cc-yr and reached statistical significance at 166 fibers/cc-yr. Chronic bronchitis defined as coughing up phlegm "for at least 3 months of the year for the past 2 years" was reported in 8% of the workers, and a statistically significant increased risk was calculated at 24 fibers/cc-yr.

O.M. Scott, Marysville, OH plant workers

The first study of the O.M. Scott, Marysville, OH plant workers was conducted by (Lockey et al., 1984); see Table 4-8. Physical examination (for detection of pulmonary rales and nail clubbing), pulmonary function (spirometry and DL_{CO}), and chest x-rays were performed, and information pertaining to smoking history, work history at the plant, and other relevant work exposures was collected using a trained interviewer. Approximately 44% of the 512 workers in the study were current smokers, 20% former smokers, and 35% lifetime nonsmokers, but smoking history (i.e., smoking status, pack-years) did not differ by exposure group. An increased risk of costophrenic angle blunting (n = 11), other pleural and parenchymal abnormalities (n = 11), or any of these outcomes (n = 22) was observed in relation to exposure assessed by job title and area (see description of exposure groups in Section 4.1.1.2.2) and categorized into groups based on the cumulative fiber estimates. The prevalence of any radiographic change was 2.8% in Group I, 3.9% in Group II, and 5.8% in Group III. Using the cumulative fiber metric, the prevalence of any radiographic change was 2.4% in the <1 fiber/cc-yr group, 5.0% in 1−10 fibers/cc-yr group, and 12.5% in the >10 fibers/cc-yr group. Lockey et al. (1984) used a modification of the ILO 1971 guidelines; one modification was that costophrenic angle blunting was considered a category separate from other pleural lesions.

A follow-up study of this cohort [(Rohs et al., 2008); see Table 4.4] included 298 workers, of whom 280 completed the study interview (with work history and smoking history) and chest x-ray. The evaluation of each worker included an interview to determine work and health history, pulmonary examination, and chest x-ray. Exposure was estimated using the procedure described (Lockey et al., 1984). Exposure was assumed to occur from 1963 to 1980 in this study, assuming an 8-hour workday and 365 days of exposure per year (Benson, 2014). Each worker supplied a detailed work history (start and end date for each area within the facility). The exposure reconstruction resulted in a cumulative exposure estimate for each individual. The estimated cumulative exposure for this follow-up study ranged from 0.01 to

19.03 fibers/cc-yr (mean = 2.48). The time from first exposure ranged from 23 to 47 years. Exposure outside of work was assumed to be zero.

Table 4-8. Pulmonary function and chest radiographic studies of the O.M. Scott, Marysville, OH plant workers

Reference(s)	Inclusion criteria and design details			Results
Lockey (1985) Lockey et al. (1984)[a]	1980, *n* = 512 Three exposure groups, based on jobs and area: Mean cumulative exposure[b]			Cumulative fiber exposure related to history of pleuritic chest pain and shortness of breath. No relation between cumulative exposure and forced vital capacity, forced expiratory volume, or diffusing capacity. Costophrenic angle blunting (*n* = 11); other pleural thickening or plaques in (*n* = 10); bilateral, small opacities (*n* = 1). Abnormality (combined outcomes) increased with increasing cumulative exposure.
	Group I	0.45 fiber/cc-yr	(*n* = 112)	
	Group II	1.13 fibers/cc-yr	(*n* = 206)	
	Group III	6.16 fibers/cc-yr	(*n* = 194)	
	Radiographs read independently by two board-certified radiologists (B Readers), with a reading by a third reader when the initial two readings did not agree. Modification of ILO 1971 classification guidelines (e.g., separated costophrenic angle blunting from other pleural thickening) (see Table 4-4 for additional details).			
Rohs et al. (2008)	*n* = 280 with interviews (2004) and readable chest x-rays (2002−2005) Three B Readers based on 2000 ILO classification guidelines (see Table 4-4 for additional details).			Pleural abnormalities in 80 workers (28.7%). Small opacities (≥1/0) in eight workers (2.9%). Increasing risk of pleural abnormalities with increasing cumulative fiber exposure: odds ratios (adjusting for age, date of hire, body mass index) by exposure quartile were 1.0 (referent), 2.7, 3.5, and 6.9.

[a]Lockey et al. (1984) is the published paper based on the unpublished thesis (Lockey, 1985).
[b]Calculated based on stratified data presented in Table 2 of Lockey et al. (1984).

Three board-certified radiologists, blinded to all identifiers, independently classified the radiographs using the 2000 ILO classification system (ILO, 2002). Rohs et al. (2008) determined that diffuse pleural thickening was present when at least two of the three readers recorded pleural thickening with blunting of the costophrenic angle, localized pleural thickening was present when at least two of the three readers recorded thickening, with or without calcification, excluding solitary costophrenic angle blunting, and that interstitial abnormalities indicative of asbestosis were present if at least two of the three readers identified small irregular opacities of profusion 1/0 or greater. Radiographs classified as unreadable (*n* not reported) were not used in the analysis.

Pleural thickening was observed in 80 workers (28.7%), and small opacities (≥1/0) were observed in 8 (2.9%). The 80 workers with pleural thickening included 68 with LPT only (85%) and 12 with DPT (15%). Six of the eight participants with small opacities also had pleural

thickening (four as LPT, two as DPT). The prevalence of pleural thickening increased across exposure quartiles from 7.1% in the first quartile to 24.6, 29.4, and 54.3% in the second, third, and fourth quartiles, respectively [see Table 4-9 (Rohs et al., 2008)].

Table 4-9. Prevalence of pleural pathological alterations according to quartiles of cumulative fiber exposure in 280 participants

Exposure quartile	Exposure range, fibers/cc-yr, (mean)	Number of workers	Number of workers with pleural thickening (%)[b]	Crude OR (95% CI)	Age-adjusted OR (95% CI)	BMI-adjusted OR (95% CI)	Number of workers with small opacities (%)
First	0.01−0.28 (0.12)	70	5 (7.1)	1.0 (referent)	1.0 (referent)	1.0 (referent)	0 (0)
Second	0.29−0.85 (0.56)	72[a]	17 (24.6)	4.0 (1.4−11.6)	3.2 (1.0−9.7)	4.9 (1.3−18.2)	0 (0)
Third	0.86−2.20 (1.33)	68[a]	20[c] (29.4)	5.4 (1.9−15.5)	4.0 (1.3−12.8)	7.6 (2.1−27.5)	1 (1.5)
Fourth	2.21−19.03 (7.93)	70	38 (54.3)	15.4 (5.6−43)	10.0 (3.1−32)	17.0 (4.8−60.4)	7 (10)
Total	(2.48)	280	80 (28.6)				8 (2.9)

[a]Two observations in the second quartile and two in the third quartile had exact exposure values at the 50th percentile cutoff point. Rounding put these four observations in the second quartile.
[b]Statistically significant trend across exposure groups, p <0.001.
[c]Typographical error in publication corrected.
OR = odds ratio; BMI = body mass index.

Source: Rohs et al. (2008), Table 3 and Figure 2; mean exposure levels and number of workers with parenchymal abnormalities by quartile obtained from J. Lockey, University of Cincinnati (Benson, 2014).

Pleural thickening was strongly associated with hire on or before 1973 and age at time of interview, but not with body mass index (BMI) or smoking history (ever smoked; see Table 4-10); BMI is a potentially important confounder because fat pads can sometimes be misclassified on chest x-rays as localized pleural thickening. A hire date of on or before 1973 and age at time of interview are each highly correlated with cumulative exposure to fibers. The small number of females (n = 16) in the cohort limits the analysis of the association with gender.

Table 4-10. Prevalence of pleural thickening in 280 participants according to various cofactors

Variable	Number of workers	Number with pleural thickening (%)	Crude OR	95% CI	*p*-value
Hired after 1973	94	10 (10.6)	Reference		
Hired on or before 1973	186	70 (37.6)	5.07	2.47−10.41	<0.001
Body Mass Index,[a] kg/m^2					
≤24.9	28	8 (28.6)	Reference		
25−29.9	101	31 (30.7)	1.11	0.44−2.79	0.52
≥30	110	27 (24.5)	0.81	0.32−2.06	0.43
Ever smoked[b]					
No	96	25 (26.04)	Reference		
Yes	184	55 (29.9)	1.21	0.70−2.11	0.50
Age at time of interview					
40−49	55	5 (9.1)	Reference		
50−59	116	28 (24.1)	3.18	1.16−8.76	0.03
≥60	109	47 (43.1)	7.58	2.80−20.49	<0.001
Female	16	1 (6.3)	Reference		
Male	264	79 (29.9)	6.40	0.83−49.32	0.07

[a]*n* = 239 for BMI due to 38 persons undergoing phone interview and 3 persons with onsite interviews who were not measured for height and weight.
[b]Smoking history as recorded in 2004 questionnaire. Of these 280 participants, 20 persons reported never smoking in the 1980 questionnaire but subsequently reported a history of smoking in the 2004 questionnaire (either current or ex-smoker).

Source: Rohs et al. (2008).

Odds ratios (ORs) for quartiles of cumulative fiber exposure were also estimated including various cofactors (age, hired before 1973, or BMI). Each model demonstrated the same trend: increased prevalence of pleural thickening with increasing cumulative exposure to fibers. Adjusting for age, date of hire, and BMI resulted in odds ratios of 2.7, 3.5, and 6.9 for the second, third, and fourth quartiles, respectively. There was no evidence of significant interactions using this modeling.

There was potential coexposure to a number of fertilizers, herbicides, pesticides, and other chemicals in the facility (Smith, 2014).[15] No quantitative information on exposure to these chemicals is available. However, the addition of the other chemicals to the vermiculite carrier occurred in a different part of the facility after expansion of the vermiculite ore. Industrial hygiene monitoring in these areas showed very low levels of fibers in the air. It is unlikely that workers would be coexposed by inhalation to these other chemicals. In addition, EPA has no information indicating that exposure to any of these individual chemicals causes pleural thickening or small opacities typical of those found in workers employed in the Marysville facility, and thus EPA does not consider the presence of these coexposures likely to produce any confounding in the observed associations between LAA exposure and the pulmonary effects seen in this cohort.

The Rohs et al. (2008) study demonstrates that exposure to LAA can cause radiographic evidence of pleural thickening and parenchymal abnormalities (small opacities) in exposed workers. The prevalence of pleural abnormalities was 28.7% in 2004 (80/280), compared to a 2% prevalence observed in 1980 (10/501). In addition, the prevalence of small opacities increased from 0.2% (n = 1) in 1980 to 2.3% (n = 8) in the 2004 study. These increases in prevalence are most likely due to the length of follow-up in the later study, giving additional time for the abnormalities to become apparent in conventional x-rays; little additional exposure occurred after 1980. The follow-up study also shows an increasing prevalence of pleural thickening with increasing cumulative exposure to LAA.

The influence of some potential sources of selection bias in Rohs et al. (2008) is difficult to qualitatively or quantitatively assess. One type of conceivable selection bias is the loss of participants due to the death of 84 of the 513 (16%) workers in the first study; this group may represent a less healthy or more susceptible population. Exclusion of the very sick or susceptible may imply that the population of eligible participants was somewhat healthier than the whole population of workers; this exclusion may result in an underestimation of risk. Another type of selection is the loss due to nonparticipation among the 431 individuals identified as alive in 2004 (n = 135 refusals and nonresponders; 31%). Participation rates in epidemiologic studies can be associated with better health status, and participation is often higher among nonsmokers compared with smokers. This type of selection of a relatively healthier group (among the living) could also result in an underestimation of the risk of observed abnormalities within the whole exposed population. However, if participation was differentially related to exposure and

[15]The herbicides and pesticides used during the time when Libby ore was used included atrazine, benomyl, bensulide, chloroneb, chlorothalonyl, chlorpyrifos, 2,4-D, dacthal, diazinon, dicamba, dephenamid, disodium methanearsonate, dyrene, ethoprop, linuron, MCPP, monuron, neburon, oxadiazon, terrachlor, pentachlorophenol, phenylmercuric acetate, siduron, terrazole, thiophannate-methyl, and thiram. Other chemicals used included ammonium hydroxide, brilliant green crystals, caustic soda, corncobs, ferrous ammonium sulfate, ferrous sulfate, florex RVM, frit-504, frit-505, hi sil, lime, magnesium sulfate, mon-a-mon, potash, potassium sulfate, sudan orange, sudan red, sulfur, sulfuric acid, UFC, urea, and Victoria green liquid dye.

outcome (i.e., if workers experiencing pulmonary effects and who were more highly exposed were more likely to participate than the highly exposed workers who were not experiencing pulmonary effects), the result would be to overestimate the exposure response relationship. This latter scenario is less likely to occur for asymptomatic effects (i.e., abnormalities detected by chest x-ray), such as those that are the focus of this study, than for symptoms such as shortness of breath or chest pain.

Some information is available on differences by participation status in the Rohs et al. (2008) study. Although current age was similar (mean: 59.1 and 59.4 years, respectively, in participants and living nonparticipant groups, $p = 0.53$), participants were more likely to have been hired before or during 1973 (66.4 and 49.7%, respectively, $p = 0.001$) and were also somewhat less likely to ever be smokers (58.6%) compared with the living nonparticipants (66.2%). Participants had higher mean exposure levels (mean cumulative exposure: 2.48 and 1.76 fibers/cc-yr, respectively, in participants and nonparticipants, $p = 0.06$), but when combining living and deceased nonparticipants, there is no evidence of major differences in exposure distribution in participants compared with the original full population.

4.1.2.1.1.3. ***Results: pathological alterations of lung parenchyma and pleura, pulmonary function, and respiratory symptoms—community-based studies***

Pathological alterations of parenchyma and pleura

In the ATSDR community health screening [(ATSDR, 2001b) see Table 4-15], two board-certified radiologists (B Readers) examined each radiograph, and a third reader was used in cases of disagreement (see Tables 4-5 and 4-11). Readers were aware that the radiographs were from participants in the Libby, MT health screening but were not made aware of exposure histories and other participant characteristics (Peipins et al., 2004a; Price, 2004; Peipins et al., 2003). The radiographs revealed pleural abnormalities in 17.9% of participants, with prevalence increasing with increasing number of "exposure pathways" (defined on the basis of potential work-related and residential exposure to asbestos within Libby and from other sources). The authors noted that the relationship between number of exposure pathways and increasing prevalence of pleural abnormalities was somewhat attenuated after excluding those who had formerly worked at the vermiculite mining and milling operations. The prevalence of pleural abnormalities decreased from approximately 35 to 30% in individuals with 12 or more exposure pathways when these workers were excluded from the analysis. Among individuals with no defined exposure pathways, the prevalence of pleural anomalies was 6.7%, which the authors report is higher than reported in other population studies (Peipins et al., 2004a; Price, 2004). The direct comparability between study estimates is difficult to make; the possibility of over- or under ascertainment of findings from the x-rays based on knowledge of conditions in Libby was not assessed in this study. No information is provided regarding analyses excluding all potential work-related asbestos exposures.

Weill et al. (2011) used the ATSDR community health screening data to analyze the prevalence of x-ray abnormalities in relation to age, smoking history, and types of exposures (see Tables 4-5 and 4-11). Analysis was based on five exposure categories in *n* = 4,397 participants ages 25 to 90 years. The prevalence of x-ray abnormalities (plaques, or diffuse pleural thickening, and/or costophrenic angle obliteration) also generally increased with age (divided into 25−40, 41−50, 51−60, and 61−90 years) within each of the exposure categories, with the highest prevalence seen among former workers in the vermiculite mining and milling operations. Among those with environmental exposure only (i.e., no household or occupational exposures), the prevalence increased from approximately 2% at ages 41−50 years to 12% at ages 61−90 years.

The community-based study by Alexander et al. (2012) was conducted in an area other than Libby, MT. The Western Minerals plant in Minneapolis, MN processed Libby vermiculite ore to produce insulation material from 1939 to 1989. The plant was surrounded by residential neighborhoods, and the waste material from the plant was offered to community residents for use as filler in their yards and driveways. The Minnesota Department of Health and ATSDR initiated a study of community exposures in 2000, including a baseline survey of >6,400 residents. Residential history information was combined with period-specific air dispersion models and data on facility emissions to classify the level of background exposure (Kelly et al., 2006); details pertaining to the input parameters and modeling assumptions are limited and result in considerable uncertainty in exposure estimates. Intermittent high exposures were estimated for specific activities (e.g., playing on waste piles, moving waste from the plant) based on experiments reconstructing exposure occurring during these activities (Adgate et al., 2011). In a follow-up study of people who had not worked in the plant (or lived with a worker employed at the plant), measures of background exposure and activity-based (intermittent) exposure were associated with increased prevalence of pleural abnormalities [(Alexander et al., 2012) see Table 4-11].

Table 4-11. Pathological alterations of lung parenchyma and pleura in community-based studies

<table>
<tr><th>Reference(s)</th><th>Inclusion criteria and design details</th><th colspan="4">Results</th></tr>
<tr><td colspan="5">Libby, MT community</td></tr>
<tr><td>Peipins et al. (2003)
ATSDR (2001b)</td><td>Participants in ATSDR community health screening, n = 6,668 with chest x-rays (see Table 4-5).
19 “exposure pathways” including Libby mining company work, contractor work, dust exposure at other jobs, vermiculite exposure at other jobs, potential asbestos exposure at other jobs or in the military, cohabitation with Libby mining company worker, and residential and recreational use of vermiculite.
Pleural abnormality: (a) any unilateral or bilateral pleural calcification on the diaphragm, chest wall, or other site or (b) any unilateral or bilateral pleural thickening or plaque on the chest wall, diaphragm, or costophrenic angle site, consistent with asbestos-related pleural disease.</td><td colspan="4">Peipins et al. (2003) and ATSDR (2001b): Pleural abnormalities seen in 17.9% of participants; increasing prevalence with increasing number of exposure pathways (6.7% among those with no specific pathways, 34.6% among those with 12 or more pathways).

ATSDR (2001b): Moderate-to-severe restriction (FVC <70% predicted): 2.2% of men >17 yr old; 1.6% of women >17 yr old</td></tr>
<tr><td>Weill et al. (2011)</td><td>Participants in ATSDR community health screening, n = 4,397 ages 25 to 90 yr (see Table 4-5).
Analysis based on five exposure categories: (1) Vermiculite mining or milling workers employed directly by the company (W.R. Grace; n = 255), (2) other vermiculite worker (contractor work; n = 664), (3) dusty occupation (n = 831), (4) household (combination of three household categories; n = 880), and (5) environment (“no” to work and household exposures in Categories 1−4; n = 1,894).
Outcomes: (1) Small lung opacities defined as “any two readers reporting any profusion ≥1/0”; (2) Plaque, defined as “any two readers reporting any diaphragm or wall, or other site plaques, even if the readers did not agree on specifics”; (3) DPT or CAO defined as “any two readers reporting any DPT or CAO, even if the readers did not agree on specifics.”</td><td colspan="4"><table>
<tr><th rowspan="2">Exposure Source</th><th colspan="3">Prevalence (%)</th></tr>
<tr><th>Small opacities</th><th>Plaque</th><th>DPT/CAO</th></tr>
<tr><td colspan="4">Age 25−40 (n = 1,075)</td></tr>
<tr><td>Vermiculite worker by company</td><td>0.0</td><td>20.0</td><td>5.0</td></tr>
<tr><td>Other vermiculite worker</td><td>0.8</td><td>0.8</td><td>0.0</td></tr>
<tr><td>Dusty work</td><td>0.0</td><td>3.8</td><td>0.4</td></tr>
<tr><td>Household</td><td>0.0</td><td>2.2</td><td>0.0</td></tr>
<tr><td>Environment</td><td>0.0</td><td>0.4</td><td>0.0</td></tr>
<tr><td colspan="4">Age 41−50 (n = 1,187)</td></tr>
<tr><td>Vermiculite worker by company</td><td>0.0</td><td>26.2</td><td>5.0</td></tr>
<tr><td>Other vermiculite worker</td><td>0.5</td><td>7.8</td><td>1.0</td></tr>
<tr><td>Dusty work</td><td>0.0</td><td>3.8</td><td>0.9</td></tr>
<tr><td>Household</td><td>0.0</td><td>11.1</td><td>0.4</td></tr>
<tr><td>Environment</td><td>0.0</td><td>1.9</td><td>0.2</td></tr>
</table></td></tr>
</table>

Table 4-11. Pathological alterations of lung parenchyma and pleura in community-based studies (continued)

Reference(s)	Inclusion criteria and design details	Results			
Weill et al. (2011) (continued)		Exposure Source	Prevalence (%) Profusion ≥1/0	Plaque	DPT/CAO
		Age 51−60 (*n* = 1,034)			
		Vermiculite worker by company	3.2	34.9	3.2
		Other vermiculite worker	0.6	13.7	0.6
		Dusty work	1.0	12.6	0.0
		Household	1.0	20.1	1.5
		Environment	0.0	7.7	0.9
		Age 61−90 (*n* = 1,101)			
		Vermiculite worker by company	11.0	45.7	8.6
		Other vermiculite worker	0.6	24.8	8.5
		Dusty work	1.1	21.9	3.3
		Household	2.4	38.3	5.7
		Environment	1.3	12.7	2.2
Minneapolis, MN community					
Alexander et al. (2012)	Participants with personal or family work history at the plant; 1,765 of 2,222 individuals randomly chosen within three strata based on exposure scenarios, (intense intermittent, long-term high ambient background, and low ambient background); *n* = 461completed the study. Clinical examination, chest x-rays read by 2000 ILO classification guidelines. Participants more likely than nonparticipants to report exposure-related activities (48 and 32%, respectively), but similar history of occupational asbestos exposure (28 and 27%, respectively). Exposure based on modeling by Kelly et al. (2006) and Adgate et al. (2011).		Prevalence		
		Pleural abnormality (any)	49 (10.6%)		
		DPT	5 (1.1%)		
		LPT	45 (9.9%)		
		Regression analysis:			
		Exposure type	Beta(±SE)	OR (95% CI)	
		Background	0.322 (±0.125)	1.38 (1.08, 1.77)	
		Intermittent	0.063 (±0.039)	1.07 (0.99, 1.15)	
		Per unit increase in exposure measure; adjusted for yr of birth, history of asbestos-related job, gender, and the other exposure measure.			

SE = standard error.

Respiratory symptoms

Vinikoor et al. (2010) used the 2000−2001 health screening data to examine respiratory symptoms and pulmonary function results among 1,003 adolescents and young adults (≤18 years in 1990 when the mining/milling operations closed), excluding individuals with a work history

that could result in vermiculite or dust exposure (see Tables 4-5 and 4-12). The potential for vermiculite exposure outside of the workplace was classified based on responses to questions about six activities (e.g., handling vermiculite insulation, playing in vermiculite piles, "popping" vermiculite by heating it to make it expand). The medical history questionnaire included information on three respiratory symptoms: (1) usually have a cough (*n* = 108, 10.8%); (2) troubled by shortness of breath when walking up a slight hill or when hurrying on level ground (*n* = 145, 14.5%); or (3) coughed up phlegm that was bloody in the past year (*n* = 59, 5.9%). A question on history of physician-diagnosed lung disease (*n* = 51, 5.1%) was also included. The pulmonary function results were classified as normal in 896 (90.5%), obstructive in 62 (6.3%), restrictive in 30 (3.0%), and mixed in 2 (0.2%). There was little variation in prevalence of shortness of breath, physician-diagnosed lung disease, or abnormal spirometry across the exposure categories; for two symptoms, the highest relative risk was seen in the highest exposure group, but neither of these estimates was statistically significant (OR 2.93, 95% confidence interval (CI) 0.93, 9.25 for usually having a cough and OR 1.49, 95% CI: 0.41, 5.43 for coughing up bloody phlegm).

Table 4-12. Pulmonary function and respiratory symptoms and conditions changes in the Libby, MT community

Reference(s)	Inclusion criteria and design details	Results			
Vinikoor et al. (2010)	Participants in the ATSDR community health screening (see Table 4-5); limited to *n* = 1,003, ages 10−29 yr when screened (age ≤18 yr in 1990 when the mining/milling operations closed). Excluded if employed in vermiculite mining or milling operations, exposed to dust at other jobs, or exposed to vermiculite at other jobs. Analysis of respiratory symptoms and spirometry in relation to six vermiculite exposure activities (handling vermiculite insulation, recreational activities on a vermiculite-contaminated gravel road leading to the mine, playing at ball fields near the expansion plant, playing in or around the vermiculite piles, heating the vermiculite to "pop" it, other activities involving vermiculite).		OR (95% CI) by exposure category[a]		
			Sometimes	Frequently 1−2 activities	Frequently ≥3 activities
		Usual cough	1.88 (0.71, 5.00)	2.00 (0.76, 5.28)	2.93 (0.93, 9.25)
		Shortness of breath	1.16 (0.55, 2.44)	1.27 (0.61, 2.63)	1.32 (0.51, 3.42)
		Bloody phlegm	0.85 (0.31, 2.38)	1.09 (0.41, 2.98)	1.49 (0.41, 5.43)
		Physician-diagnosed lung disease	1.95 (0.57, 6.71)	1.51 (0.43, 5.24)	1.72 (0.36, 8.32)
		Abnormal spirometry[b]	1.34 (0.60, 2.96)	1.20 (0.53, 2.70)	1.33 (0.42, 4.19)
		[a]Adjusted for age, gender, personal smoking history, and living with a smoker; referent group = "never" response to each of the six vermiculite exposure activities. [b]Obstructive ($FEV_1/FVC < LLN$ and $FVC \geq LLN$), restrictive ($FEV_1/FVC \geq LLN$ and $FVC < LLN$) or mixed ($FEV_1/FVC < LLN$ and $FVC < LLN$) compared with normal ($FEV_1/FVC \geq LLN$ and $FVC \geq LLN$).		

Pathological alterations of lung parenchyma and pleura in relation to pulmonary function

Two studies that examined LAA specifically provide insight into the question of the relation between specific types pleural or parenchymal lesions and pulmonary function (see Table 4-13). These studies, based on data from the community health screening conducted by ATSDR, reported an association between the presence of pleural plaques and a reduced mean FVC (approximately 5% below predicted) (Weill et al., 2011), and of an increased risk of restrictive pulmonary function (Larson et al., 2012b). The authors of the first study (Weill et al., 2011) concluded that the mean reduction in FVC associated with pleural plaques (in the absence of other pleural abnormality or small opacities in the lung parenchyma) was "probably clinically insignificant." The second study (Larson et al., 2012b) focused on the likelihood of an "abnormal" pulmonary function test (restrictive lung function), rather than on a difference in population means. Although the association with a restrictive pulmonary function was weaker for circumscribed pleural plaques (OR = 1.4) than for DPT (OR = 4.1), the risk of restrictive lung function increased with increasing index score based on plaque width and extent. Among those with restrictive impairment, risk of functionally significant pulmonary impairment was associated with the presence of plaques with a high index score (OR 1.7, 2.1, and 2.3 for outcomes of mild, moderate, and severe levels of impairment, respectively). These two analyses, using essentially the same data set, illustrate that what may appear on first thought to be an "insignificant" impact on lung function (i.e., a relatively small mean decrement in lung function among an affected population) is entirely compatible with the presence of clinically important individual lung function decrements for some individuals within that population. An additional point that can be drawn from both studies is the relative strength of the influence of DPT on FVC, for example, with a >20% decrease in percent predicted associated with DPT (in the absence of small opacities in the lung parenchyma) in Weill et al. (2011).

Table 4-13. Analyses of pulmonary changes seen on radiographs in relation to pulmonary function in the Libby, MT community

Reference(s)	Inclusion criteria and design details	Results			
Weill et al. (2011)	Participants in ATSDR community health screening, *n* = 4,397, ages 25 to 90 yr. ILO 1980 classification guidelines. Profusion ≥1/0: any two readers reporting any profusion ≥1/0. Plaque: any two readers reporting any diaphragm or wall, or other site plaques, even if the readers did not agree on specifics. DPT or CAO: defined as any two readers reporting any DPT or CAO, even if the readers did not agree on specifics.	Radiographic results	% Predicted FVC		
			n	Mean	(±SE)
		DPT, CAO	33	78.76	(±3.64)
		Profusion ≥1/0	40	82.16	(±3.34)
		Other pleural abnormality	482	95.63	(±0.76)
		None of above	4,065	103.15	(±0.25)
Larson et al. (2012b)	Participants in the ATSDR community health screening, *n* = 6,476, ages ≥18 yr. Pulmonary function classified as normal, restrictive only (FVC < lower limit of normal and FEV_1/FVC > lower limit of normal), obstructive only,(FVC ≥ lower limit of normal and FEV_1/FVC < lower limit of normal) or mixed based on reference values for FVC and FEV_1/FVC for the U.S. population (Hankinson et al., 1999). Analysis adjusted for parenchymal abnormalities, age, gender, smoking history, BMI, exposure group, number of exposure pathways, duration of residence in Libby, and shortness of breath; referent group = "normal" pulmonary function. ILO 1980 classification guidelines modified such that plaques definition was equivalent to ILO 2000 LPT guidelines.	Radiographic results	Risk of restriction		
			n	OR	(95% CI)
		DPT, CAO	58	4.1	(2.1, 7.8)
		Profusion ≥1/0	50	2.9	(1.4, 6.0)
		Calcification	254	2.7	(1.2, 2.4)
		Circumscribed plaques	708	1.4	(1.1, 1.8)
		By index of degree of abnormality (median = 3.0 for DPT, 2.5 for LPT)			
		DPT Only			
		≤median	78	2.1	(1.1, 3.7)
		>median	57	5.6	(2.7, 11.6)
		Index of plaque size			
		≤median	562	1.3	(1.0, 1.7)
		>median	499	1.9	(1.5, 2.5)
		By severity of impairment, for index of plaque size > median			
		Mild (FEV_1 >70%)	63	1.7	(1.3, 2.5)
		Moderate (50% ≤ FEV_1 <69%)	50	2.1	(1.4, 3.2)
		Severe (FEV_1 <50%)	6	2.3	(0.8, 6.7)

4.1.2.1.1.4. ***Clinic-based reports and case reports of respiratory disease (noncancer).***

Whitehouse (2004) examined changes in pulmonary function measures in 123 patients (86 former employees of the vermiculite operations, 27 family members of employees, 10 Libby residents with only environmental exposures) seen in a pulmonary disease practice serving the Libby, MT area. The referral patterns and selection into this case series was not described. The mean age of these patients was 66 years. Of these 123 patients, 56 (45%) were reported to have

radiographic evidence of interstitial changes at profusion category 0/1 or 1/0 evident on their initial chest x-ray. No evidence of interstitial changes were found in the other 67 (55%), but all 67 had evidence of pleural disease (either pleural plaques or diffuse pleural thickening). For the entire group of 123, the average yearly loss of pulmonary function over a mean follow-up time of 35 months was 2.2% for FVC, 2.3% for total lung capacity, and 3.0% for DL_{CO}. For the subset of 67 patients with pleural disease (in the absence of interstitial abnormality), the corresponding mean declines were 2.2%, 2.3%, and 2.9%, respectively. Although the details of the classification system used for the radiographic readings was not described, the analysis of the pulmonary function testing incorporated appropriate analytic procedures.

A study by Winters et al. (2012) was conducted among patients seen for annual examinations at a clinic in Libby, MT specializing in the diagnosis and treatment of asbestos-related disease (see Table 4-14). The x-rays (posterior-anterior and lateral views) were read by one radiologist. In this clinic sample, 60 individuals were considered to have no abnormality, 182 had pleural abnormality only, 18 had interstitial abnormality, and 69 had both pleural and interstitial abnormalities. FVC was lower among those with pleural abnormalities compared with the no abnormalities group, and the decrement in FEV_1 was similar for the pleural and the interstitial abnormalities groups. Higher scores on the respiratory quality of life scale (indicating increased impairment) were also seen in relation the presence of pleural abnormalities. One limitation of this study is that the ILO classification criteria were not used and a description or definition of the classification categories was not provided; in addition, factors influencing the decision of residents (and past residents) to receive asbestos-related health care through this clinic introduces additional challenges to the interpretation of these data.

Table 4-14. Pulmonary function and respiratory system changes in the Libby, MT community: clinic-based study

Reference(s)	Inclusion criteria and design details	Results				
Winters et al. (2012)	Patients seen at Center for Asbestos-Related Disease clinic in Libby, MT. *N* = 329 (2/3 local, 1/3 distant), seen for annual examination; 70% between ages 50−69 yr. (156 other patients excluded because of missing data). Analysis of chest x-ray (diagnostic criteria not provided), pulmonary function, and respiratory health quality of life (questionnaire).		Mean %predicted (SD)			
			Normal (*n* = 60)	Abnormalities		
				Pleural only (*n* = 182)	Interstitial only (*n* = 18)	Both (*n* = 69)
		Pulmonary function				
		FVC	103.8 (15.0)	94.9 (20.2)[a]	95.6 (12.0)	88.8 (16.3)
		FEV_1	92.8 (21.8)	87.7 (20.0)	86.4 (16.5)	80.4 (18.6)
		FEV_1/FVC_1	94.8 (13.6)	95.9 (10.8)	94.7 (12.6)	95.6 (13.5)
		DL_{CO}	90.2 (19.5)	85.7 (20.1)	68.1 (24.5)	73.7 (22.4)
		Respiratory symptoms and quality of life[b]				
		Total score	29.8 (20.8)	39.1 (22.5)[a]	41.3 (21.5)	43.8 (20.4)
		Symptoms	47.1 (24.2)	51.8 (25.1)	54.5 (27.0)	56.3 (23.8)
		Activity	36.5 (26.8)	49.9 (27.4)[a]	54.6 (22.3)	57.7 (23.0)
		Impact	20.1 (19.2)	28.4 (21.2)[a]	28.5 (23.4)	31.4 (21.8)
		[a] p <0.05 for comparison with no abnormality ("normal") group. [b]Measured with St. George Respiratory Questionnaire; total score from 0 (better health) to 100 (worse health); symptoms = frequency and severity of respiratory symptoms; activity = activities that cause or are limited by breathlessness; impact = social function and psychological disturbances related to respiratory problems.				

Additional studies in the form of case reports provide ancillary evidence that exposure to LAA may lead to respiratory disease. Progressive disease from exposure to LAA was noted in a case report of fatal asbestosis in an individual who died 50 years after working at a vermiculite processing plant for a few months at about age 17 (Wright et al., 2002). In another case report, exposures that stemmed from playing for a few years as a child in contaminated vermiculite waste materials around a former Libby vermiculite processing facility was reportedly associated with the development of asbestosis and fatal lung cancer (Srebro and Roggli, 1994). Although these case reports do not provide quantitative exposure measures, they do illustrate the potential for demonstrable health effects from exposures of short duration and from exposures in a community setting.

4.1.2.1.1.5. ***Summary of respiratory effects, other than cancer.***

Epidemiology studies demonstrate consistent results pertaining to the association between LAA exposure and various adverse forms of respiratory effects, with effects seen in both

occupationally exposed worker populations and in community populations with nonoccupational exposure. The risk of mortality related to asbestosis and other forms of nonmalignant respiratory disease is elevated in the Libby vermiculite mining and processing operations workers, with a pattern of increasing risk with increasing cumulative exposure (more than a 10-fold increased risk of asbestosis and a 1.5- to 3-fold increased risk of nonmalignant respiratory disease) in the analyses using internal, referent groups in McDonald et al. (2004), Sullivan (2007), and Larson et al. (2010b). Radiographic evidence of small opacities (evidence of parenchymal damage) and pleural thickening has also been shown in studies of Libby workers (Larson et al., 2012a; Larson et al., 2010a; Whitehouse, 2004; Amandus et al., 1987a; McDonald et al., 1986b), and in the studies of workers in the Marysville, OH plant (Rohs et al., 2008; Lockey et al., 1984). In the Marysville cohort, the prevalence of small opacities (interstitial changes in the lung) increased from 0.2% in the original study to 2.9% in the follow-up study, and the prevalence of pleural thickening increased from 2 to 28.6%. No effects on lung function were found in the original study (Lockey et al., 1984), and lung function was not reported for the Rohs et al. (2008) analysis of the cohort follow-up. Data from the ATSDR community health screening study in Libby, MT indicate that the prevalence of pleural abnormalities, identified by radiographic examination, increases substantially with increasing number of exposure pathways (Peipins et al., 2003). The presence of pleural plaques is associated with a small decrement in lung function (approximately 5%) when evaluated based on mean values (Weill et al., 2011), and is associated with an increased risk of restrictive lung function (Larson et al., 2012b). Stronger associations are seen with the presence of DPT in both of these studies. Additional evidence of respiratory effects of LAA exposure comes from the study of residents in an area surrounding a processing plant in Minneapolis, MN (Alexander et al., 2012).

4.1.3. Other Effects, Noncancer

4.1.3.1. *Cardiovascular Disease*

Larson et al. (2010b) present data on mortality due to cardiovascular diseases (CVDs) among the Libby cohort of vermiculite workers, with SMRs of 0.9 (95% CI: 0.9, 1.0) for heart disease (n = 552) and 1.4 (95% CI: 1.2, 1.6) for circulatory system diseases (n = 258). Similar results were seen in the analysis by Sullivan (2007) of this cohort, with an SMR for heart disease of 0.9 (95% CI 0.8–1.1), and SMR for diseases of the circulatory system (specifically, diseases of circulatory diseases involving the arteries, veins, and lymphatic vessels) of 1.8 (95% CI, 1.2−2.6). In the study by Larson et al. (2010b), deaths due to heart diseases were further categorized into ischemic heart disease (n = 247) and other heart disease (n = 120, for pericarditis, endocarditis, heart failure, and ill-defined descriptions and complications of heart disease). The SMR for ischemic heart disease was 0.7 (95% CI: 0.6, 0.8), and the SMR for other heart disease was 1.5 (95% CI: 1.2, 1.8). Circulatory diseases included hypertension without heart disease (n = 42), with an SMR of 1.7 (95% CI: 1.2, 2.4) and diseases of arteries,

veins, or lymphatic vessels (*n* = 136), SMR = 1.6 (95% CI: 1.4, 2.0). The combined category of cardiovascular mortality resulted in modestly increased risks across quartiles of exposure, with RRs of 1.0 (referent), 1.3 (95% CI: 1.0, 1.6), 1.3 (95% CI: 1.0, 1.6), and 1.5 (95% CI: 1.1, 2.0) with exposure groups of <1.4, 1.4 to <8.6, 8.6 to <44.0, and ≥44.0 fibers/cc-yr, respectively. In the Monte Carlo simulation used to estimate the potential bias in cardiovascular disease risk that could have been introduced by differences in smoking patterns between exposed and unexposed workers in the cohort, the bias adjustment factor was relatively small ($RR_{unadjusted}/RR_{adjusted}$ = 1.1), reducing the overall RR estimate from 1.6 to 1.5. The observed association between asbestos exposure and cardiovascular disease mortality may reflect, at least in part, a consequence of an underlying respiratory disease.

4.1.3.2. *Autoimmune Disease and Autoantibodies*

Three epidemiology studies have examined the potential role of LAA and autoimmunity. Noonan et al. (2006) used the data from the community health screening to examine self-reported histories of autoimmune diseases (rheumatoid arthritis, scleroderma, or lupus) in relation to the asbestos exposure pathways described above (see Tables 4-5 and 4-15). To provide more specificity in the self-reported history of these diseases, a follow-up questionnaire was mailed to participants to confirm the initial report and obtain clarifying information regarding the type of disease, whether the condition had been diagnosed by a physician, and whether the participant was currently taking medication for the disease. Responses were obtained from 208 (42%) of the 494 individuals who had reported these conditions. Of these 208 responses, 129 repeated the initial report of the diagnosis of rheumatoid arthritis, and 161 repeated the initial report of the diagnosis of one of the three diseases (rheumatoid arthritis, scleroderma, or lupus); approximately 70% of those confirming the diagnosis also reported taking medication for the condition. Among people aged 65 and over (*n* = 34 rheumatoid arthritis cases, determined using responses from the follow-up questionnaire), a twofold to threefold increase in risk was observed in association with several measures reflecting potential exposure to asbestos (e.g., asbestos exposure in the military) or specifically to LAA (e.g., past work in mining and milling operations, use of vermiculite in gardening, and frequent playing on vermiculite piles when young). Restricted forced vital capacity (defined as FVC <80% predicted and a ratio of FEV_1 to FVC ≥70% predicted), presence of parenchymal abnormalities, playing on vermiculite piles, and other dust or vermiculite exposures were also associated with rheumatoid arthritis in the group younger than 65 years (*n* = 95 cases). For all participants, an increased risk of rheumatoid arthritis was observed with increasing number of exposure pathways. Although the information gathered in the follow-up questionnaire and repeated reports of certain diagnoses decreased the false-positive reports of disease, the reliance of self-reported data is a limitation of this study. Considerable misclassification (over-reporting and under-reporting) is likely, given the relatively low confirmation rate of self-reports of

physician-diagnosed rheumatoid arthritis (and other autoimmune diseases) seen in other studies (Karlson et al., 2003; Rasch et al., 2003; Ling et al., 2000).

Another study examined serological measures of autoantibodies in 50 residents of Libby, MT, and a comparison group of residents of Missoula, MT [(Pfau et al., 2005) see Table 4-15] The Libby residents were recruited for a study of genetic susceptibility to asbestos-related lung disease, and the Missoula residents were participants in a study of immune function. None of the 50 Missoula residents and three of the Libby participants reported a history of a rheumatoid arthritis, systemic lupus erythematosus, or other systemic autoimmune disease (SAID). Libby residents exhibited an increased prevalence (22%) of high-titer (≥1:320) antinuclear antibodies when compared to Missoula residents (6%), and similar increases were seen in the Libby samples for rheumatoid factor, antiribonucleoprotein (RNP), anti-Scl-60, anti-Sm, anti-Ro (SSA), and anti-La (SSB) antibodies. Although neither sampling approach was based on a random selection from the community residents, an individual's interest in participating in a gene and lung-disease study would not likely be influenced by the presence of autoimmune disease or autoantibodies in that individual. Thus selection bias would not be considered likely in this study.

In a follow-up study, Marchand et al. (2012) examined the association of autoantibodies with asbestos-related lung disease in 124 Libby residents (65 female, 59 male). Serum samples were tested for the presence of antimesothelial cell antibodies (MCAA) to determine if the mesothelial cells of the pleural lining are targets for autoimmune responses. Mean concentrations of MCAA were increased in Libby residents, particularly in those with lung or pleural lesions compared to a reference population of Missoula residents. In addition, Libby residents positive for antinuclear antibodies or MCAA had an increased odds ratio of also presenting with pleural abnormalities (odds ratio 3.60 and 4.88, respectively). However, the cross-sectional nature of this study design makes it difficult to determine if these autoantibodies were a principal mechanism for inducing pleural disease, or if their presence is an indication of tissue damage.

Table 4-15. Autoimmune-related studies in the Libby, MT community

Reference(s)	Inclusion criteria and design details	Results
Noonan et al. (2006)	Nested case-control study among 7,307 participants in 2000−2001 community health screening. Conducted interviews, gathered self-reported history of rheumatoid arthritis, scleroderma, or lupus. Follow-up questionnaire mailed to participants concerning self-report of "physician-diagnosis" of these diseases and medication use. Outcome: self-reported cases of physician-diagnosed rheumatoid arthritis, lupus, or scleroderma	Association with work in Libby mining/milling operations (ages 65 and older): Rheumatoid arthritis OR: 3.2 (95% CI: 1.3, 8.0) Rheumatoid arthritis, lupus, scleroderma OR: 2.1 (95% CI: 0.90, 4.1) Risk increased with increasing number of asbestos exposure pathways: Zero pathways: 1.0 (Referent) One pathway: 1.02 Two to three pathways: 1.79 Four to five pathways: 2.51 ≥Six pathways: 3.98 (trend p <0.001, adjusting for restrictive spirometry, parenchymal abnormalities, and smoking history)
Pfau et al. (2005)	Libby residents (n = 50) recruited for study of genetic susceptibility to asbestos-related lung disease. Missoula, MT comparison group (n = 50), recruited for study of immune function; age- and gender-matched to Libby participants. Outcome: serum samples obtained for measurement of IgA levels and autoantibody prevalence (antinuclear, anti-dsDNA, anti-rheumatoid factor, anti-Sm, anti-RNP, anti-Ro, anti-La, and anti-Scl-70 antibodies).	Increased prevalence of high-titer (≥1:320) antinuclear antibodies in Libby sample (22%) compared to Missoula sample (6%). Similar increases for rheumatoid factor, anti-RNP, anti-Scl-60, anti-Sm, anti-R_o (SSA), and anti-La (SSB) antibodies observed in Libby sample.
Marchand et al. (2012)	Follow-up to Pfau et al. (2005) study (see row above). Randomly selected 124 out of 318 banked samples from Libby residents, mean age 50 yr (ranging from 14 to 84 yr). Compared with 25 samples from Missoula, MT, mean age 45 yr (ranging from 19 to 78 yr). Positive autoantibody test for mesothelial cells defined based on mean + 3 SD of Missoula samples. Outcome: results of chest radiographs for Libby residents obtained from community screening program described in (ATSDR, 2001b); see Section 4.1.2, Table 4-11.	Prevalence in Libby residents: Pleural abnormalities 25% Interstitial abnormalities only 52% No abnormalities 23% Association with pulmonary abnormality: ANA: n = 76, (61.3), OR = 3.6 MCAA: n = 23, (18.5), OR = 3.8

ANA = antinuclear antibody; dsDNA = double-stranded DNA; MCAA = antimesothelial cell autoantibodies; RNP = ribonucleoprotein.

4.1.4. Cancer Effects

4.1.4.1. *Lung Cancer*

Several analyses of the mortality experience of Libby vermiculite workers have been conducted (see Section 4.1.1 for a summary of exposure measures and cohort descriptions for these studies). The studies of the Libby worker cohort by Amandus and Wheeler (1987), Sullivan (2007), and Larson et al. (2010b) defined lung cancer mortality based on a more specific cause of death codes (e.g., cancers of the trachea, bronchus, and lung) compared to the broader classification of "all respiratory cancer" used by McDonald et al. (2004) and McDonald et al. (1986a), which would include laryngeal and "other" respiratory cancers. In the national Surveillance, Epidemiology, and End Results cancer data from 2003−2007, the age-adjusted mortality rate for cancer of the larynx was 1.2 per 100,000 person-year, compared to 52.5 per 100,000 person-year for lung and bronchial cancer (NCI, 2011). Thus, these additional categories (larynx and "other" respiratory cancers) represent a relatively small proportion of respiratory cancers. Although they could also be a source of some misclassification of the outcome if these other cancers are not related to asbestos exposure, the magnitude of this bias would be small.

In the more recent study by McDonald et al. (2004), 44 respiratory cancers were observed among 406 men who had worked at least 1 year in the vermiculite mining and milling facilities. Sullivan (2007) and Larson et al. (2010b) included workers with less than 1 year of work, resulting in a larger sample size (approximately 1,700) and more than 80 lung cancer deaths. Each of these studies observed an increased overall risk, with SMRs of 1.4, 1.6, and 2.4, respectively in Sullivan (2007), Larson et al. (2010b), and McDonald et al. (2004). Exposure-response analyses from these studies demonstrated increasing mortality with increasing exposure, using categorical and continuous measures of exposure, different lag periods, and different exposure metrics, with approximately a twofold to threefold increased risk in the highest exposure group (see Table 4-16 and Figure 4-3). Larson et al. (2010b) uses a referent category of 0 to <1.4 fibers/cc-yrs for all analyses (based on the distribution among all deaths); this is a lower level compared with the other studies. In addition, as described in Section 4.1.1.1.2, the cumulative exposure distribution in (Larson et al., 2010b) is lower than in (Sullivan, 2007).

Table 4-16. Respiratory (lung) cancer mortality and exposure-response analyses based on related studies of the vermiculite mining and milling workers in Libby, MT[a]

Reference(s)	Inclusion criteria and design details	Standardized mortality ratio (95% CI)	Exposure-response analyses—lung cancer
Amandus and Wheeler (1987)	Men, hired before 1970, worked at least 1 yr, follow-up through 1982 (n = 575); 161 deaths (159 with death certificates) Mean duration: 8.3 yr Mean fiber-yr: 200.3 12 female workers not included in this analysis	*No exclusions:* All cancer (n = 38) SMR: 1.3 (0.9, 1.8) Lung (n = 20) SMR: 2.2 (1.4, 3.4) *20 or more yr since first hire (latency):* Lung (n = 12) SMR: 2.3 (p <0.05)	*No exclusions:* Cumulative exposure — n — SMR (95% CI)[b] 0.0−49 fibers/cc-yr — 6 — 1.5 (not reported) 50−99 fibers/cc-yr — 2 — 1.6 (not reported) 100−399 fibers/cc-yr — 2 — 1.1 (not reported) ≥400 fibers/cc-yr — 10 — 5.8 (not reported, but p < 0.01) *20 or more yr since first hire (20-yr latency)* Cumulative exposure — n — SMR (95% CI)[b] 0.0−49 fibers/cc-yr — 2 — 0.85 (not reported) 50−99 fibers/cc-yr — 2 — 2.3 (not reported) 100−399 fibers/cc-yr — 1 — 1.1 (not reported) ≥400 fibers/cc-yr — 7 — 6.7 (not reported, but p < 0.01) In linear regression analysis of data with at least 20-yr latency, results per fiber-yr: beta (standard error) = 0.60 (0.13) and 0.58 (0.08), respectively, for threshold and nonthreshold models. Using a survival (Cox) model, the corresponding estimate is 0.11 (0.04). All estimates are statistically significant (p <0.05).

Table 4-16. Respiratory (lung) cancer mortality and exposure response analyses based on related studies of the vermiculite mining and milling workers in Libby, MT[a] (continued)

Reference(s)	Inclusion criteria and design details	Standardized mortality ratio (95% CI)	Exposure-response analyses—lung cancer
McDonald et al. (2004) McDonald et al. (1986a)	Men, hired before 1963, worked at least 1 yr (*n* = 406); follow-up through 1999 (McDonald et al., 2004); 165 deaths before July 1983 (163 with death certificates); 120 deaths July 1983−1998 coded by nosologists using ICD-8 classifications; cause of death for deaths from 1983−1998 obtained from National Death Index. Mean duration: 8.7 yr Mean fiber-yr: 144.6	Respiratory (*n* = 44) SMR: 2.4 (1.7, 3.2)	*Excluding first 10 yr of follow-up:* Cumulative exposure / *n* / RR (95% CI)[d] 0.0−11.6 fibers/cc-yr / 5 / 1.0 (referent) 11.7−25.1 fibers/cc-yr / 9 / 1.7 (0.58, 5.2) 25.2−113.7 fibers/cc-yr / 10 / 1.9 (0.63, 5.5) ≥113.8 fibers/cc-yr / 16 / 3.2 (1.2, 8.8) Per 100 fibers/cc-yr increase (linear model, RR = 1 + b*exposure) 0.36 (0.03, 1.2) (*p* = 0.02) Similar patterns were reported for analyses of intensity and residence-weighted exposure, but results not presented in paper.
Sullivan (2007)	White men, enumerated in 1982, alive in 1960 or hired after 1960, worked at least 1 d, follow-up 1960−2001 (2.2% loss to follow-up) (*n* = 1,672); 767 deaths (95% with known cause of death) Mean duration: 4.0 yr (808, ~50% worked less than 1 yr) Median fibers/cc-yr: 8.7 Underlying cause of death data from death certificates or National Death Index-Plus.	*15-yr exposure lag:* All cancer (*n* = 202) SMR: 1.4 (1.2, 1.6) Lung (*n* = 89) SMR: 1.7 (1.4, 2.1)	*15-yr exposure lag:* Cumulative exposure / *n* / SMR (95% CI)[b] / SRR (95% CI)[c] 0.0−4.49 fibers/cc-yr / 19 / 1.5 (0.9, 2.3) / 1.0 (referent) 4.5−22.9 fibers/cc-yr / 24 / 1.6 (1.1, 2.5) / 1.1 (0.6, 2.0) 23.0−99.0 fibers/cc-yr / 23 / 1.8 (1.1, 2.7) / 1.4 (0.7, 2.7) ≥100 fibers/cc-yr / 23 / 1.9 (1.2, 2.9) / 1.5 (0.8, 2.8) Linear trend test / (p <0.001) Duration / *n* / SMR (95% CI)[b] / SRR (95% CI)[c] <1 yr / 41 / 1.6 (1.1, 2.1) / 1.0 (referent) 1−9.9 yr / 34 / 1.7 (1.1, 2.3) / 1.1 (0.7, 1.8)

Table 4-16. Respiratory (lung) cancer mortality and exposure response analyses based on related studies of the vermiculite mining and milling workers in Libby, MT[a] (continued)

Reference(s)	Inclusion criteria and design details	Standardized mortality ratio (95% CI)	Exposure-response analyses—lung cancer			
			≥10 yr	14	2.5 (1.4, 4.3)	1.8 (0.9, 3.4)
			Linear trend test			p <0.05
Larson et al. (2010b)	Inclusion criteria not described (n = 1,862); follow-up through 2006 (10% loss to follow-up); 952 deaths (87% with known cause of death). Median duration: 0.8 yr Median fibers/cc-yr = 4.3 Immediate and underlying causes of death data from death certificates or National Death Index-Plus (In a follow-up of the Sullivan (2007) cohort through 2006, 1,009 deaths were identified, indicating an underascertainment of approximately 5.6% of the deaths by Larson et al. (2010b); this difference could be related to the higher loss to follow-up in this study).	Lung (n = 104) SMR: 1.6 (1.3, 2.0)	*20-yr exposure lag:*			
			Cumulative exposure	n	SMR (95% CI)[b]	RR (95% CI)[e]
			0.0−<1.4 fibers/cc-yr	19	(not reported)	1.0 (referent)
			1.4 to <8.6 fibers/cc-yr	20	(not reported)	1.1 (0.6, 2.1)
			8.6 to <44.0 fibers/cc-yr	21	(not reported)	1.7 (1.0, 3.0)
			≥44.0 fibers/cc-yr	38	(not reported)	3.2 (1.8, 5.3)
			Per 100 fibers/cc-yr increase			1.11 (1.05, 1.18) (p = 0.006)

[a]Includes miners, millers, and processors; workers in the screening plant, loading docks, and expansion plants; and office workers.
[b]SMR based on external referent group.
[c]In Sullivan (2007), the SRR is a ratio of sums of weighted rates in which the weight for each stratum-specific rate is the combined person-yr for the observed cohort across all duration (or cumulative level of exposure) categories. The Life Table Analysis System provides the SRR for each duration (or cumulative level of exposure) group compared to the referent group. The cutoff points for the categories are specified by the user. Taylor-series-based confidence intervals are given for each specific SRR.
[d]In McDonald et al. (2004), the RR is based on Poisson analysis using an internal referent group.
[e]In Larson et al. (2010b), the RR is based on Cox proportional hazards modeling using an internal referent group.
SMR = standardized mortality ratio; CI = confidence interval; SRR = standardized rate ratio; RR = relative risk.

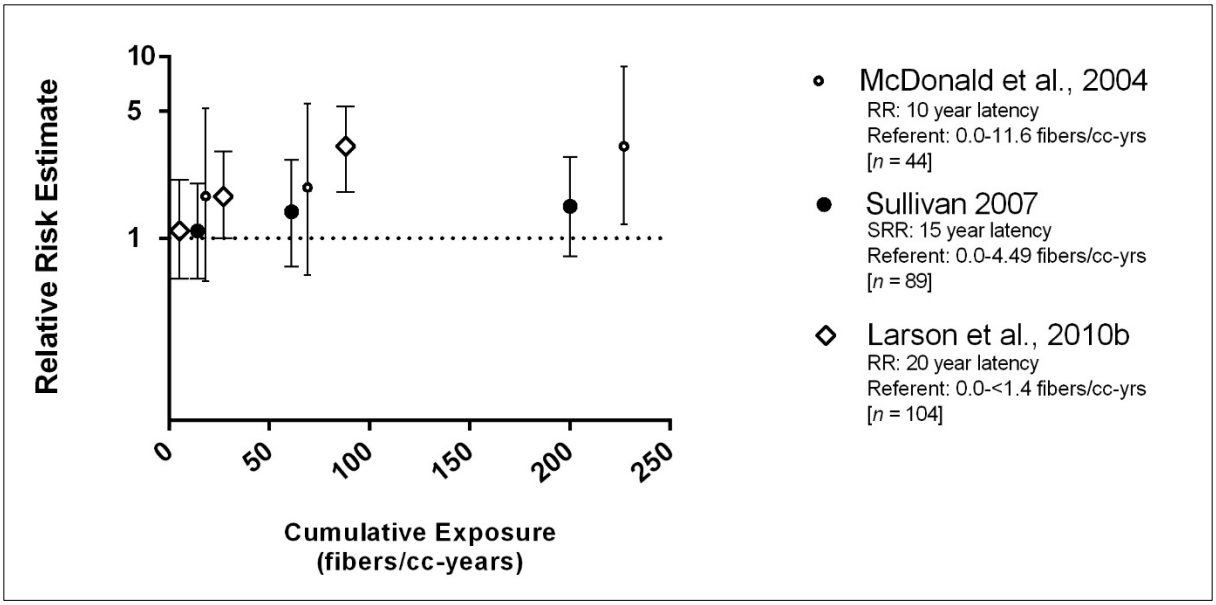

Figure 4-3. Lung cancer mortality risk among workers in the Libby, MT vermiculite mine and mill workers. Data from the three studies with updated follow-up (through 1998, 2001, and 2006, respectively, in McDonald et al. (2004), Sullivan (2007), and Larson et al. (2010b). Size of symbols is proportional to number of observed cases. Midpoint of the highest exposure category in each group is estimated as twice the value of the lower cut-point.

Two of these studies included data addressing the question of the extent to which the results could be confounded by smoking (Larson et al., 2010b; Amandus and Wheeler, 1987). Amandus and Wheeler (1987) provide some information on the smoking history of a sample of 161 male workers employed during 1975−1982 with at least 5 years of employment in the Libby cohort study and comparison data based on surveys conducted in the United States from 1955−1978. Among the workers, 35% were current smokers and 49% were former smokers. This smoking information was obtained from questionnaires the company administered to workers after 1975 (Amandus et al., 1987a). The prevalence of current smokers was similar in the worker cohort compared to the U.S. white male population data (ranging from 37.5−41.9% current smokers between 1975 and 1978). The only year in this range with data on former smokers in the national survey is 1975, and at that time, the prevalence of former smokers in the population data was 29.2%, about 20% lower than among the workers. Using an estimated RR of lung cancer of 14 among smokers, Amandus and Wheeler (1987) estimated that the difference in smoking rates between workers and the comparison population could have resulted in a 23% increase in the observed risk ratio and commented that the increased risk observed in the lower dose range (<50 fiber-year) could be the result of confounding by smoking status.

Smoking patterns in the U.S. population changed considerably over the period corresponding to the data reported by Amandus and Wheeler (1987). W. R. Grace and Co. instituted a smoking ban on the property in 1979 (Peacock, 2003), which may have affected

smoking habits, reporting of smoking habits, or both. In the National Health Interview Surveys conducted between 1974 and 1983, the prevalence of smoking in males age 20 and older decreased from 42.1 to 35.5% (HHS, 1990). Based on 1986 survey data, the percentage of adults age 17 and older classified as former smokers varied between 14.7% and 25.8% using different definitions for time since last smoked [e.g., from quitting 5 or more years ago to quitting within the past 3 months; (HHS, 1990)]. Thus, given the lack of information pertaining to the period in which smoking information was collected and the specifics of the sources that were used, EPA concludes there is considerable uncertainty regarding the evidence for differences in smoking rates between the workers and the external comparison population.

Larson et al. (2010b) used data from the ATSDR community health screening in Libby (described in Section 4.1.1.3) pertaining to smoking history to estimate that the proportion of smokers ranged from 50 to 66% in the unexposed group (defined as exposure <8.6 fibers/cc-yr) and between 66 and 85% among the exposed (defined as ≥8.6 fibers/cc-yr). Larson et al. (2010b) used these estimates in a Monte Carlo simulation to estimate the potential bias in lung cancer risks that could have been introduced by differences in smoking patterns. The bias adjustment factor ($RR_{unadjusted}/RR_{adjusted}$ = 1.3) reduced the overall RR estimate for lung cancer from 2.4 to 2.0.

O.M. Scott, Marysville, OH plant workers

There was no evidence of an increased risk of lung cancer in the analysis of mortality among the 465 Marysville, OH plant workers (Dunning et al., 2012). The SMR was 0.9 (95% CI: 0.5−1.5), based on 16 observed lung cancer deaths, and there was no indication of an increased risk in analyses stratifying by tertiles of cumulative exposure (SMRs varying between 0.8 and 1.0, and standardized rate ratios (SRRs) varying between 0.9 and 1.0).

Geographic mortality analysis

In the geographic mortality analysis (1979−1998) conducted by ATSDR (2000), the SMR for lung cancer ranged from 0.9−1.1 and 0.8−1.0 for each of the six geographic boundaries using Montana and U.S. reference rates, respectively. These analyses did not distinguish between deaths among workers and deaths among other community members.

4.1.4.2. *Mesothelioma*

Prior to the 10th revision of the ICD, which was implemented in the United States in 1999, there was no unique ICD code for mesothelioma. The updated NIOSH study by Sullivan (2007) identified 15 deaths for which mesothelioma was mentioned on the death certificate. Only two deaths occurring between 1999 and 2001 were coded to mesothelioma under ICD-10 (Code C45). Larson et al. (2010b) classified all death certificates listing mesothelioma as ICD-10 code C45. The updated McGill study [(McDonald et al., 2004); with analysis through

1998] noted that the classification of mesothelioma was based on a nosologist's review of death certificates; 5 of the 12 cases classified as mesothelioma had a cause of death listed as pleural cancer (ICD-9 code 163).

Data pertaining to mesothelioma risk from the available occupational studies are summarized in Table 4-17. McDonald et al. (2004) presented dose-response modeling using Poisson regression of mesothelioma risk based on 12 cases. Note that the referent group was also at excess risk of dying from mesothelioma; that is, one to three cases of mesothelioma were observed in the referent group, depending on the exposure index. Three exposure indices were used in the analysis: average intensity over the first 5 years of employment, cumulative exposure, and residence-weighted cumulative exposure. Because of the requirement for 5 years of employment data, 199 individuals (including three mesothelioma cases) were excluded from the analysis of average intensity. The residence-weighted cumulative exposure was based on the summation of exposure by year, weighted by years since the exposure. This metric gives greater weight to exposures that occurred a longer time ago. Although evidence of an excess risk of dying from mesothelioma was seen in all groups, only the residence-weighted cumulative exposure metric exhibited a monotonically increasing pattern, with an RR of 1.57 among those with 500.1−1,826.8 fibers/cc-yr exposure, and an RR of 1.95 among workers with higher residence-weighted cumulative exposure. In the study by Sullivan (2007), which identified 15 deaths from mesothelioma through a manual review of death certificates, the SMR for mesothelioma was 14.1 (95% CI: 1.8, 54.4), based on the two mesothelioma deaths occurring between 1999 and 2001, the period for which comparison data using the ICD-10 classification criteria were available.

Table 4-17. Mesothelioma mortality risk based on studies of the vermiculite mine workers in Libby, MT[a]

Reference(s)	Inclusion criteria and design details	Results		
Amandus and Wheeler (1987)	Men, hired before 1970, worked at least 1 yr, follow-up through 1982 (*n* = 575); 161 deaths (159 with death certificates). Mean duration: 8.3 yr (0 worked less than 1 yr) Mean fiber-yr: 200.3. Twelve female workers not included in this analysis.	Two mesothelioma deaths observed (hired in 1946, 33-yr latency, exposure >300 fibers/cc-yr); 1.2% of all deaths.		
McDonald et al. (2004) McDonald et al. (1986a)	Men, hired before 1963, worked at least 1 yr (*n* = 406), follow-up through 1999 (McDonald et al., 2004); 165 deaths before July 1983 (163 with death certificates); 120 deaths from July 1983−1998 coded by nosologists using ICD-8 classifications; cause of death for deaths from 1983−1998 obtained from National Death Index. Mean duration: 8.7 yr (0 worked less than 1 yr). Mean fiber-yr: 144.6.	12 mesothelioma deaths observed; 4.2% of all deaths		
		Excluding first 10 yr of follow-up:		
		Cumulative exposure	*n*	RR (95% CI)[b]
		0.0−11.6 fibers/cc-yr	1	1.0 (referent)
		11.7−25.1 fibers/cc-yr	4	3.7 (0.41, 33.5)
		25.2−113.7 fibers/cc-yr	3	3.4 (0.35, 33.2)
		≥113.8 fibers/cc-yr	4	3.7 (0.41, 33.2)
		per 100 fibers/cc-yr increase		0.10 (<0, 1.81)
				(*p* >0.20)
		Intensity category		
		0.0−11.6 fibers/cc-yr	*n*	RR (95% CI)[b]
		11.7−25.1 fibers/cc-yr	1	1.0 (referent)
		25.2−113.7 fibers/cc-yr	4	3.4 (0.37, 30.9)
		≥113.8 fibers/cc-yr	2	2.3 (0.21, 26.1)
		per 100 fibers/cc-yr increase	2	2.1 (0.19, 23.9)
				0.02 (<0, 1.08)
				(*p* >0.20)
		Residence-weighted		
		0.0−25.1 fibers/cc-yr	*n*	RR (95% CI)[b]
		25.2−113.7 fibers/cc-yr	3	1.0 (referent)
		≥113.8 fibers/cc-yr	4	1.57 (0.35, 7.07)
		per 100 fibers/cc-yr increase	5	1.95 (0.41, 8.51)
				0.03 (<0, 6.4)

Table 4-17. Mesothelioma mortality risk based on studies of the vermiculite mine workers in Libby, MT[a] (continued)

Reference(s)	Inclusion criteria and design details	Results		
Sullivan (2007)	White men, enumerated in 1982, alive in 1960 or hired after 1960, worked at least 1 d, follow-up 1960−2001 (2.2% loss to follow-up) (*n* = 1,672); 767 deaths (95% with known cause of death) Mean duration: 4.0 yr (808, ~50% worked less than 1 yr) Median fibers/cc-yr: 8.7 Underlying cause of death data from death certificates or National Death Index-Plus. SMR analysis limited to 1999−2001 because this is the period for which comparison data from ICD-10 are available.	15 mesothelioma deaths observed; 2% of all deaths *N* = 2 for 1999−2001: SMR: 15.1 (95% CI: 1.8, 54.4) Pleural (*n* = 4) SMR: 23.3 (95% CI: 6.3, 59.5)		
Larson et al. (2010b)	Inclusion criteria not described (*n* = 1,862); follow-up through 2006 (10% loss to follow-up); 952 deaths (87% with known cause of death). Median duration: 0.8 yr Median fibers/cc-yr = 4.3 Immediate and underlying causes of death data from death certificates or National Death Index-Plus.	19 mesothelioma deaths observed		
		20-yr exposure lag:		
		Cumulative exposure	*n*	RR (95% CI)
		<1.4 fibers/cc-yr	1	1.0 (referent)
		1.4 to <8.6 fibers/cc-yr	2	1.9 (0.31, 13.6)
		8.6 to <440 fibers/cc-yr	5	4.5 (0.8, 24.6)
		≥44.0 fibers/cc-yr	11	17.1 (3.7, 78.1)
		per 100 fibers/cc-yr increase		1.15 (1.03, 1.28)
				(*p* = 0.0134)

[a]Includes miners, millers, and processors; workers in the screening plant, loading docks, and expansion plants; and office workers.
[b]In McDonald et al. (2004), the RR is based on Poisson analysis using an internal referent group.
[c]In Larson et al. (2010b), the RR is based on Cox proportional hazards modeling using an internal referent group.

A more descriptive presentation of a collection of mesothelioma cases was reported by Whitehouse et al. (2008). This report reviewed 11 cases of mesothelioma diagnosed between 1993 and 2006 in residents in or around Libby, MT (*n* = 9) and in family members of workers in the mining operations (*n* = 2). Three cases were men who might have had occupational asbestos exposure through construction work (Case 1), working in the U.S. Coast Guard and as a carpenter (Case 5), or through railroad work involving sealing railcars in Libby (Case 7). One case was a woman whose father had worked at the mine for 2 years; although the family lived 100 miles east of Libby, her exposure may have come through her work doing the family laundry, which included laundering her father's work clothes. The other seven cases (four women, three men) had lived or worked in Libby for 6−54 years and had no known occupational or family-related exposure to asbestos. Medical records were obtained for all 11 patients;

pathology reports were obtained for 10 of the 11 patients. The Centers for Disease Control and Prevention estimated the death rate from mesothelioma, using 1999 to 2005 data, as approximately 23.2 per million per year in males and 5.1 per million per year in females (CDC, 2009). The rate in females is more likely to reflect a population that is not occupationally exposed to asbestos, and is closer to the background incidence of mesothelioma estimated by as about 1 per million in a population with little or no asbestos exposure (Hillerdal, 1983). Although not calculated by Whitehouse et al. (2008), the observation of seven cases without known personal or familial occupational exposure, over a 15-year observation period and an estimated Libby area (Lincoln Country) population of 9,500 (142,000 person-year) would result in an incidence rate of approximately 49 per million per year. Whitehouse et al. (2008) stated that a W.R. Grace unpublished report of measures taken in 1975 indicated that exposure levels of 1.1 fibers/cc were found in Libby, and 1.5 fibers/cc were found near the mill and railroad facilities. Because the mining and milling operations continued to 1990, and because of the expected latency period for mesothelioma, Whitehouse et al. (2008) suggested that additional cases can be expected to occur within this population, as well as in transitory workers and in workers who had left the area.

4.1.4.2.1. ***O.M. Scott, Marysville, OH plant workers.*** In the analysis of mortality through June 30, 2011 among the Marysville, OH plant workers, 2 of the 465 workers died of mesothelioma compared to an expected 0.2 cases (SMR 10.5, 95% CI 1.3, 38) (Dunning et al., 2012). The cumulative exposure for each of these two cases was approximately 45 fibers/cc-yr. One other incident mesothelioma case (diagnosed in 2010 and alive through the defined mortality follow-up period in the study) was identified in the cohort. This case is not included in the mortality analysis, but the cumulative exposure of the individual was 5.73 fibers/cc-yr.

4.1.4.3. *Other Cancers*

Larson et al. (2010b) presented data on cancers other than respiratory tract and mesothelioma. The category of malignant neoplasms of digestive organs and peritoneum included 39 observed deaths, for an SMR of 0.8 (95% CI: 0.6, 1.1). No risk in relation to asbestos exposure was seen with a 20-year lag.

4.1.4.4. *Summary of Cancer Mortality Risk in Populations Exposed to Libby Amphibole Asbestos*

The studies conducted in the 1980s (Amandus and Wheeler, 1987; McDonald et al., 1986a) as well as the extended follow-up studies published in more recent years (Larson et al., 2010b; Sullivan, 2007; McDonald et al., 2004) provide consistent evidence of an increased risk of lung cancer mortality and of mesothelioma mortality among the workers in the Libby vermiculite mining and processing operations. The lung cancer analyses using an internal

referent group in the larger follow-up studies (Larson et al., 2010b; Sullivan, 2007; McDonald et al., 2004) observed increasing risks with increasing cumulative exposure when analyzed using quartiles or as a continuous measure. Increased risks are also seen in the studies reporting analyses using an external referent group [i.e., standardized mortality ratios (Sullivan, 2007; Amandus and Wheeler, 1987; McDonald et al., 1986a)]. Although an increased lung cancer risk was not observed in the Marysville, OH plant workers, three cases of mesothelioma (two of whom were included in the mortality analysis) have been identified as of June, 2011. These observations further support the identification of cancer (specifically, lung cancer and mesothelioma) as a hazard of LAA.

4.1.5. Comparison With Other Asbestos Studies—Environmental Exposure Settings

The literature pertaining to risks of asbestos is extensive; of particular interest is the set of studies examining environmental exposures to constituents of LAA (e.g., tremolite) or other amphiboles. This literature provides findings consistent with those identified for LAA.

Several communities have been exposed in environmental or residential settings to tremolite or tremolite-chrysotile mixtures from natural soils and outcroppings as well as construction materials found in the home (see Table 4-18). Studies on these affected populations (published as early as 1979) reported an increased risk of pleural and peritoneal malignant mesothelioma (Sichletidis et al., 1992b; Baris et al., 1987; Langer et al., 1987; Baris et al., 1979). Clinical observations include a bilateral increase in pleural calcification accompanied by restrictive lung function decrements as the disease progresses, a condition known as “Metsovo lung,” named after a town in Greece where this abnormality was observed among tremolite-exposed residents (Constantopoulos et al., 1985). These health effects are consistent with the health effects documented for workers exposed to commercial forms of asbestos.

Table 4-18. Exposure levels and health effects observed in communities exposed to tremolite, chrysotile, and crocidolite asbestos

Area, population	Fiber type, exposure levels, and fiber size	Effects observed			References
Tremolite and tremolite-chrysotile mixtures: whitewash material used in homes					
Turkey—Anatolia (Eshisehir district) ~2,000	Fiber: tremolite, tremolite/chrysotile mixtures Exposure: indoor 0.089 fiber/mL; outdoor 0.013 fiber/mL Size: not available	Mesothelioma			Metintas et al. (2005) Metintas et al. (2002) Yazicioglu et al. (1980) Yazicioglu (1976) Baris et al. (1979)
		Men	SIR	53	
		Women	SIR	144	
		Pleural plaques prevalence ~14% Diffuse pleural thickening prevalence ~10%			
Greece—Metsovo ~5,000	Fiber: tremolite Exposure: Variable (1 to >200 fibers/mL) Size: length ≤10 μm, diameter 0.2 μm	Mesothelioma SIR ~280 Pleural plaques prevalence ~45%			Constantopoulos et al. (1987) Constantopoulos et al. (1985) Bazas et al. (1985)
Greece—Almopa ~4,000	Fiber: tremolite, chrysotile Exposure: indoors 0.01−17.9 fibers/cc Size: not available	Mesothelioma four incident cases among 198 people with pleural plaques over 15-yr follow-up period. Pleural plaques prevalence ~24% among people over age 40 yrs, with increasing prevalence with increasing age. Longitudinal study (1988−2003) also observed increase prevalence and extent (surface area) of plaques.			Sichletidis et al. (2006) Sichletidis et al. (1992a) Sichletidis et al. (1992b)
New Caledonia ~40,000	Fiber: tremolite Exposure: not available Size: not available	Mesothelioma SMR 41 Lung cancer			Luce et al. (2000)
		Men	SMR	~1.0	
		Women	SMR	2.4	

Table 4-18. Exposure levels and health effects observed in communities exposed to tremolite, chrysotile, and crocidolite asbestos (continued)

<table>
<tr><th>Area, population</th><th>Fiber type, exposure levels, and fiber size</th><th>Effects observed</th><th>References</th></tr>
<tr><td colspan="4">Crocidolite: communities surrounding amphibole asbestos mines or mills</td></tr>
<tr><td>Australia (Wittenoom) ~4,700 nonworker residents</td><td>Fiber: Crocidolite
Cumulative exposure: 76% ≤7 fibers/mL-yr, 5.5% >20 fibers/mL-yr
Size: length >5 µm</td><td>2,500 women follow-up through 2004:
<table>
<tr><td></td><td>(n)</td><td>SMR</td></tr>
<tr><td>Mesothelioma</td><td>(30)</td><td>Not reported</td></tr>
<tr><td>Lung cancer</td><td>(30)</td><td>~1.9</td></tr>
<tr><td>Ovarian cancer</td><td>(9)</td><td>~1.4</td></tr>
<tr><td>Pneumoconiosis</td><td>(2)</td><td>~11</td></tr>
</table>
2,460 people initially exposed age <15 yr:
<table>
<tr><td rowspan="2">Cancer type</td><td colspan="2">(n) SIR</td></tr>
<tr><td>Women</td><td>Men</td></tr>
<tr><td>Mesothelioma</td><td>(13) ~ 90</td><td>(29) ~ 60</td></tr>
<tr><td>Lung</td><td>(5) ~ 2.0</td><td>(3) ~ 1.0</td></tr>
<tr><td>Brain</td><td>(4) ~ 3.6</td><td>(5) ~ 3.4</td></tr>
<tr><td>Leukemia</td><td>(4) ~ 3.0</td><td>(7) ~ 4.2</td></tr>
<tr><td>Ovary</td><td>(6) ~ 3.3</td><td>--</td></tr>
</table>
(SMRs and SIRs based on means of two different censoring methods)</td><td>Reid et al. (2013)
Reid et al. (2007)
Hansen et al. (1998)
Hansen et al. (1997)
Hansen et al. (1993)</td></tr>
</table>

SIR = standardized incidence ratio; SMR = standardized mortality ratio.

Although it is not a constituent of LAA, crocidolite is another type of amphibole asbestos that has been studied with respect to health effects arising from environmental exposures. Several studies have examined cancer risk and pneumoconiosis risk among nonworker residents of Wittenoom, Australia, an area surrounding a crocidolite asbestos mine and mill [(Reid et al., 2007; Hansen et al., 1998) see Table 4-18]. Increased risk of mesothelioma and pneumoconiosis and more modestly increased risk of lung cancer were reported in these studies.

4.2. SUBCHRONIC- AND CHONIC-DURATION STUDIES AND CANCER BIOASSAYS IN ANIMALS—ORAL, INHALATION, AND OTHER ROUTES OF EXPOSURE

Laboratory animal studies of exposure to Libby Amphibole or tremolite asbestos show effects similar to those observed in occupationally exposed human populations, including pleural pathology, mesothelioma, and lung cancer. Tremolite is an amphibole asbestos fiber that is a component of LAA (~6%). Also, in early studies, LAA was defined as tremolite. Therefore, laboratory animal studies examining the effect of tremolite exposure have been reviewed and are

summarized below to potentially increase understanding of the effects and mechanisms of LAA. Detailed study summaries can be found in Appendix D and summarized in Tables 4-19 and 4-20. As noted in Section 3, the primary route of human exposure is inhalation. Thus, studies that expose animals through a pulmonary route are the most relevant for hazard identification. No inhalation studies have been performed for LAA, but chronic intrapleural injection studies in hamsters demonstrate carcinogenicity following exposure. The chronic inhalation and intrapleural injection laboratory animal studies with tremolite asbestos demonstrated pleural pathology and carcinogenicity in rats. These studies support the epidemiology studies of LAA exposure (see Section 4.1) and aid in informing the mechanisms of LAA-induced disease.

Table 4-19. In vivo data following exposure to Libby Amphibole asbestos

Species (gender)	Exposure route	Fiber type	Mean fiber length	Mean fiber diameter	Effects[a]	Reference
LVG:LAK Hamsters (M) (*n* ~ 60/group)	Intraperitoneal injection (once) 25 mg/0.5 mL 0.9% NaCl solution	Tremolite (Sample 60) and tremolite + vermiculite (Sample 63)	n/a	n/a	Pleural adhesions (fibrosis): examined 10 animals/group at ~3 mo post exposure: Sample 60: 10/10; Sample 63: 10/10; Control: 0/10 Mesothelioma: Sample 60: 5/66; Sample 63: 5/64; Control: 0/60	Smith (1978) (W.R. Grace study)
C57Bl/6 mice (M, F) (*n* = 7/group)	Intratracheal instillation (once) 1 wk, 1 mo, 3 mo 100 µg of sample in 30 µL saline	LAA (Six Mix) and crocidolite	LAA: 7.21 ± 7.01 µm Crocidolite: 4.59 ± 4.22 µm	LAA: 0.61 ± 1.22 µm Crocidolite: 0.16 ± 0.09 µm	Altered gene expression in mice exposed to both samples; increase in collagen in exposed animals	Putnam et al. (2008)
C57Bl/6 mice (M, F) (*n* = 7/group)	Intratracheal instillation (once) 1 wk, 1 mo, 3 mo 100 µg of sample in 30 µL saline	LAA (Six Mix) and crocidolite	LAA: 7.21 ± 7.01 µm Crocidolite: 4.59 ± 4.22 µm	LAA: 0.61 ± 1.22 µm Crocidolite: 0.16 ± 0.09 µm	Collagen gene expression and protein levels increased following exposure to both forms of asbestos (~1 mo post exposure).	Smartt et al. (2010)
Wistar-Kyoto rats (M) (*n* = 12/group) SH (*n* = 6/group) SHHF (*n* = 6/group)	Intratracheal instillation (once) 1 d, 1 wk, 1 mo 0.25 or 1.0 mg/rat	LAA (Six Mix)	5.0 ± 4.5 µm	0.29 ± 0.19 µm	Strain-related differences observed in biomarkers of inflammation following exposure to LAA. No differences were observed in histopathology.	Shannahan et al. (2011a)

Table 4-19. In vivo data following exposure to Libby Amphibole asbestos (continued)

Species (gender)	Exposure route	Fiber type	Mean fiber length	Mean fiber diameter	Effects[a]	Reference
SH (M) (*n* = 8/group)	Intratracheal instillation (once) 4 h, 1 d 1.0 mg DEF; 21 µg $FeCl_3$; 0.5 mg LAA, 0.5 mg FeLAA; 0.5 mg LAA + 1 mg DEF in 300 µL saline	LAA (Six Mix)	5.0 ± 4.5 µm	0.29 ± 0.19 µm	Statistically significant increases in neutrophils was observed in BALF in animals exposed to LAA, FeLAA, and LAA + DEF with the greatest increase observed in the LAA + DEF animals.	Shannahan et al. (2011b)
Fischer 344 rats (M) (*n* = 8/group)	Intratracheal instillation (once) 1 d, 3 d, 7 d, 2 wk, 3 mo 0.65 or 6.5 mg/rat LAA; 0.65 mg amosite in 250 µL saline	LAA (Six Mix) Amosite	5.0 ± 4.5 µm	0.29 ± 0.19 µm	Statistically significant increases in inflammatory markers were observed following exposure to LAA and amosite, including increased neutrophils and inflammatory gene expression, with the greatest increase in amosite-exposed rats.	Padilla-Carlin et al. (2011)

Table 4-19. In vivo data following exposure to Libby Amphibole asbestos (continued)

Species (gender)	Exposure route	Fiber type	Mean fiber length	Mean fiber diameter	Effects[a]	Reference
Four separate study designs: (A) WKY rats (M) (*n* = 12/group) SH (M) (*n* = 6/group) SHHF (M) (*n* = 6/group) (B) F344 rats (M) (*n* = 8−12/group) (C) F344 rats (M) (*n* = 8/group) (D) WKY rats (M) (*n* = 5/group)	(A) Intratracheal instillation (once) 1 d, 1 wk, 1 mo, 3 mo 0.25 or 1.0 mg/rat (B) Intratracheal instillation (once) 3 mo, 1 yr 1.0 or 5.0 mg/rat (C) Intratracheal instillation (once every other wk for 13 wk) 1 d, 2 wk Cumulative dose of 1.0 or 5.0 mg/rat (D) Intratracheal instillation (once every wk for 4 wk) 1 d, 1 mo 0.25 or 0.5 mg/rat LA or 0.5 mg/rat of diesel exhaust particles	LAA (Six Mix)	5.0 ± 4.5 µm	0.29 ± 0.19 µm	Analysis of biomarker expression following exposure to LAA in healthy (WKY, F344) or susceptible (SH, SHHF) rats demonstrated increases in acute phase proteins associated with inflammatory response; biomarkers associated with cancer (e.g., mesothelin) were increased only at 1 d postexposure. Biomarker expression in all four studies occurred rapidly and returned to homeostatic levels after 1 d postinstillation.	Shannahan et al. (2012a)

Table 4-19. In vivo data following exposure to Libby Amphibole asbestos (continued)

Species (gender)	Exposure route	Fiber type	Mean fiber length	Mean fiber diameter	Effects[a]	Reference
Three separate study designs: (A) WKY rats (M) (*n* = 12/group) SH (M) (*n* = 6/group) SHHF (M) (*n* = 6/group) (B) F344 rats (M) (*n* = 8−24/group) (C) F344 rats (M) (*n* = 24/group)	(A) Intratracheal instillation (once) 1 d, 1 wk, 1 mo, 3 mo 0.25 or 1.0 mg/rat (B) Intratracheal instillation (once) 1 d, 1 wk, 1 mo, 3 mo, 1 yr, 2 yr 0.15, 0.5, 1.5 or 5.0 mg/rat (C) Intratracheal instillation (once every other wk for 13 wk) 1 d, 2 wk, 2 yr Cumulative dose of 0.15, 0.5, 1.5 or 5.0 mg/rat	LAA (Six Mix)	5.0 ± 4.5 µm	0.29 ± 0.19 µm	LAA exposure in healthy rats (WKY, F344) increased expression of biomarkers of oxidative stress, thrombosis and vasoconstriction in the aorta. These levels were similar to CVD-sensitive rats at baseline.	Shannahan et al. (2012d)
SH (M) (*n* = 8/group)	Intratracheal instillation (once) 4 h, 1 d 1.0 mg DEF; 21 µg $FeCl_3$; 0.5 mg LA, 0.5 mg FeLA; 0.5 mg LA + 1 mg DEF in 300 µL saline	LAA (Six Mix) LAA + Fe (iron-loaded LA)	5.0 ± 4.5 µm	0.29 ± 0.19 µm	LAA exposure increased expression of inflammasome-related molecules, inflammatory cytokines and upstream regulators of the inflammasome. These changes were not impacted by iron levels.	Shannahan et al. (2012b)
WKY rats (M) (*n* = 12/group) SH (M) (*n* = 6/group) SHHF (M) (*n* = 6−36/group)	Intratracheal instillation (once) 1 wk, 1 mo, 3 mo 0.25 or 1.0 mg/rat	LAA (Six Mix)	5.0 ± 4.5 µm	0.29 ± 0.19 µm	Gene expression analysis demonstrated that LAA exposure upregulated inflammatory-related genes in healthy rats (WKY) but downregulated inflammatory-related genes in CVD-susceptible rats (SH, SHHF).	Shannahan et al. (2012c)

Table 4-19. In vivo data following exposure to Libby Amphibole asbestos (continued)

Species (gender)	Exposure route	Fiber type	Mean fiber length	Mean fiber diameter	Effects[a]	Reference
Fischer 344 rats (M) (*n* = 8/group)	Intratracheal instillation (once) 1 d, 3 d, 7 d, 2 wk, 3 mo 0.65 or 6.5 mg/rat LA; 0.65 mg amosite in 250 µL saline	LAA (Six Mix)	1.9 ± 3.0 µm	0.29 ± 0.23 µm	LAA exposure induced significant fibrogenic (but not carcinogenic) effects up to 2 yr postexposure. This response differed from that of amosite exposure in the same study, with LAA being less potent than amosite on a mass basis.	Cyphert et al. (2012a)
Fischer 344 rats (M) (*n* = 8/group)	Intratracheal instillation (once) 1 d, 3 mo 0.5 or 1.5 mg/rat LA, SM, ED, ON; 250 µL saline	LAA (Six Mix) Sumas Mountain chrysotile (SM) El Dorado tremolite (ED) Ontario ferroactino-lite (ON)	1.9 ± 3.0 µm 2.0 ± 2.4 µm 0.9 ± 0.9 µm 1.1 ± 0.9 µm	0.39 ± 0.3 µm 0.31 ± 0.4 µm 0.42 ± 0.4 µm 0.40 ± 0.3 µm	Inflammatory markers were increased in BALF at 1 d postexposure, but returned to control levels by 3 mo; development of fibrosis persisted at 3 mo and was greatest in SM-exposure rats (SM > LA > ON > ED). This correlated with fiber length and AR of the different fiber types.	Cyphert et al. (2012b)
Lewis rats (F) (*n* = 8/group)	Intratracheal instillation (biweekly for 13 wk) 19 wk 0.15, 0.5, 1.5, or 5 mg/rat LA; 0.5 or 1.5 mg amosite in 250 µL saline	LAA (Six Mix) Amosite	5.0 ± 4.5 µm	0.29 ± 0.19 µm	Results failed to show a positive correlation between LA exposure and rheumatoid arthritis in two animal models. Upregulated ANA following exposure suggest an altered immunological profile similar to other systemic autoimmune diseases.	Salazar et al. (2012)

Table 4-19. In vivo data following exposure to Libby Amphibole asbestos (continued)

Species (gender)	Exposure route	Fiber type	Mean fiber length	Mean fiber diameter	Effects[a]	Reference
Lewis rats (F) (*n* = 8/group)	Intratracheal instillation (biweekly for 13 wk) 28 wk 0.15, 0.5, 1.5, or 5 mg/rat LA; 0.5 or 1.5 mg amosite in 250 µL saline	LAA (Six Mix)	5.0 ± 4.5 µm	0.29 ± 0.19 µm	ANA in serum increased at all doses of LA except 1.5 mg by Week 28 postexposure. No dose-response related histopathological effects were observed in the kidney.	Salazar et al. (2013)

BALF = bronchoalveolar lavage fluid; DEF = deferoxamine; SH = spontaneously hypertensive; SHHF = spontaneously hypertensive-heart failure; WKY = Wistar-Kyoto rat; FeLAA = LA loaded with Fe; AR = aspect ratio.
[a]When available, results are shown as number of animals with tumors/total number of animals examined.

Table 4-20. In vivo data following exposure to tremolite asbestos

Species (gender)	Exposure route	Fiber type	Mean fiber length	Mean fiber diameter	Effects[a]	Reference
F344 rats (M, F) (*n* = 100 to 250/group)	Oral 1% bw in feed pellets; lifetime exposure starting in dam	Tremolite-nonfibrous (Governeur Talc Co., Governeur, NY)	N/A	N/A	Offspring from exposed mothers were smaller at weaning and throughout life. No toxicity or increase in neoplasia in tremolite rats as compared to controls.	McConnell et al. (1983a)
Wistar rats (M) (*n* = 48)	Inhalation 10 mg/m^3 (7 h each d, 5 d per wk, total of 224 d)	South Korean tremolite and brucite	>5 µm	<3 µm	Increased fibrosis (19/39) and carcinogenesis (18/39).	Davis et al. (1985)
AF/Han rats (*n* = 33−36/group)	Intraperitoneal injection 10 mg/2 mL PBS; single exposure	Tremolite (six samples)	N/A	N/A	All six fibers could induce mesothelioma: California: 36/36[b] Swansea: 35/36[b] Korea: 32/36[b] Italy: 24/36 Carr Brae: 4/33 Shininess: 2/36	Davis et al. (1991)
Hamsters (*n* ≤ 35/group)	Intrapleural injection 10 or 25 mg	Four types of tremolite (Sample FD-14; 275; 31; 72)	FD-14: 5.7 µm 275: N/A 31: >20 µm 72: >20 µm	FD-14: 1.6 µm 275: N/A 31: <0.4 µm 72: <0.4 µm	Tumors/survivors at 350 d Sample FD-14: 0/35 Sample 275: 0/34 (10 mg); 0/31 (25 mg) Samples 31: 3/41 (10 mg); 12/28 (25 mg) Sample 72: 4/13 (10 mg); 13/20 (25 mg)	Smith et al. (1979)
Rats (*n* = 32 Wistar rats—Sample A and *n* = 48 Sprague-Dawley rats—Samples B and C)	Intrapleural injection 20 mg/rat	Tremolite (three samples)	California: <6 µm Greenland: <3 µm Korea: >8 µm	California: <0.8 µm Greenland: <1.2 µm Korea: <1.5 µm	No tumors following exposure to Samples A and B; Sample C: 14/47	Wagner et al. (1982)
Osborne-Mendel rats (*n* = 28/group)	Hardened gelatin technique 40 mg	Tremolite (two samples)	N/A	N/A	Sample 1: 21/28 pleural sarcomas Sample 2: 22/28 pleural sarcomas	Stanton et al. (1981)

Table 4-20. In vivo data following exposure to tremolite asbestos (continued)

Species (gender)	Exposure route	Fiber type	Mean fiber length	Mean fiber diameter	Effects[a]	Reference
Wistar rats (F) (*n* = 40/group)	Intraperitoneal injection 1 × 3.3 and 1 × 15 mg, lifetime observation	Tremolite	N/A 22% of fibers >5 µm	N/A	Limited details in text. Increase in mesothelioma following exposure to tremolite: 3.3 mg sample: 9/29; 15 mg sample: 30/37	Roller et al. (1997) Roller et al. (1996)
Wistar rats (M) (*n* = 56)	Inhalation (flow-past nose only) 100 fibers/cm^3 longer than 20 µm, 5 d, follow-up 1 yr later	Tremolite	5.49 ± 13.97 µm	0.32 ± 3.52 µm	Tremolite had a pronounced inflammatory response with rapid granuloma development (1 d postexposure); Slight interstitial fibrosis observed at 90 and 180 d postexposure.	Bernstein et al. (2005b) Bernstein et al. (2003)
C57Bl/6 mice (F) (*n* = 10/group)	Intratracheal instillation Two doses of 60 µg each given wk apart in the first and second wk of a 7-mo experiment	Tremolite and wollastonite	Wollastonite: 4.46 ± 7.1 µm Tremolite: N/A	Wollastonite: 0.75 ± 1.02 µm Tremolite: N/A	Tremolite-exposed mice demonstrated increased IgG immune complex deposition in the kidneys, increased size of local lymph nodes, and increased total cell count.	Pfau et al. (2008)

BW = body weight; PBS = phosphate buffer saline.
[a]When available, results are shown as number of animals with tumors/total number of animals examined.
[b]Asbestiform types led to mesothelioma in most if not all exposed animals in this study.

4.2.1. Inhalation

There are no laboratory animal studies following inhalation exposure to LAA; however, three studies have examined the effect of inhalation exposure to tremolite in Wistar rats (Bernstein et al., 2005b; Bernstein et al., 2003; Davis et al., 1985). Davis et al. (1985) performed a chronic inhalation study examining response in male Wistar rats exposed in a chamber to 10 mg/m^3 (~1,600 fibers/mL, >5 µm) of commercially mined tremolite over a 12-month period. Bernstein et al. (2005b) and Bernstein et al. (2003) exposed Wistar rats to tremolite (100 fibers/cm^3) and chrysotile for 13 consecutive weeks (6 hours per day, 5 days per week) with 1-year follow-up. The results of these inhalation studies produced pronounced inflammation and very high levels of pulmonary fibrosis. Davis et al. (1985) also demonstrated an increase in carcinomas and mesotheliomas following exposure to tremolite, with no pulmonary tumors

observed in the controls. These results show that Wistar rats exposed to tremolite exhibited increased numbers of pulmonary lesions and possibly tumors.

4.2.2. Intratracheal Instillation Studies

Intratracheal instillation has been used to examine the effect of exposure to Libby Amphibole (Cyphert et al., 2012b; Cyphert et al., 2012a; Shannahan et al., 2012a; Shannahan et al., 2012c; Shannahan et al., 2012b; Shannahan et al., 2012d; Padilla-Carlin et al., 2011; Shannahan et al., 2011a; Shannahan et al., 2011b; Smartt et al., 2010; Putnam et al., 2008) and tremolite asbestos (Blake et al., 2008; Pfau et al., 2008; Sahu et al., 1975). These studies exposed C57Bl/6 mice (100 μg/mouse), Wistar-Kyoto (WKY) rats (0.25 or 1 mg/rat) or Fischer 344 rats (0.25 or 6.5 mg/rat) once to LAA and analyzed the results up to 2 years postexposure. Putnam et al. (2008) observed statistically nonsignificant increases in collagen following exposure to LAA, as well as gene expression alterations related to membrane transport, signal transduction, epidermal growth factor signaling, and calcium regulation. Smartt et al. (2010) followed up this study by analyzing specific genes by quantitative reverse transcription polymerase chain reaction for genes involved in collagen accumulation and scar formation (Col1A1, Col1A2, Col3A1). LAA exposure led to increased gene expression of Col1A2 at 1 week postinstillation and Col3A1 at 1 month postexposure. Both studies observed increased inflammation; however, LAA exposure demonstrated minimal inflammation that did not progress in the time points examined. These studies demonstrate that exposure to LAA may lead to inflammation and fibrosis.

Shannahan et al. (2011a) exposed two rat models of human cardiovascular disease to LAA to determine whether the preexisting CVD in these models would impact the lung injury and inflammation following exposure. Healthy WKY rats were compared to spontaneously hypertensive (SH) and spontaneously hypertensive-heart failure (SHHF) rats following exposure. 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. While inflammation and cell injury were observed in all strains, no strain-related differences were observed following exposure to LAA (Shannahan et al., 2011a).

A series of studies further examined SH, SHHF, and WKY rats over several durations of exposure to identify potential biomarkers of LAA exposure and determine if asbestos exposure shifts biomarker expression in healthy rats to resemble CVD (Shannahan et al., 2012a; Shannahan et al., 2012d). Acute-phase response molecules involved in inflammatory responses such as α2-macroglobulin and α1-acid glycoprotein, as well as the metabolic molecule lipocalin-2 were generally increased 1 day after exposure regardless of duration (Shannahan et al., 2012a). In addition, LAA generally did not change biomarker expression similarly to the CVD rat strains (Shannahan et al., 2012b). However, the expression of two vasoconstriction

genes, eNOS and ETR-A, were altered in Libby Amphibole-exposed WKY rats to resemble untreated SH and SHHF rats (Shannahan et al., 2012b). Biomarkers for cancer were largely unaffected in all three strains following LAA exposure (Shannahan et al., 2012a).

In a follow-up study to further examine the role of iron in the inflammatory response to LAA exposure, Shannahan et al. (2011b) exposed SH rats to LAA alone and with bound Fe as well as with an iron chelator (deferoxamine [DEF]). Exposure to LAA led to significant increases in inflammatory markers (e.g., neutrophils, interleukin [IL]-8) with the greatest increase occurring in the presence of DEF. Iron bound to LAA was not released following instillation except in the presence of DEF as supported by the lack of increase of iron in bronchoalveolar lavage fluid (BALF). These results suggest that chelation of iron bound to LAA as well as endogenous proteins increases the toxicity of LAA in vivo.

A pair of studies further examined the effect of iron in the context of Libby Amphibole-induced lung injury and inflammasome activation. DEF treatment in addition to LAA significantly affected cyclooxygenase-2 (COX-2), IL-6, and CCL-11 in lung tissue compared to LAA treatment alone (Shannahan et al., 2012c). Addition of iron to LAA significantly altered NF-kβ and IL-1β compared to LAA alone (Shannahan et al., 2012c). However, iron overload and DEF treatment generally were not significantly changed from each other, suggesting that iron has little impact on the inflammasome cascade. Histological examination and gene array analysis of inflammatory genes in WKY, SH, and SHHF rats did not identify significant differences in the progression of pulmonary fibrosis between the three strains (Shannahan et al., 2012d). These data do not indicate that the iron overload conditions that are characteristic of the cardiovascular disease-rat strains amplify the pulmonary effects of LAA. Padilla-Carlin et al. (2011) exposed Fischer 344 rats (male only) to LAA (0.65 or 6.5 mg/rat) or amosite (0.65 mg/rat; positive control) by intratracheal instillation to examine inflammatory response for 3 months postexposure. LAA exposure led to statistically significant increases of neutrophils in BALF as early as 1 day postexposure, with other inflammatory markers (e.g., protein, lactate dehydrogenase [LDH], gamma-glutamyl transpeptidase [GGT]) increased statistically significantly at different time points during the 3-month-period postexposure. However, on a mass basis, amosite produced a greater inflammatory response as measured by inflammatory markers (e.g., neutrophil influx, gene expression changes) and histopathological analysis demonstrating interstitial fibrosis. Examination of male Fischer 344 rats from this study at 2 years postexposure demonstrated that LAA induced a significant fibrogenic (but not carcinogenic) effect (Cyphert et al., 2012b). Response to LAA exposure in this study was less potent than amosite on a mass basis. Further comparison of LAA to other fiber types (Sumas Mountain chrysotile [SM], El Dorado tremolite [ED], and Ontario ferroactinolite [ON]) demonstrated that LAA exposure increased inflammatory markers at 1 day postexposure which returned to control levels by 3 months (Cyphert et al., 2012a). LAA exposure also led to an increased fibrogenic response at 3 months postexposure. As compared to other fibers tested,

fibrogenic response was correlated with the fiber length and width of each fiber, with SM-exposed rats demonstrating the greatest fibrogenic response (SM > LAA > ON > ED). These studies demonstrate a statistically significant increase in inflammatory response to LAA in mice and rats as measured in BALF by cytology, histopathology, and gene expression analysis. Follow-up studies are needed to inform the chronic effects of exposure to LAA.

Laboratory animal studies of tremolite intratracheal instillation exposure have been performed in mice in doses ranging from 60 μg to 5 mg. Male Swiss albino mice exposed to tremolite (5 mg) via intratracheal instillation demonstrated histological changes (Sahu et al., 1975). 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.

4.2.3. Injection/Implantation Studies

There are no laboratory animal studies examining intraperitoneal injection or implantation of LAA. Biological effects following exposure to tremolite have been examined in five intraperitoneal injection studies (Roller et al., 1997, 1996; Davis et al., 1991; Wagner et al., 1982; Smith et al., 1979; Smith, 1978) and one implantation study (Stanton et al., 1981).

Studies by Smith and colleagues (Smith et al., 1979; Smith, 1978), Wagner et al. (1982), Davis et al. (1991), Roller et al. (1997), and Roller et al. (1996) demonstrated that intrapleural injections of tremolite asbestos[16] is associated with an increase in pleural fibrosis and mesothelioma in hamsters and rats compared to controls or animals injected with less fibrous materials. Doses ranged from 10−25 mg/animal for each study, and although carcinogenesis was observed in these studies, there was a variable level of response to the different tremolite forms examined. Although these studies clearly show the carcinogenic potential of Libby Amphibole or tremolite asbestos fibers, intrapleural injections bypass the clearance and dissolution of fibers from the lung after inhalation exposures. Further, limited information was provided confirming the presence or absence of particles or fibers less than 5 μm in length in these studies, limiting the interpretation of results.

One laboratory animal study examined the effect of tremolite exposure following implantation of fibers in the pleural cavity. Stanton et al. (1981) examined tremolite and described 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, as the dynamics of fiber deposition and pulmonary clearance mechanisms are not accounted for in the study design. Studies using two tremolite

[16]Smith (1978) used tremolite from Libby, MT; Smith et al. (1979) may also have used tremolite from Libby, MT (i.e., Libby Amphibole asbestos).

asbestos samples from the same lot were described as being in the optimal size range for carcinogenesis; the fibers were distinctly smaller in diameter than the tremolite fibers Smith et al. (1979) used. These samples both had a high number of fibers in the size range (>8-μm long and <0.25 μm in diameter; i.e., "Stanton fibers"). Exposure to both 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.

There are no studies currently available in laboratory animals exposed to LAA by inhalation. However, the chronic intraperitoneal injection study in hamsters (Smith et al., 1979; Smith, 1978) demonstrated tumor formation following exposure to tremolite obtained from the Libby, MT mine. No other chronic inhalation studies of LAA are available. A recent study in rats examining the impact of preexisting cardiovascular disease on pulmonary inflammation demonstrated an increase in inflammatory markers following exposure to LAA via intratracheal instillation in SH rats as compared to normal healthy controls exposed to the same dose (Shannahan et al., 2011b). More recent studies examined gene expression changes (Hillegass et al., 2010; Putnam et al., 2008) and early protein markers of fibrosis (Smartt et al., 2010) in mice exposed to LAA via intraperitoneal injection. These studies demonstrated an increase in gene and protein expression related to fibrosis following exposure to LAA. Tremolite fibers, although obtained from different locations throughout the world, consistently led to pulmonary lesions and/or tumor formation with various routes of exposure (inhalation, injection, instillation) and in multiple species [rats, hamsters, and mice (Bernstein et al., 2005b; Bernstein et al., 2003; Roller et al., 1997, 1996; Davis et al., 1985; Wagner et al., 1982; Stanton et al., 1981)]. Although comparing potency of the various forms of tremolite is difficult given the limited information on fiber characteristics and study limitations (e.g., length of follow-up postexposure), these results show potential increased risk for cancer (lung and mesothelioma) following exposure to tremolite asbestos.

The results of the studies described above show the fibrogenic and carcinogenic potential of Libby Amphibole and tremolite asbestos. Further, the more recent studies by Salazar et al. (2013), Salazar et al. (2012), Blake et al. (2008), and Pfau et al. (2008) support human studies demonstrating potential autoimmune effects of asbestos exposure (see Section 4.3.1).

4.2.4. Oral

No studies in laboratory animals with oral exposure to LAA were found in the literature. However, one chronic cancer bioassay was performed following oral exposure to tremolite. McConnell et al. (1983a) describe part of a National Toxicology Program study (NTP, 1990b) performed to evaluate the toxicity and carcinogenicity of ingestion of several minerals, including tremolite. The tremolite (Governeur Talc Co, Governeur, NY) used was not fibrous. No significant tumor induction was observed in the animals with oral exposure to tremolite animals. 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 observed lesions included chronic inflammation, ulceration, and necrosis of the stomach (McConnell et al., 1983a). McConnell et al. (1983a) suggested that nonfibrous nature of this tremolite sample could account for the lack of toxicity following exposure in this group of animals. Also, oral studies of asbestos, in general, show decreased toxicity and carcinogenicity as compared to inhalation and implantation/injection studies (Condie, 1983).

4.2.5. Summary of Animal Studies for Libby Amphibole and Tremolite Asbestos

Tables 4-19 and 4-20 summarize the studies described in this section, with full study details available in Appendix D. Limited in vivo studies have been performed exposing laboratory animals to LAA. One intrapleural injection study using tremolite from the Libby, MT area is included in this section under LAA because earlier terminology for LAA was often tremolite (Smith, 1978). Hamsters in this study exposed to LAA developed fibrosis and mesothelioma following exposure. Intratracheal instillation studies of LAA in rats showed increased collagen gene expression at 2-years postexposure (Cyphert et al., 2012a). Subchronic-duration studies in mice (Smartt et al., 2010; Putnam et al., 2008) demonstrated gene and protein expression changes related to fibrosis production following exposure to LAA. Finally, short-term-duration studies in rats demonstrated an increase in inflammatory and cardiovascular disease markers following exposure to LAA (Padilla-Carlin et al., 2011; Shannahan et al., 2011a; Shannahan et al., 2011b).

Because tremolite is a component of LAA, results from tremolite studies were also described. In general, fibrous tremolite has been shown to cause pulmonary inflammation, fibrosis, and/or mesothelioma or lung cancer in rats (Bernstein et al., 2005b; Bernstein et al., 2003; Davis et al., 1991; Davis et al., 1985; Wagner et al., 1982) and hamsters (Smith et al., 1979). The single short-term-duration study on mice showed limited response to tremolite (Sahu et al., 1975). The one chronic-duration oral study (McConnell et al., 1983a) did not show increased toxicity or carcinogenicity; this study, however, used only nonfibrous tremolite, which later studies showed to be less toxic and carcinogenic than fibrous tremolite (Davis et al., 1991).

Chronic inflammation is hypothesized to lead to a carcinogenic response through the production of reactive oxygen species and increased cellular proliferation (Hanahan and Weinberg, 2011). Although limited, the data described in Section 4.2 suggest an increase in inflammatory response following exposure to LAA and tremolite asbestos similar to that observed for other durable mineral fibers [reviewed in (Mossman et al., 2007)]. Whether this inflammatory response then leads to cancer is unknown. Studies examining other types of asbestos (e.g., crocidolite, chrysotile, and amosite) have demonstrated an increase in chronic inflammation as well as respiratory cancer related to exposure [reviewed in (Kamp and Weitzman, 1999)]. Chronic inflammation has also been linked to genotoxicity and mutagenicity following exposure to some particles and fibers (Driscoll et al., 1997; Driscoll et al., 1996;

Driscoll et al., 1995). The evidence described above suggests chronic inflammation is observed following LAA and tremolite asbestos exposure; however, the role of inflammation and whether it leads to lung cancer or mesothelioma following exposure to LAA is unknown.

ROS production has been measured in response to both LAA and tremolite asbestos exposure. Blake et al. (2007) demonstrated an increase in the production of superoxide anions following exposure to LAA. Blake et al. (2007) also demonstrated that total superoxide dismutase (SOD) was inhibited, along with a decrease in intracellular glutathione (GSH), both of which are associated with increased levels of ROS. These results are supported by a recent study in human mesothelial cells (Hillegass et al., 2010) (described in Section 4.4 and Appendix D). Increased ROS production was also observed in human airway epithelial cells (HAECs) following exposure to LAA (Duncan et al., 2010) (described in Section 4.4 and Appendix D). This increase in ROS and decrease in glutathione are common effects following exposure to asbestos fibers and particulate matter. Pfau et al. (2012) examined the role of the amino acid transport system x^-_c, which is one of the pathways murine macrophages use to detect and respond to stressful conditions. This study demonstrated that ROS production increase system x^-_c activity. Although ROS production is relevant to humans, based on similar human responses as compared to animals, information on the specifics of ROS production following exposure to LAA is limited to the available data described here. Therefore, the role of ROS production in lung cancer and mesothelioma following exposure to LAA is unknown.

Recent studies have also examined the role of the inflammasome and iron in the development of fibrosis in male SH rats. The role of inflammasome activation and iron in the development of LAA-induced fibrosis was studied in Shannahan et al. (2012c). 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 phosphorylated ERK (pERK)/extracellular signal-related kinases (ERK), which is an upstream activator of the inflammasome cascade, was increased in the lung of LAA exposed rats 1 day post exposure. Rats treated with LAA + DEF or LAA + Fe 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. (2012d) valuated the effect of Fe overload on LAA-induced lung injury in rats with cardiovascular disease. 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 cluster 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 1 and 3 months post exposure;

however, no differences in the progression of pulmonary fibrosis were noted between the three strains. Altogether, these data do not suggest that the iron overload conditions that are characteristic of the cardiovascular disease strains amplify the pulmonary effects of LAA.

4.3. OTHER DURATION- OR ENDPOINT-SPECIFIC STUDIES

4.3.1. Immunological

Salazar et al. (2013), Salazar et al. (2012), Rasmussen and Pfau (2012), Blake et al. (2008), Pfau et al. (2008), Serve et al. (2013) and Hamilton et al. (2004) examined the role of asbestos in autoimmunity in laboratory animal or in vitro studies. Blake et al. (2008) performed in vitro assays with LAA (see Section 4.4), 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. 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), by 26 weeks, the tremolite-exposed animals had a significantly higher frequency of positive antinuclear antibody (ANA) tests compared to wollastonite and saline. Most of the tests were positive for double-stranded DNA (dsDNA) and SSA/Ro52. Serum isotyping showed no major changes in immunoglobulin (Ig) subclasses (IgG, IgA, IgM), but serum IgG in tremolite-exposed mice decreased overall. Further, 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 sizes were significantly increased following exposure to tremolite, percentages of T- and B-cells did not significantly change.

Hamilton et al. (2004) investigated the ability of LAA, crocidolite, and particulate matter 2.5 μm in diameter or less ($PM_{2.5}$, collected over a 6-month period in Houston, TX, from EPA site 48-201-1035) to alter the antigen-presenting cell (APC) function in cultured human alveolar macrophages. Asbestos exposure (regardless of type) and $PM_{2.5}$ up-regulated a Th1 lymphocyte-derived cytokine, interferon gamma (IFNγ), and the Th2 lymphocyte-derived cytokines IL-4 and IL-13. However, extreme variation among subjects was noted in the amount of response. In addition, no correlation was present between the response of an individual's cells to asbestos versus particulate matter, suggesting that more than one possible mechanism exists for a particle-induced APC effect and individual differential sensitivities to inhaled bioactive particles. Rasmussen and Pfau (2012) examined the role of macrophages in the development of autoantibody production following exposure to LAA. LAA exposure alone did not affect cell proliferation or antibody production; however, culturing lymphocytes with macrophage medium following exposure to LAA did lead to increased cellular proliferation and antibody production. Serve et al. (2013) examined a possible role of autoimmunity in fibrosis by an in vitro

examination of potential mechanisms of MCAA leading to collagen deposition, a precursor to fibrosis. This study demonstrated MCAA binding leads to increased collagen deposition through altering matrix metalloproteinase (MMP) expression.

In two studies examining potential autoimmune effects of LAA exposure, Salazar et al. (2013) and Salazar et al. (2012) examined the potential impact of LAA exposure on rheumatoid arthritis and on ANA increases associated with systemic autoimmune disease. Salazar et al. (2013) and Salazar et al. (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 and peptidoglycan-polysaccharide (PG-PS) models of rheumatoid arthritis to determine whether LAA exposure increased the onset, 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 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 1.5 and 5.0 mg and amosite 0.5 and 1.5 mg reduced total serum IgM. LAA 5.0 mg and amosite 1.5 mg reduced anti-PG-PS IgG in the serum 17 weeks after the final instillation. Finally, the number of rats positive for 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.

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 (Salazar et al., 2012). 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 was increased 8 weeks postexposure to LAA 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 and the Jo-1 antigen. Urinalysis found that all doses of LAA exposure induce 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 no evidence of autoimmune disease was identified. However, the lack of SAID in the Lewis rat may be due to strain-specific factors and suggests that other animal models may be more appropriate for studying autoimmune effects of LAA.

Although the number of studies is limited, the results suggest a possible effect on autoimmunity following exposure to LAA. Further studies are needed to increase understanding of this potential effect.

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

For asbestos in general, International Agency for Research on Cancer (IARC) has proposed a mechanism for the carcinogenicity of asbestos fibers [see Figure 4-4; (IARC, 2012)]. Asbestos fibers lead to oxidant production through interactions with macrophages and through hydroxyl radical generation from surface iron. Inhaled fibers that are phagocytosed by macrophages may be cleared or lead to frustrated phagocytosis, which results in macrophage activation, release of oxidants, and increased inflammatory response, in part due to inflammasome activation. Free radicals may also be released by interaction with the iron on the surface of fibers. Increased oxidant production may result in epithelial cell injury, including DNA damage. Frustrated phagocytosis may also lead to impaired clearance of fibers, with fibers being available for translocation to other sites (e.g., pleura). Mineral fibers may also lead to direct genotoxicity by interfering with the mitotic spindle and leading to chromosomal aberrations. Asbestos exposure also leads to the activation of intracellular signaling pathways, which in turn may result in increased cellular proliferation, decreased DNA damage repair, and activation of oncogenes. Research on various types of mineral fibers supports a complex mechanism involving multiple biologic responses following exposure to asbestos (i.e., genotoxicity, chronic inflammation/cytotoxicity leading to oxidant release, and cellular proliferation) in the carcinogenic response to mineral fibers [see Figure 4-4, reviewed in (IARC, 2012)]. These complexities of fiber toxicity need to be considered when analyzing MOA for asbestos [as reviewed in (Aust et al., 2011; Broaddus et al., 2011; Bunderson-Schelvan et al., 2011; Huang et al., 2011; Mossman et al., 2011)].

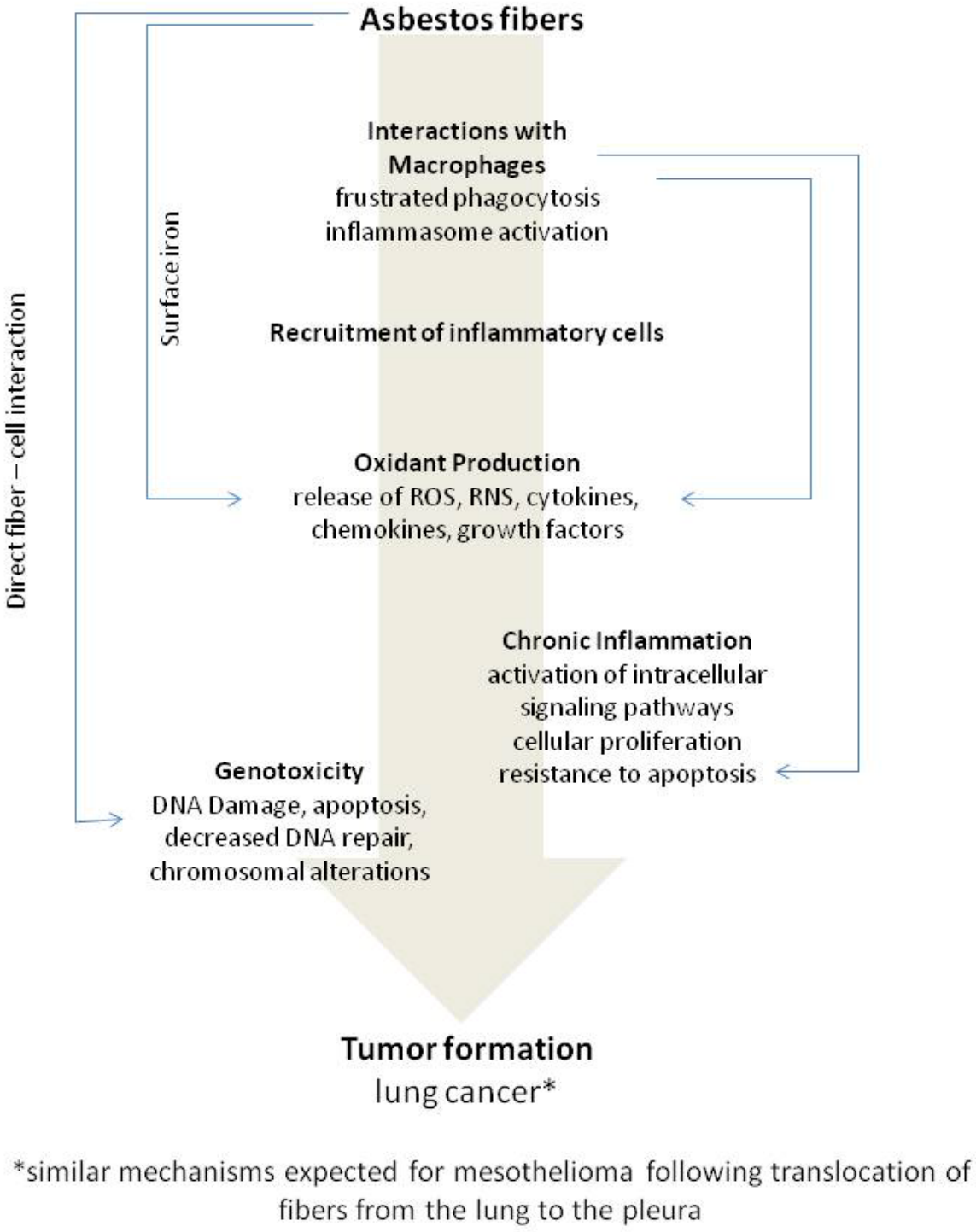

Figure 4-4. Proposed mechanistic events for carcinogenicity of asbestos fibers.

Adapted from IARC (2012).

Important considerations in evaluating the available mechanism and MOA data are fiber characteristics, route of exposure, dose metric, as well as study design and interpretation. Specific fiber characteristics impact the fiber toxicokinetics (reviewed in Section 3), and in turn the biologic response to fibers. For example, fiber length is an important determinant of fiber clearance, with shorter fibers generally being cleared more efficiently as longer fibers result in frustrated phagocytosis. Mechanisms of carcinogenesis may accordingly vary based on fiber characteristics. The biologic response to respirable fibers is also influenced by the route of exposure. Inhalation exposure studies are the most informative. Intratracheal instillation and aspiration exposures bypass normal clearance mechanisms, and therefore affect fiber dosimetry. Concerning dose metric, some studies suggest that the dose should be determined based on fiber length, width, number, or surface area (Case et al., 2011; Mossman et al., 2011). However, the majority of studies of fibers have been performed using mass as a dose. Finally, an important consideration in analysis of in vitro studies is the cell types used, particularly related to the ability to internalize fibers and produce an oxidative stress response. The discussions below highlight these considerations in presenting the available mechanistic evidence for LAA.

Limited 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., 2014; 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). Similar endpoints have been examined in vitro following exposure to tremolite asbestos (Okayasu et al., 1999; Wylie et al., 1997; Suzuki and Hei, 1996; Athanasiou et al., 1992; Wagner et al., 1982). Results from in vitro studies have demonstrated potential biological mechanisms of oxidative stress and inflammation in response to exposure to Libby Amphibole and tremolite asbestos. As discussed in Section 4.2, laboratory animal studies examining the effects of tremolite exposure have been reviewed and are summarized to potentially increase understanding of the effects and mechanisms of LAA, because tremolite is a component of LAA (~6%). These studies are summarized below and in Tables 4-21 and 4-22, with detailed study descriptions available in Appendix D.

Table 4-21. In vitro data following exposure to Libby Amphibole asbestos

Test system	Fiber type	Dose/exposure duration	Effects	Reference
Primary human alveolar macrophages and lymphocytes	LAA or crocidolite	0, 25, 50 μg/mL 24 h	Upregulated Th1 and Th2 cytokines (IFNγ, IL-4, IL-13)	Hamilton et al. (2004)
Murine macrophages (primary and RAW264.7)[a]	LAA or crocidolite	Internalization: 0, 5, 62.5 μg/cm^2 3−24 h	Internalized LAA fibers were mostly less than 2 μm in length	Blake et al. (2007)
		Oxidative stress: 0, 6.25, 32.5, 62.5 μg/cm^2 3, 7, 12, and 24 h	Increased ROS over control (wollastonite) and crocidolite Decreased GSH	
		Cell viability: 0, 6.25, 32.5, 62.5 μg/cm^2 3, 7, 12, and 2 h	No effect was observed on cell viability	
		DNA damage: 0, 6.25, 32.5, 62.5 μg/cm^2 3, 7, 12, and 24 h	No increase in DNA damage and adduct formation	
Murine macrophages (primary and RAW264.7)	LAA or crocidolite	0, 62.5 μg/cm^2 0−72 h	Time-course dose-response for apoptosis; redistribution of autoantigen on cell surface	Blake et al. (2008)
Human lung epithelial cells (wild-type and XRCC1-deficient)	LAA or crocidolite	5 μg/cm^2 24 h	Dose-dependent increase in micronuclei in both cell types, but increased in the XRCC1-deficient cells as compared to wild-type	Pietruska et al. (2010)
Human mesothelial cell lines (LP9/TERT-1 and HKNM-2)	LAA or crocidolite	0, 15 × 10^6 μm^2/cm^2 (nontoxic) and 75 × 10^6 μm^2/cm^2 (toxic) for 8 or 24 h	Alterations in genes related to oxidative stress at cytotoxic doses, particularly *SOD2*	Hillegass et al. (2010)
Primary HAECs	LAA (fractionated and unfractionated), amosite (fractionated and unfractionated), crocidolite	0, 2.64, 13.2 or 26.4 μg/cm^2 2, 4 or 24 h	Increases in proinflammatory gene expression and ROS production	Duncan et al. (2010)

Table 4-21. In vitro data following exposure to Libby Amphibole asbestos (continued)

Test system	Fiber type	Dose/exposure duration	Effects	Reference
CH12.LX B-lymphocytes	LAA	35 μg/cm^2 48 h	Data from macrophage-conditioned media demonstrate that asbestos leads to immunologic changes consistent with activation of B1a B-lymphocytes.	Rasmussen and Pfau (2012)
MeT-5A human mesothelial cells	LAA	Cells exposed to sera from exposed individuals that were MCAA+ or MCAA− (1:100).	Data demonstrated that MCAA binding leads to increased collagen deposition through altering MMP expression.	Serve et al. (2013)
Primary human airway epithelial cells (HAEC)	LAA (2000, 2007); amosite (RTI, UICC)	0, 2.64, 13.2 or 26.4 μg/cm^2 24 h	Exposure to all fibers at the highest doses led to increased LDH levels (cytotoxicity) and increased mRNA expression of IL-8, IL-6, COX-2, and TNFα (inflammatory markers). On an equal mass basis LA is as potent as UICC amosite at inducing a proinflammatory response in HAEC but less potent than RTI amosite.	Duncan et al. (2014)
THP-1 cells (macrophage cell line)	Libby six-mix Chrysotile	0, 20, 40 μg/ml 24 h	LAA activated the NLRP3 inflammasome but to a lesser degree than chrysotile, but LAA exposure generated more ROS production compared to chrysotile.	Li et al. (2012)

XRCC1 = x-ray repair cross-complementing protein 1.
[a]All results for RAW264.7. Data not shown for primary cells though authors state similar response to RAW264.7.

Table 4-22. In vitro data following exposure to tremolite asbestos

Test system/species	Fiber type	Dose/exposure duration	Effects	Reference
Primary murine macrophages	Sample A (flake-like from California talc deposits); Sample B (medium-sized fibrous from Greenland); Sample C (fine-fiber material from S. Korea); Positive Control (crocidolite)	0, 50, 100, and 150 µg/mL 18 h	LDH and BGL levels increased following exposure to Sample C (longer, thinner fibers) and crocidolite (positive control). Sample C led to the greatest increases in giant cell formation (i.e., cells > 2 um in diameter) and cytotoxicity of samples tested. Sample B also led to some increased cytotoxicity.	Wagner et al. (1982)
TA98, TA100, TA102 *S. typhimurium*	Metsovo tremolite	TA98, TA100, and TA102: 0−500 µg/per plate 2 d	No significant revertants were observed in any of the three *Salmonella* strains tested.	Athanasiou et al. (1992)
V79 and BPNi cells		V79 and BPNi: 0−4 µg/cm^2 6, 24, and 48 h	No affect was observed on gap-junctional intercellular communication.	
BPNi cells		BPNi: 0−2 µg/cm^2 24 h	Tremolite led to a dose-dependent increase in micronuclei induction.	
SHE cells		SHE: 0−3 µg/cm^2 24 h	Tremolite exposure led to increased chromosomal aberrations but not in a dose-dependent fashion.	
A_L cells (hamster hybrid cells containing human chromosome 11)	UICC chrysotile, crocidolite, Metsovo tremolite, erionite	0, 2.5−40 µg/mL 24 h	Relative increase in heme oxygenase as compared to control.	Suzuki and Hei (1996)
HTE and RPM cell lines	NIEHS chrysotile, NIEHS crocidolite, FD14, S157, CPS 183 (talc fibers containing tremolite)	Varied (based on weight, fiber length, and surface area).	Fibrous talc exposure led to limited proliferation of cells.	Wylie et al. (1997)

Table 4-22. In vitro data following exposure to tremolite asbestos (continued)

Test system/species	Fiber type	Dose/exposure duration	Effects	Reference
A_L cells (hamster hybrid cells containing human chromosome 11)	Tremolite, erionite, RCF-1	0−400 μg/mL 24 h	No significant increase in hypoxanthine-guanine phosphoribosyltransferase mutations for these three fibers. Dose-dependent induction of $S1^-$ mutations in Chromosome 11 occurs for erionite and tremolite.	Okayasu et al. (1999)

A[L] cells = hamster hybrid cells containing human chromosome 11; BGL = β-glucuronidase; HTE = hamster tracheal epithelial; NIEHS = National Institute of Environmental Health Sciences; RCF-1 = refractory ceramic fibers ; RPM = rat pleural mesothelial; SHE = Syrian hamster embryo.

4.4.1. Inflammation and Immune Function

Chronic inflammation following inhalation exposure to asbestos has been studied for decades in both humans and animals [reviewed in (Mossman et al., 2011; Rom et al., 1991)]. This inflammatory response has been attributed to the role of alveolar macrophages, which attempt to engulf asbestos fibers to clear them from the respiratory tract [reviewed in Mossman et al. (2011) and Takemura et al. (1989)]. Mechanistic studies have focused on the chemokine/cytokine response of these macrophages and the subsequent signaling pathways that are activated. More recently, studies have also examined the role of inflammasome activation following exposure to asbestos in immune activation and fiber clearance (Hillegass et al., 2013; Biswas et al., 2011; Dostert et al., 2008).

Increased cytokine and chemokine production has been observed following exposure to LAA as well as other amphibole asbestos. Hamilton et al. (2004) showed an increase in Th1 and Th2 cytokines following exposure to LAA, crocidolite, and particulate matter, suggesting a similar effect of exposure to these materials on immune function. Analysis of these results is limited, as the use of primary cells in culture led to an extremely variable response. Two studies by Blake et al. (2008) and Blake et al. (2007) further examined the effect of LAA on immune response in vitro in mouse macrophages. These studies demonstrated that the size of the LAA material is such that it was able to be internalized by macrophages (<10 μm), and this internalization resulted in an increase in ROS production. These studies also showed a variable cytotoxic response, because LAA exposure did not result in a statistically significant increase in cytotoxicity, while crocidolite did. DNA damage also was increased in crocidolite-exposed cells but not in LAA-exposed cells. An increase (relative to controls) in autoantibody formation following exposure to LAA was also observed. 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).

Gene expression alterations of *IL-8*, *COX-2*, *heme oxygenase (HO)-1*, as well as other stress-responsive genes as compared to amosite was observed in primary HAEC following exposure to LAA. 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. Primary HAECs were exposed to 0, 2.64, 13.2, and 26.4 μg/cm^2 of crocidolite, amosite, amosite 2.5 (fractionated), LAA, or LAA 2.5 (fractionated) for 2 or 24 hours in cell culture. 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 hour postexposure, however, a dose-response was observed following exposure to all fiber types with the results showing a proinflammatory gene expression response (Duncan et al., 2010). Cytotoxicity was determined by measuring LDH from the maximum dose (26.4 μg/cm^2) of both amosite and LAA samples, with less than 10% LDH present following exposure to all four samples. A follow-up study with the same design by Duncan et al. (2014)was performed to

examine the in vitro determinants of asbestos fiber toxicity, comparing two samples each of LAA (LA2000, LA2007) and amosite (UICC, RTI) asbestos. Primary human airway epithelial cells (HAEC) were exposed for 24 hours to 2.64, 13.2 or 26.4 ug/cm^2 LAA and amosite asbestos that had been analyzed for fiber size distribution, surface area, and surface-conjugated iron (see Table D-11). Most characteristics were similar, except RTI amosite 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 for all four samples at the highest dose, but statistically significant compared to the no-treatment control. Results on an equal mass basis demonstrated a statistically significant increase in IL-8, IL-6, COX-2, and TNF mRNA levels for all four amphiboles at the highest two doses. The greatest increase in IL-8 mRNA levels was following exposure to the RTI amosite sample, while both LAA samples and the UICC amosite resulted in a similar level of response to each other. Therefore, IL-8 was used to further analyze the dose metrics for this response. Surface iron concentrations and surface reactivity was 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 much greater surface iron as compared to the LAA samples. UICC amosite had slightly greater iron as compared to RTI. 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. These results support a limited cytotoxicity and increased inflammatory cytokine response of both amosite and LAA under these concentrations and time frames.

The role of macrophages in the development of autoantibody production following exposure to asbestos was examined in a study performed by Rasmussen and Pfau (2012) culturing CH12.LX B-lymphocytes, a murine B1 lymphocyte cell line, with LAA alone did not affect proliferation or antibody production. However, culturing RAW264.7 macrophages with LAA, collecting the macrophage medium, and culturing CH12.LX lymphocytes in the conditioned medium reduced CH12.LX proliferation and increased IgG1, IgG3, and IgA production. Further analysis found that both IL-6 and tumor necrosis factor (TNF)-α were elevated in the medium of Libby Amphibole-treated macrophages, but only IL-6 increased IgG and IgA production. However, these data also indicate that activated macrophages may regulate CH12.LX antibody production. Altogether, these data suggest a potential mechanism for macrophages to regulate asbestos-induced autoantibody production in Libby-exposed residents.

Chronic inflammation is also associated with oxidative stress, mechanisms of which following exposure to LAA were also studied in human mesothelial cells (Hillegass et al., 2010). Gene expression changes related to oxidative stress following exposure to 15 × 10^6 μm^2/cm^2

LAA[17] as compared to the nonpathogenic control (75×10^6 $\mu m^2/cm^2$ glass beads) in the human mesothelial cell line LP9/TERT-1 for 8 and 24 hours. Gene ontology of these results demonstrated alterations in genes related to signal transduction, immune response, apoptosis, cellular proliferation, extracellular matrix, cell adhesion, and motility, and only in one gene related to reactive oxygen species processing. Oxidative stress was observed to be both dose- and time-dependent in cells exposed to LAA. GSH levels were transiently depleted following 2−8 hours exposure to the higher dose of LAA, with a gradual recovery up to 48 hours in LP9/TERT-1 cells (HKNM-2 not analyzed). 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.

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 lung expression 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. These data suggest that LAA exposures leads to the activation of the inflammasome cascade and cytokines downstream of the pathway in LAA-exposed animals. Li et al. (2012) also studied LAA inflammasome activation and demonstrated in vitro in THP-1 cells that LAA activated the NLRP3 inflammasome but to a lesser degree than chrysotile. However, this study showed that LAA exposure generated more ROS production as compared to chrysotile. Although not studied, the authors suggest that differences in fiber length and surface area may play a role in this differential inflammatory response.

[17]Libby Amphibole asbestos samples were characterized for this study with analysis of chemical composition and mean surface area (Meeker et al., 2003). Doses were measured in surface area and described based on viability assays as either the nontoxic (15×10^6 $\mu m^2/cm^2$) or the toxic dose (75×10^6 $\mu m^2/cm^2$).

4.4.2. Genotoxicity

Genotoxicity, and more specifically, mutagenicity, are associated with tumor formation through alterations in genetic material.[18] Mutagenicity refers to a permanent effect on the structure and/or amount of genetic material that can lead to heritable changes in function, while genotoxicity is a broader term including all adverse effects on the genetic information (Eastmond et al., 2009). Results of standard mutation assays like the Ames test, which analyze for point mutations, have found asbestos and other mineral fibers to be negative or only marginally positive (Walker et al., 1992). Several other studies, however, have shown that asbestos exposure can result in a variety of chromosomal alterations, which are briefly discussed below. Genotoxicity following exposure to asbestos fibers has been described as the result of two distinct mechanisms, either ROS production leading to DNA damage, or physical interference of mitosis by the fibers. For both DNA damage and mitotic interference, the fibers must first enter the cell. Some studies have shown that a direct interaction between fibers and cellular receptors might also lead to increased ROS production. ROS production is also related to surface iron on fibers, with increased surface iron leading to increased ROS production (IARC, 2012). ROS production is possibly a key event in fiber-induced direct DNA damage, as observed following exposure to other forms of asbestos, while the indirect DNA damage requires fiber interaction with cellular components (e.g., mitotic spindle, chromosomes).

ROS production and genotoxicity (micronuclei induction) following exposure to LAA has been demonstrated in x-ray repair cross-complementing protein 1 (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. Micronuclei induction was measured following treatment of cells by controls (positive, hydrogen peroxide; negative, paclitaxel) and by 5 $\mu g/cm^2$ fibers or TiO_2 particles for 24 hours. Spontaneous micronuclei induction was increased in XRCC1-deficient cells in a dose-dependent manner following exposure to crocidolite and LAA as compared to unexposed cells. These results support a potential genotoxic effect of exposure to both crocidolite and LAA.

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

[18]*Genotoxicity*: a broad term that refers to potentially harmful effects on genetic material, which may be mediated directly or indirectly, and which are not necessarily associated with mutagenicity. Thus, tests for genotoxicity include tests that provide an indication of induced damage to DNA (but not direct evidence of mutation) via effects such as unscheduled DNA synthesis, sister chromatid exchange, or mitotic recombination, as well as tests for mutagenicity; *Mutagenicity*: refers to the induction of permanent transmissible changes in the amount or structure of the genetic material of cells or organisms. These changes, "mutations," may involve a single gene or gene segment, a block of genes, or whole chromosomes. Effects on whole chromosomes may be structural and/or numerical (as defined in the European Union Technical Guidance on Risk Assessment (CEC, 1996).

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). Metsovo tremolite did not yield a statistically significant increase in revertants in the Ames assay, including in the TA102 *Salmonella* strain, which is generally sensitive to oxidative damage. This study demonstrated clastogenic effects of tremolite, including chromosomal aberrations and micronuclei induction. Tremolite exposure in Syrian hamster embryo (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; (Athanasiou et al., 1992)]. 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) in BPNi cells after 24-hour exposure. Literature 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. No effect on the gap-junctional intercellular communication following tremolite exposure was observed in both Chinese hamster lung fibroblasts (V79) and Syrian hamster embryo BPNi cells, which are sensitive to transformation (Athanasiou et al., 1992).

Okayasu et al. (1999) analyzed the mutagenicity of Metsovo tremolite, erionite, and the man-made refractory ceramic fiber (RCF-1). 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 this chromosome is quantifiable by an antibody complement-mediated cytotoxicity assay. The study 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. A dose-dependent increase in CD59 mutant induction was observed following exposure to erionite and tremolite, but not RCF-1.

In summary, one in vitro study examined genotoxicity of LAA by measuring DNA adduct formation following exposure via murine macrophages [primary and immortalized; (Blake et al., 2007)]. The data showed no increase in adduct formation as compared to unexposed controls. A second study observed increases in micronuclei induction in both normal human lung epithelial cells and XRCC1-deficient cells for both LAA and crocidolite asbestos

(Pietruska et al., 2010). Two studies of tremolite examined genotoxicity. The first found no significant increase in revertants in the Ames assay (Athanasiou et al., 1992), which is similar to results obtained for other forms of asbestos. This study did find, however, that tremolite exposure led to a dose-dependent increase in chromosome number and micronuclei formation, which has also been described for other asbestos fibers [as reviewed in Hei et al. (2006) and Jaurand (1997)]. Hei and colleagues (Okayasu et al., 1999) performed mutation analysis with tremolite and found a dose-dependent increase in mutations in CD59 in hamster hybrid cells. Genotoxicity analysis in humans, following exposure to LAA or tremolite, has not been measured, although other types of asbestos fibers have led to increases in genotoxicity in primary cultures and lymphocytes (Dopp et al., 2005; Poser et al., 2004). In general, these studies have examined genotoxicity with a focus on ROS production as a key event. Although LAA- and tremolite-specific data are limited to in vitro studies, given the similarities in response to other forms of asbestos, there is some evidence to suggest genotoxicity following exposure to Libby Amphibole and tremolite asbestos. However, the potential role of this genotoxicity in lung cancer or mesothelioma following exposure to LAA is unknown.

4.4.3. Cytotoxicity and Cellular Proliferation

The initial stages of tumorigenicity may be an increased cellular proliferation at the site of fiber deposition, which can increase the chance of cancer by increasing the population of spontaneous mutations, thereby affording genotoxic effects an opportunity to multiply. Increased cell proliferative regeneration may be associated with tumor clonal expansion and can occur in response to increased apoptosis. In macrophages, increased cytotoxicity leads to an increased oxidant release, which in turn may lead to increased cell damage, signaling activation and inflammatory cell recruitment.

Wagner et al. (1982) examined the in vitro cytotoxicity of three forms of tremolite used in their in vivo studies. LDH and β-glucuronidase 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. The Korean tremolite (Sample C) produced results similar to the positive control: increased toxicity of primary murine macrophages, increased cytotoxicity of Chinese hamster ovary cells, and increased formation of cells >25 μm diameter 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). 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 may be due, at least in part, to differential fiber counts.

Wylie et al. (1997) examined the mineralogical features associated with cytotoxic and proliferative effects of asbestos in hamster tracheal epithelial (HTE) 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 mesotheliomas. The results of the

analysis with fiber exposure by mass (μg/cm^2) show elevated colonies in HTE cells following exposures to both asbestos fibers (p <0.05) at the lowest concentrations, while significant decreases were observed for both asbestos fibers at the higher concentrations [0.5 μg/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 greater than 0.05 μg/cm^2 (p <0.05). All talc samples were less cytotoxic in both cell types. Analyzing the data for cytotoxicity and proliferation based on the exposure measurement demonstrated differences in response depending solely on how the fibers were measured: by mass, number, or surface area. These results show variability in interpreting the results of 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 would help elucidate the role of these metrics, particularly for in vivo studies.

Tremolite and LAA exposure led to increases in both fibrosis and tumorigenicity in all but one animal study, supporting a possible role for proliferation in response to these fibers (see Tables 4-19 and 4-20). However, there are limited data to demonstrate that increased cytotoxicity and cellular proliferation following exposure to LAA leads to lung cancer or mesothelioma.

Summary

The review of these studies clearly highlights the need for more controlled studies examining LAA in comparison with other forms of asbestos and for examining multiple endpoints—including ROS production, DNA damage, inflammasome activation, and proinflammatory gene expression alterations—to improve understanding of mechanisms involved in cancer and other health effects. Data gaps still remain to determine specific mechanisms involved in LAA-induced disease. Studies that examined cellular response to tremolite also found that tremolite exposure may lead to increased ROS production, toxicity, and genotoxicity (Okayasu et al., 1999; Wagner et al., 1982). As with the in vivo studies, the definition of fibers and how the exposures were measured varies among studies.

4.5. SYNTHESIS OF MAJOR NONCANCER EFFECTS

The predominant noncancer health effects observed following inhalation exposure to LAA are effects on the lungs and pleural lining surrounding the lungs. These effects have been observed primarily in studies of exposed workers and community members, and are supported by laboratory animal studies. Recent studies have also examined other noncancer health effects following exposure to Libby Amphibole, including autoimmune effects and cardiovascular disease; this research base is currently not as well developed as that of respiratory noncancer effects. Adequate data are not available to differentiate the health effects of the predominant

mineralogical forms composing LAA. Although the adverse effects of asbestiform tremolite are reported in the literature, the contribution of winchite and richterite to the aggregate effects of LAA has not been determined.

4.5.1. Pulmonary Effects

4.5.1.1. *Pulmonary Fibrosis (Asbestosis)*

Asbestosis is the interstitial pneumonitis (inflammation of lung tissue) and fibrosis caused by inhalation of asbestos fibers and is characterized by a diffuse increase of collagen in the alveolar walls (fibrosis) and the presence of asbestos fibers, either free or coated with a proteinaceous material and iron (asbestos bodies). Fibrosis results from a sequence of events following lung injury, which includes inflammatory cell migration, edema, cellular proliferation, and accumulation of collagen. Asbestosis is associated with dyspnea (shortness of breath), bibasilar rales, and changes in pulmonary function: a restrictive pattern, mixed restrictive-obstructive pattern, and/or decreased diffusing capacity (ATS, 2004). In clinical practice, fibrotic scarring of lung tissue consistent with mineral dust and mineral fiber toxicity is most commonly identified as small opacities in the lung on radiographic examination. The scarring of the parenchymal tissue of the lung contributes to changes in pulmonary function, including restrictive pulmonary deficits due to increased stiffness (reduced elasticity) of the lung, impaired gas exchange due, in part, to alveolar wall thickening, and sometimes mild obstructive deficits due to asbestos-induced airways disease.

Workers exposed to LAA from vermiculite mining and processing facilities in Libby, MT, as well as plant workers in Marysville, OH, where vermiculite ore was exfoliated and processed, have been found to have an increased prevalence of small opacities on chest x-rays, which is indicative of fibrotic damage to the parenchymal tissue of the lung (Rohs et al., 2008; Amandus et al., 1987a; McDonald et al., 1986b; Lockey et al., 1984). Significant increases in asbestosis as a cause of death have been documented in studies of the Libby worker cohort report [see Table 4-6 for details; (Larson et al., 2010b; Sullivan, 2007; Amandus and Wheeler, 1987; McDonald et al., 1986a)]. For both asbestosis mortality and radiographic signs of asbestos (small opacities), positive exposure-response relationships are described where these effects are greater with greater cumulative exposure to LAA.

Deficits in pulmonary function consistent with pulmonary fibrosis have been reported in individuals exposed to LAA in community-based studies.[19] Data from the ATSDR community screening, which included workers, provide support for functional effects from parenchymal changes. The original report of the health screening data indicated moderate to severe

[19]The initial study of the Marysville, OH cohort measured and reported no change in pulmonary function (Lockey et al., 1984). Pulmonary function was not reported for the cohort follow-up, although prevalence of pleural and parenchymal abnormalities was increased (Rohs et al., 2008). The initial studies of the occupational Libby worker cohort do not include assessment of pulmonary function (Amandus et al., 1987a; McDonald et al., 1986b).

pulmonary restriction in 2.2% of men (Peipins et al., 2003; ATSDR, 2001b). A recent reanalysis of these data show that for study participants with small opacities viewed on the radiographs (category 1/0 or greater) and DPT, the mean FVC is reduced to 78.76 (±3.64), 82.16 (±3.34), respectively, of the expected value (Weill et al., 2011). A mean FVC of 95.63 (±0.76) was reported for those with other pleural abnormalities versus 103.15 (±0.25) in participants with no radiographic abnormalities. The strongest effects of diffuse pleural thickening and/or costophrenic angle obliteration on FVC were seen among men who had never smoked (−23.77, p <0.05), with smaller effects seen among men who had smoked (−9.77, p <0.05) and women who had smoked (−6.73, p <0.05). Laboratory animal and mechanistic studies of LAA are consistent with the noncancer health effects observed in both Libby workers and community members. Pleural fibrosis was increased in hamsters after intrapleural injections of LAA (Smith, 1978). More recent studies have demonstrated increased collagen deposition consistent with fibrosis following intratracheal instillation of LAA fibers in mice and rats (Padilla-Carlin et al., 2011; Shannahan et al., 2011a; Shannahan et al., 2011b; Smartt et al., 2010; Putnam et al., 2008). Pulmonary fibrosis, inflammation, and granulomas were observed after tremolite inhalation exposure in Wistar rats (Bernstein et al., 2005b; Bernstein et al., 2003) and intratracheal instillation in albino Swiss mice (Sahu et al., 1975). Davis et al. (1985) also reported pulmonary effects after inhalation exposure in Wistar rats, including increases in peribronchiolar fibrosis, alveolar wall thickening, and interstitial fibrosis.

4.5.1.2. *Other Nonmalignant Respiratory Diseases*

Mortality studies of the Libby workers indicate increased mortality not only from asbestosis, but also from other respiratory diseases. Deaths attributed to chronic obstructive respiratory disease and deaths attributed to "other" nonmalignant respiratory disease were elevated more than twofold [see Table 4-6; (Larson et al., 2010b; Sullivan, 2007)]. These outcomes are consistent with asbestos toxicity, and the evidence of a positive exposure-response relationship for mortality from all nonmalignant respiratory diseases supports this association.

4.5.2. Pleural Effects

Pleural thickening caused by mineral fiber exposure mainly includes two distinct biological lesions: localized pleural plaques in the parietal (outer) pleura and diffuse pleural thickening of the visceral (inner) pleura. Both of these forms of pleural thickening can be identified on standard radiographs; however, smaller/thinner plaques and thinner diffuse thickening may not be detected, particularly if they are not calcified or are obscured by other normal chest structures. High resolution computed tomography is a radiographic method that is more sensitive and specific than standard chest x-rays (i.e., it can detect pleural abnormalities that are not evident on standard chest x-rays and it can more reliably exclude fat tissue that can sometimes be mistaken for pleural thickening on standard chest x-ray

Data from the ATSDR community health screening study indicate that the prevalence of pleural abnormalities, identified by radiographic examination, increases substantially with increasing number of exposure pathways (Peipins et al., 2003). A reanalysis of these data also considered age, smoking history, and types of exposures (Weill et al., 2011). Increased pleural thickening is reported for Libby workers, those with other vermiculite work, and those who had worked in other jobs with dust exposures (in locations other than Libby, MT). The prevalence of pleural plaques increased with age; in the 61−90 age group the prevalence was 38.3% and 12.7%, respectively, among those exposed only through household contacts and those exposed through environmental exposure pathways. The community-based study in Minneapolis, MN also provides evidence of increased risk of pleural abnormalities among residents surrounding an exfoliation plant, with positive associations seen with measures of background and of intermittent (activity-based) exposures (Alexander et al., 2012).

Increased pleural thickening (including LPT) is reported for both of the studied worker cohorts, with evidence of positive exposure-response relationships (Larson et al., 2012a; Larson et al., 2010a; Rohs et al., 2008; Amandus et al., 1987a; McDonald et al., 1986b; Lockey et al., 1984). Both McDonald et al. (1986b) and Amandus et al. (1987a) indicate that age is also a predictor of pleural thickening in exposed individuals, which may reflect the effects of time from first exposure. Smoking data were limited on the Libby workers and analyses do not indicate clear relationships between smoking and pleural thickening (Amandus et al., 1987a; McDonald et al., 1986b). Pleural thickening in workers at the Scott Plant (Marysville, OH) was associated with hire on or before 1973 and age at time of interview but was not associated with BMI or smoking history [ever smoked (Rohs et al., 2008)].

4.5.3. Other Noncancer Health Effects (Cardiovascular Toxicity, Autoimmune Effects)

Limited research is available on noncancer health effects occurring outside the respiratory system and pleura. Larson et al. (2010b) examined cardiovascular disease-related mortality in the cohort of exposed workers from Libby (see Section 4.1). Mechanistic studies have examined the potential role of iron and the associated inflammation for both respiratory and cardiovascular disease (Shannahan et al., 2012a; Shannahan et al., 2012c; Shannahan et al., 2012b; Shannahan et al., 2012d; Shannahan et al., 2011b). Other studies examined the association between asbestos exposure and autoimmune disease (Noonan et al., 2006) or autoantibodies and other immune markers [(Pfau et al., 2005); see Table 4-15]. However, limitations in the number, scope, and design of these studies make it difficult to reach conclusions as to the role of asbestos exposure in either cardiovascular disease or autoimmune disease.

4.5.4. Summary of Noncancer Health Effects of Exposure to Libby Amphibole Asbestos

The studies of humans summarized in Section 4.1 have documented an increase in mortality from nonmalignant respiratory disease, including asbestosis, in workers exposed to LAA (Larson et al., 2010b; Sullivan, 2007; McDonald et al., 2004; Amandus and Wheeler, 1987). Additional studies have documented an increase in radiographic changes in the pleura (pleural thickening) and parenchyma among employees of a manufacturing facility in Marysville, OH that processed LAA-containing vermiculite ore (Rohs et al., 2008; Lockey et al., 1984). Radiographic evidence of pleural thickening and interstitial damage (small opacities) are also well documented among employees of the Libby vermiculite mining operations (Larson et al., 2012a; Larson et al., 2010a; Amandus et al., 1987a; McDonald et al., 1986b). Positive exposure-response relationships for these health effects for both occupational cohorts studied, as well as the observed latency, support an association between exposure to LAA and these pleural and/or pulmonary effects. Studies of community members exposed to LAA have documented similar pleural abnormalities and pulmonary function deficits consistent with effects of tissue damage caused by LAA (Weill et al., 2011; Whitehouse, 2004; Peipins et al., 2003). Animal studies also support the toxicity of LAA to pleural and pulmonary tissues. Developing research supports a role of inflammatory processes in the toxic action of LAA, consistent with the observed health effects (Cyphert et al., 2012b; Shannahan et al., 2012c; Shannahan et al., 2011b; Duncan et al., 2010; Hamilton et al., 2004). Taken together, the strong evidence in human studies, defined exposure-response relationships, and supportive animal studies provide compelling evidence that exposure to LAA causes nonmalignant respiratory disease, including asbestosis, pleural thickening, and deficits in pulmonary function associated with mineral fiber exposures. Existing data regarding cardiovascular effects and the potential for autoimmune disease are limited.

4.5.5. Mode-of-Action Information (Noncancer)

The precise mechanisms causing toxic injury from inhalation exposure to LAA have not been established. However, nearly all durable mineral fibers with dimensional characteristics that allow penetration to the terminal bronchioles and alveoli of the lung have the capacity to induce pathologic response in the lung and pleural cavity (ATSDR, 2001a; Witschi and Last, 1996). The physicochemical attributes of mineral fibers are important in determining the type of toxicity observed. Fiber dimension (width and length), density, and other characteristics, such as chemical composition, surface area, solubility in physiological fluids, and durability, all play important roles in both the type of toxicity observed and the biologically significant dose. As described in Section 3, these characteristics also play a role in fiber dosimetry. Fibrosis results from a sequence of events following lung injury, which includes inflammatory cell migration, edema, cellular proliferation, and accumulation of collagen. Fibers do migrate to the pleural space, and it has been hypothesized that a similar cascade of inflammatory events may contribute

to fibrotic lesions in the visceral pleura. Thickening of the visceral pleura is more often localized to lobes of the lung with pronounced parenchymal changes, and it has also been hypothesized that the inflammatory and fibrogenic processes within the lung parenchyma in response to asbestos fibers may influence the fibrogenic process in the visceral pleura. The pathogenic mechanism(s) through which mineral fiber exposure effects parietal plaques is largely unknown.

There is currently insufficient evidence to establish the noncancer MOA for LAA. Limited in vitro studies have demonstrated oxidative stress following LAA exposures in various cell types (Duncan et al., 2010; Hillegass et al., 2010; Pietruska et al., 2010; Blake et al., 2007). LAA fibers increased intracellular ROS in both murine macrophages and human epithelial cells (Duncan et al., 2010; Blake et al., 2007). Surface iron and inflammatory marker gene expression was increased following exposure to LAA in human epithelial cells [(Shannahan et al., 2012a; Shannahan et al., 2012c; Shannahan et al., 2012b; Shannahan et al., 2012d; Shannahan et al., 2011b; Duncan et al., 2010; Pietruska et al., 2010); see Table 4-18]. Tremolite studies demonstrate cytotoxicity in various cell culture systems (see Table 4-22).

The initial stages of any fibrotic response involve cellular proliferation, which may be compensatory for cell death due to cytotoxicity. Analysis of cellular proliferation has demonstrated both increases and decreases following exposure to asbestos fibers in vitro and in vivo depending on the specific fiber or cell type (Mossman et al., 1985; Topping and Nettesheim, 1980). Other studies have focused on the activation of cell-signaling pathways that lead to cellular proliferation following exposure to asbestos (Scapoli et al., 2004; Shukla et al., 2003; Ding et al., 1999; Zanella et al., 1996; Zhang et al., 1993).

Although slightly increased compared to controls, cytotoxicity in murine macrophage cells exposed to LAA was decreased compared to other fiber types (Blake et al., 2008). Cytotoxicity was slightly, but statistically significantly, increased compared to an unexposed control at 24 hours postexposure to LAA, while crocidolite exposure resulted in even higher levels of cytotoxicity. No other in vitro study examined cytotoxicity following exposure to LAA, although an increase in apoptosis was demonstrated in this same cell system (Blake et al., 2008). Recent studies in mice exposed to LAA demonstrated increased collagen deposition and collagen gene expression, markers of fibrosis (Smartt et al., 2010; Putnam et al., 2008). Short-term-duration studies in rats also demonstrated an increased inflammatory response (Padilla-Carlin et al., 2011; Shannahan et al., 2011a; Shannahan et al., 2011b). Tremolite or LAA exposure both led to increases in fibrosis in all but one animal study, supporting a role for proliferation in response to these fibers. Taken together with studies on other asbestos fibers, these data suggest that cytotoxicity and cell proliferation may play a role in the noncancer health effects following exposure to LAA.

Although continued research demonstrates that the LAA has biologic activity consistent with the inflammatory action and cytotoxic effects seen with other forms of asbestos, the data are not sufficient to establish a MOA for the pleural and/or pulmonary effects of exposure to LAA.

4.6. EVALUATION OF CARCINOGENICITY

4.6.1. Summary of Overall Weight of Evidence

Under the EPA *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a), LAA is *carcinogenic to humans* following inhalation exposure based on epidemiologic evidence that shows a convincing association between exposure to LAA and increased lung cancer and mesothelioma mortality (Larson et al., 2010b; Moolgavkar et al., 2010; Sullivan, 2007; McDonald et al., 2004; Amandus and Wheeler, 1987; McDonald et al., 1986a). These results are further supported by animal studies that demonstrate the carcinogenic potential of LAA and tremolite asbestos in rodent bioassays (see Section 4.1, 4.2, Appendix D). As a durable mineral fiber of respirable size, this conclusion is consistent with the extensive published literature that documents the carcinogenicity of amphibole fibers [as reviewed in (Aust et al., 2011; Broaddus et al., 2011; Bunderson-Schelvan et al., 2011; Huang et al., 2011; Mossman et al., 2011)].

EPA's *Guidelines for Carcinogenic Risk Assessment* (U.S. EPA, 2005a) indicate that for tumors occurring at a site other than the initial point of contact, the weight of evidence for carcinogenic potential may apply to all routes of exposure that have not been adequately tested at sufficient doses. An exception occurs when there is convincing information (e.g., toxicokinetic data) that absorption does not occur by other routes. Information on the carcinogenic effects of LAA via the oral and dermal routes in humans or animals is absent. The increased risk of lung cancer and mesothelioma following inhalation exposure to LAA has been established by studies in humans, but these studies do not provide a basis for determining the risk from other routes of exposure. Mesothelioma occurs in the pleural and peritoneal cavities and, therefore, is not considered a portal-of-entry effect. However, the role of indirect or direct interaction of asbestos fibers in disease at these extrapulmonary sites is still unknown. No information exists on the translocation of LAA to extrapulmonary tissues following either oral or dermal exposure, and limited studies have examined the role of these routes of exposure in cancer. Therefore, LAA is considered *carcinogenic to humans* by the inhalation route of exposure.

4.6.1.1. *Synthesis of Human, Animal, and Other Supporting Evidence*

Libby, MT workers have been the subject of multiple mortality studies demonstrating increased cancer mortality in relation to estimated fiber exposure. Occupational studies conducted in the 1980s (Amandus and Wheeler, 1987; McDonald et al., 1986a) as well as the extended follow-up studies published in more recent years (Larson et al., 2010b; Sullivan, 2007; McDonald et al., 2004) and additional analyses of the extended follow-up (Moolgavkar et al., 2010) provide evidence of an increased risk of lung cancer mortality and of mesothelioma mortality among the workers exposed to LAA in the Libby vermiculite mining and processing operations. This pattern is seen in the lung cancer analyses using an internal referent group in the larger follow-up studies (Larson et al., 2010b; Sullivan, 2007; McDonald et al., 2004), with cumulative exposure analyzed using quartiles or as a continuous measure, and in the studies

reporting analyses using an external referent group [i.e., standardized mortality ratios; (Sullivan, 2007; Amandus and Wheeler, 1987; McDonald et al., 1986a)]. McDonald et al. (2004) also reported increasing risk of mesothelioma across categories of exposure; the more limited number of cases available in earlier studies precluded this type of exposure-response analysis. This association is also supported by the case series of 11 mesothelioma patients among residents in or around Libby, MT, and among family members of workers in the mining operations (Whitehouse et al., 2008), and by the observation of three cases of mesothelioma (two of which resulted in death) in the Marysville, OH worker cohort identified as of June 2011 (Dunning et al., 2012).

Although experimental data in animals and data on toxicity mechanisms are limited for LAA, tumors that were observed in animal tissues were similar to those in humans (e.g., mesotheliomas, lung cancer) indicating the existing data are consistent with the cancer effects observed in humans exposed to LAA. Smith (1978) reported an increased incidence of mesotheliomas in hamsters after intrapleural injections of LAA. Additionally, studies in laboratory animals (rats and hamsters) exposed to tremolite via inhalation (Bernstein et al., 2005b; Bernstein et al., 2003; Davis et al., 1985), intrapleural injection (Roller et al., 1997, 1996; Davis et al., 1991; Wagner et al., 1982; Smith et al., 1979), or implantation (Stanton et al., 1981) have shown increases in mesotheliomas and lung cancers. Tremolite from various sources was used and varied in fiber content and potency (see Section 4.2, Appendix D). The most sensitive model for mesothelioma induction is the Syrian golden hamster following asbestos inhalation, with different susceptibility between species attributed to more rapid translocation to the pleural space (Donaldson et al., 2010). Although McConnell et al. (1983a) observed no increase in carcinogenicity following oral exposure to nonfibrous tremolite, the ability of this study to inform the carcinogenic potential of fibrous tremolite through inhalation is unclear, and these study results contribute little weight to the evaluation of the carcinogenicity of fibrous LAA.

The available mechanistic information suggests LAA induces effects that may play a role in carcinogenicity (see Section 4.2 Appendix D). Several in vitro studies have demonstrated oxidative stress and genotoxicity following LAA exposures in various cell types (Duncan et al., 2010; Hillegass et al., 2010; Pietruska et al., 2010; Blake et al., 2007). LAA increased intracellular ROS in both murine macrophages and human epithelial cells (Duncan et al., 2010; Blake et al., 2007). Additionally, surface iron, inflammatory marker gene expression, and aneugenic micronuclei were increased following exposure to LAA in human epithelial cells (Duncan et al., 2010; Pietruska et al., 2010). Tremolite studies demonstrate cytotoxic and clastogenic effects (e.g., micronucleus induction and chromosomal aberrations) of the fibers in various cell culture systems.

In summary, the epidemiologic data demonstrate an association between exposure to LAA and increased cancer risk. Supporting evidence of carcinogenic potential was observed in the limited number of laboratory animal studies exposed to LAA or tremolite (see Tables 4-19

and 4-20 summarizing in vivo studies). Overall, the available evidence supports the conclusion that LAA is *carcinogenic to humans*.

4.6.2. Mode-of-Action Information (Cancer)

4.6.2.1. *Description of the Mode-of-Action Information*

EPA guidance provides a framework for analyzing the potential mode(s) of action by which physical, chemical, and biological information is evaluated to identify key events in an agent's carcinogenicity (U.S. EPA, 2005a). Agents can work through more than one MOA, and MOA can differ for various endpoints (e.g., lung cancer vs. mesothelioma). Reasonably, the analysis of a MOA would start with some knowledge of an agent's biological activity that leads to cellular transformation resulting in cancer. Although early steps in the process often can be identified, carcinogenicity is a complex process resulting from multiple changes in cell function. Due to the limited data available specific to LAA, the MOA of LAA for lung cancer and mesothelioma following inhalation exposure cannot be established.

Occupational studies demonstrate human health effects (e.g., lung cancer, mesothelioma) following exposure to LAA. Although the limited mechanistic data demonstrate biological effects similar to those of other mineral fibers following exposure to LAA, the existing literature is insufficient to establish a MOA for LAA for lung cancer or mesothelioma. These biological effects following exposure to LAA and/or tremolite are demonstrated in a limited number of laboratory animal and in vitro studies. Multiple key events for one particular MOA have not been identified; therefore, the MOA for LAA carcinogenicity cannot be established. However, multiple mechanisms of action (e.g., mutagenicity, chronic inflammation, cytotoxicity, and regenerative proliferation) can be hypothesized based on the available asbestos literature. These are described in Section 4.4, and discussed below.

4.6.2.2. *Evidence Supporting a Mutagenic Mode of Action*

Strength, consistency and specificity of the association

Only limited genotoxicity analysis following exposure to LAA or tremolite has been reported, although studies of other types of asbestos fibers have shown increases in genotoxicity both in vitro and in vivo [reviewed in (Huang et al., 2011)]. One in vitro study examined genotoxicity of LAA by measuring DNA adduct formation following exposure via murine macrophages [primary and immortalized; (Blake et al., 2007)]. The data showed no increase in adduct formation as compared to unexposed controls. A second study observed increases in micronuclei induction in both normal human lung epithelial cells and XRCC1-deficient cells for both Libby Amphibole and crocidolite asbestos (Pietruska et al., 2010). Two studies of tremolite examined genotoxicity. The first found no significant increase in revertants in the Ames assay (Athanasiou et al., 1992), which is similar to results obtained for other forms of asbestos. This study did find, however, that tremolite exposure led to a dose-dependent increase in chromosome

number and micronuclei formation, which has also been described for other asbestos fibers [as reviewed in (Hei et al., 2006; Jaurand, 1997)]. Hei and colleagues (Okayasu et al., 1999) performed mutation analysis with tremolite and found a dose-dependent increase in mutations in CD59 in hamster hybrid cells. Although LAA- and tremolite-specific data are limited to in vitro studies, given the similarities in response to other forms of asbestos, there is some evidence to suggest genotoxicity following exposure to Libby Amphibole and tremolite asbestos.

Dose-response concordance and temporal relationship

A dose-response concordance has not been established between the development of genotoxicity and exposure to LAA or other amphibole asbestos. Genotoxicity studies of other amphibole asbestos have examined gene mutations and chromosomal mutations, as well as DNA damage resulting from ROS production following exposure. As recently reviewed by Huang et al. (2011), there are a large number of in vitro studies that support possible genotoxic mechanisms following exposure to fibers. There are fewer in vivo studies of the genotoxicity of amphibole asbestos, and a very limited number of these were following inhalation exposure. Some of these studies were performed in nonrelevant cell types for inhalation endpoints, and some also were performed at doses higher than observed in environmental or occupational asbestos exposures. Temporal relationship would be impacted by direct or indirect genotoxic mechanism playing a role in asbestos-induced tumorigenesis. There is insufficient data to conclude whether the observed genotoxic effects following exposure to amphibole asbestos result from direct (e.g., spindle interference) or indirect (e.g., ROS production) mechanisms. The available evidence suggests a role for both direct and indirect genotoxicity, but requires further research (Huang et al., 2011). Therefore, although these results suggest a possible role for genotoxicity in the MOA of LAA, dose-response concordance and a temporal relationship are difficult to determine.

Biological plausibility and coherence

Although only limited genotoxicity studies of LAA and tremolite have been published, these studies are supported by similar results for other amphibole asbestos studies that demonstrate genotoxicity in both in vitro and in vivo studies [as reviewed in (Huang et al., 2011)]. Although studies of asbestos genotoxicity need to be carefully reviewed to determine relevance of routes of exposure, target cell, and dose, taking these parameters into account, this review of these studies supports the biological plausibility of the genotoxicity of LAA.

4.6.2.3. *Evidence Supporting Mechanisms of Action of Chronic Inflammation, Cytotoxicity, and Cellular Proliferation*

Chronic inflammation has been observed following fiber exposure, which is often followed by fibrosis at the site of inflammation if the fibers persist [reviewed in (Mossman et al.,

2011)]. Macrophages phagocytose fibers and particulate matter and are activated to trigger the release of inflammatory cytokines, ROS, and growth factors. These responses lead to a sustained inflammatory response that can result in fibrosis at the site of fiber deposition. Chronic inflammation is hypothesized to contribute to a carcinogenic response through the production of ROS and increased cellular proliferation (Hanahan and Weinberg, 2011).

The initial stages of any fibrotic response involve cellular proliferation, which may be compensatory for cell death due to cytotoxicity. The same may be true for tumorigenicity, as increased cell proliferation can increase the chance of cancer by increasing the population of spontaneous mutations affording genotoxic effects an opportunity to multiply. Analysis of cellular proliferation of epithelial cells has demonstrated both increases and decreases following exposure to asbestos fibers in vitro and in vivo (Mossman et al., 1985; Topping and Nettesheim, 1980). Other studies have focused on the activation of cell-signaling pathways that lead to cellular proliferation following exposure to asbestos (Scapoli et al., 2004; Shukla et al., 2003; Ding et al., 1999; Zanella et al., 1996).

The inflammatory response to fibers in vivo has been studied following inhalation exposure to many types of fibers but not for LAA [reviewed in (Broaddus et al., 2011; Mossman et al., 2011; Mossman et al., 2007)]. Results following inhalation exposure to tremolite have demonstrated increased inflammatory response as early as 1 day postexposure (Bernstein et al., 2005b; Bernstein et al., 2003). Earlier data from Davis et al. (1985) following inhalation exposure to other forms of tremolite showed increased fibrosis and carcinogenesis; however, inflammatory response was not described. In vivo studies of LAA and tremolite through other routes of exposure have demonstrated increased inflammation following exposure (Padilla-Carlin et al., 2011; Shannahan et al., 2011a; Shannahan et al., 2011b). Inhalation studies examining other types of asbestos (crocidolite, chrysotile, and amosite) have clearly demonstrated an increase in chronic inflammation and respiratory cancer related to exposure [reviewed in (Mossman et al., 2011)]. This effect is observed in animal studies for LAA and tremolite and is relevant to humans based on similar responses in cohorts analyzed (Musk et al., 2008; Hein et al., 2007; Levin et al., 1998).

Although limited, the data described here for LAA, and to a greater extent for tremolite, suggest a similar response as to other amphibole asbestos. In vivo exposure to tremolite led to an increase in inflammation for all studies where it was measured. This increase appeared in some cases to depend on fiber size and morphology (Davis et al., 1991; Smith et al., 1979). In vitro analysis of LAA showed increases in inflammatory cytokines (Hamilton et al., 2004) and in proinflammatory gene expression (Duncan et al., 2010). Bernstein et al. (2005b) and Bernstein et al. (2003) observed that exposure to tremolite led to pronounced inflammation as soon as 1 day after inhalation exposure in male Wistar rats. Inflammation also occurred in male albino Swiss mice in an acute-duration study that did not lead to fibrosis or carcinogenesis, possibly due to the short study duration [150 days (Sahu et al., 1975)].

Chronic inflammation has also been associated with increased ROS production [reviewed in (Aust et al., 2011; Kamp et al., 1992)]. Fibers can directly lead to the production of ROS by iron-catalyzed generation through the Fenton reaction. ROS are also produced following phagocytosis of fibers. ROS production following exposure to asbestos has been shown to be associated with DNA damage (described below), chronic inflammation, and lipid peroxidation. As described in the previous section, chronic inflammation may lead to increased cell proliferation and DNA damage, which in turn may lead to tumor formation. The hydroxyl radical produced has been shown to directly interact with DNA (Leanderson et al., 1988).

ROS production has been measured in response to both LAA and tremolite exposure. The study of LAA (Blake et al., 2007) demonstrated an increase in superoxide anions, not hydrogen peroxide, as has been demonstrated with crocidolite. Blake et al. (2007) also demonstrated that total SOD was inhibited following exposure to LAA, along with a decrease in intracellular glutathione. These results are supported by a recent study in human mesothelial cells (Hillegass et al., 2010). Further, increased ROS production was also observed in human airway epithelial cells following exposure to LAA (Duncan et al., 2010). This increase in ROS and decrease in glutathione are common effects following exposure to asbestos fibers and particulate matter. Limited studies, however, have examined the specific type of ROS produced following exposure to each type of asbestos.

A dose-response concordance has not been established between the development of chronic inflammation and exposure to LAA. Dose-response information is limited to inhalation studies of other amphibole asbestos, which were recently reviewed (Case et al., 2011; Mossman et al., 2011). Many of the early studies of amphiboles described above were performed using only one dose. Therefore, while these studies demonstrate an exposure-response relationship between amphibole asbestos and chronic inflammation, dose-response concordance cannot be determined.

A temporal relationship has not been established between the development of chronic inflammation and inhalation exposure to LAA. Chronic inhalation studies of tremolite demonstrate an increase in chronic inflammation over time (Bernstein et al., 2005b; Bernstein et al., 2003) that may lead to fibrosis, or possibly tumor formation. A similar pattern has also been observed in inhalation studies with other amphibole asbestos [as reviewed in Mossman et al. (2011)].

Chronic inflammation following exposure to fibers has been associated with the development of both malignant and nonmalignant lung and pleural diseases (Bringardner et al., 2008; Mossman and Churg, 1998). In vivo and in vitro studies have shown increases in inflammation and inflammatory markers following exposure to LAA and tremolite up to 1 month following single intratracheal instillation exposures in animal models (see Section 4.2, Appendix D). Although inhalation studies are limited, the results of those studies demonstrate an increase in chronic inflammation over time, similar to studies of other amphibole asbestos fibers

(Mossman et al., 2011). Overall, the evidence described above suggests chronic inflammation is observed following Libby Amphibole and tremolite asbestos exposure.

Although slightly increased compared to controls, cytotoxicity in murine macrophage cells exposed to LAA was decreased compared to other fiber types (Blake et al., 2008). No other in vitro study examined cytotoxicity following exposure to LAA, although an increase in apoptosis was demonstrated in this same cell system (Blake et al., 2008).

Compensatory proliferation in epithelial cells following cytotoxicity can lead to an increase in mutations (both spontaneous and induced). This increase is generally offset by increased levels of apoptosis, as in Blake et al. (2008). Recent studies in mice exposed to LAA demonstrated increased collagen deposition and collagen gene expression, markers of fibrosis (Smartt et al., 2010; Putnam et al., 2008). Tremolite and LAA exposure led to increases in both fibrosis and tumorigenicity in all but one animal study, supporting a role for proliferation in response to these fibers. Taken together with studies on other asbestos fibers, these data suggest that cytotoxicity and cell proliferation may play a role in tumor formation.

Neither a dose-response concordance nor temporal relationship has been established between the development of cytotoxicity and regenerative cellular proliferation and exposure to LAA. However, cytotoxicity and regenerative cellular proliferation has been observed following exposure to LAA as well as other amphibole asbestos through other routes of exposure in in vivo assays (e.g., intratracheal instillation). Also, increases in markers of proliferative response have been observed in in vitro studies of LAA and other amphibole asbestos in epithelial cells. These results suggest exposure to LAA may lead to increases in cytotoxicity and regenerative proliferation; however, the data are not sufficient to determine a dose-response relationship.

It is generally accepted that sustained cell proliferation in response to cytotoxicity can be a significant risk factor for cancer (Correa, 1996). Sustained cytotoxicity and regenerative cell proliferation may result in the perpetuation of mutations (spontaneous or directly or indirectly induced by the chemical), resulting in uncontrolled growth. It is also possible that continuous proliferation may increase the probability that damaged DNA will not be repaired. Reparative proliferation alone is not assumed to cause cancer. Tissues with naturally high rates of turnover do not necessarily have high rates of cancer, and tissue toxicity in animal studies does not invariably lead to cancer. Nevertheless, regenerative proliferation associated with persistent cytotoxicity appears to be a risk factor of consequence.

4.6.2.4. *Conclusions About the Hypothesized Modes of Action*

Is the hypothesized mode of action sufficiently supported in the test animals?

There are a limited number of studies on the genotoxicity of LAA and/or tremolite. However, the studies described in Section 4 suggest a possible role for mutagenicity in asbestos-induced carcinogenicity. These studies showed chromosomal aberrations, increases in micronuclei induction, and increased ROS production which has been shown to lead to

mutagenicity (see Section 4, Table 4-21). One study of DNA adduct formation did not show any DNA damage or adducts following exposure to LAA. Laboratory animal studies of other amphibole asbestos have demonstrated similar results (Huang et al., 2011). Further research in this area is needed in order to inform the possibility of a mutagenic MOA for LAA.

Chronic inflammation is observed following exposure to most fibers studied (Mossman et al., 2011). Laboratory animal studies of LAA and tremolite demonstrated increases in inflammation, inflammatory markers, and increases in inflammatory cells. Further, in vitro studies have shown that exposure to LAA and tremolite lead to increases in expression of inflammatory cytokines. Available data are limited but consistent with the hypothesis that a MOA involving chronic inflammation contributes to asbestos-induced pulmonary and pleural tumors, either independently or in combination with a mutagenic MOA. However, it has not been determined whether chronic inflammation is a necessary precursor of carcinogenesis, and experimental support for causal links, such as compensatory cellular proliferation or clonal expansion of initiated cells, is lacking between toxicity and pulmonary or pleural tumor formation. However, further research is needed to determine if this MOA could be established for LAA and/or tremolite.

As reviewed in Section 4.2, in vivo and in vitro studies have shown a consistent cytotoxic and proliferative response to LAA and/or tremolite. Therefore, it has been proposed that cytotoxicity following pulmonary exposure to LAA and/or tremolite is a precursor to carcinogenicity. A more biologically plausible MOA may involve a combination of chronic inflammation, genotoxicity, and cytotoxicity, with genotoxicity increasing the rate of mutation and regenerative proliferation enhancing the survival or clonal expansion of mutated cells. However, this hypothesis has yet to be tested experimentally.

Is the hypothesized mode of action relevant to humans

Although limited for LAA, the evidence discussed above demonstrates that LAA exposure results in genotoxicity in in vitro and in vivo studies in test animal species. Therefore, the presumption is LAA would be genotoxic in humans. The few available data from human and in vivo laboratory animal studies concerning the genotoxicity of amphibole asbestos suggest consistency with this mechanism, but the studies are not sufficiently conclusive to provide direct supporting evidence for a mutagenic MOA. This MOA is considered relevant to humans.

The evidence discussed above demonstrates that exposure to LAA and/or tremolite asbestos lead to chronic inflammation. The available human data following exposure to LAA and other amphibole asbestos suggest consistency with this mechanism being relevant to humans. Data are inadequate to determine that a cytotoxic mechanism is operative following exposure to LAA in exposed populations; however, none of the available data suggest that this mechanism is biologically precluded in humans. Furthermore, both animal and in vitro studies

suggest that LAA causes cytotoxicity at exposures that may induce pulmonary cancers, constituting positive evidence of the human relevance of this hypothesized MOA.

Which populations or life stages can be particularly susceptible to the hypothesized mode of action

A mutagenic MOA is considered relevant to all populations and life stages. According to EPA's Cancer Guidelines (U.S. EPA, 2005a) and Supplemental Guidance (U.S. EPA, 2005b), there may be increased susceptibility to early-life exposures for carcinogens with a mutagenic MOA. The weight of evidence is insufficient to support a mutagenic MOA for LAA carcinogenicity and in the absence of chemical-specific data to evaluate differences in susceptibility, 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 is not recommended.

Populations that may be more susceptible include those with varied fiber toxicokinetics related to potential anatomical, physiological, and biochemical differences which may impact fiber dosimetry (see Section 4.7). No data are available as to whether other factors may lead to different populations or life stages being more susceptible to the hypothesized MOA for LAA-induced tumors (e.g., chronic inflammation, cytotoxicity or mutagenicity). For instance, it is not known how the hypothesized key events in chronic inflammatory response (e.g., increased oxidative stress) to fibers interact with known risk factors for human pulmonary or pleural carcinomas.

As with chronic inflammation, populations that may be more susceptible to increased cytotoxicity following exposure to LAA include those that may have varied fiber toxicokinetics related to potential anatomical, physiological, and biochemical differences which may impact fiber dosimetry (see Section 4.7). No data are available as to whether other factors may lead to different populations or life stages being more susceptible to a cytotoxic MOA for LAA-induced tumors. For instance, it is not known how the hypothesized key events (e.g., interference with the spindle apparatus) in this MOA interact with known risk factors for human pulmonary or pleural carcinomas.

Summary

Research on multiple types of elongate mineral fibers supports the role of multiple modes of action following exposure to LAA. Of the MOAs described above, the evidence that chronic inflammation, genotoxicity and cytotoxicity, and cellular proliferation may all play a role in the carcinogenic response to LAA is only suggestive (see Table 4-23). In vitro studies provide evidence that amphibole asbestos is capable of eliciting genotoxic and mutagenic effects in mammalian respiratory cells; however, direct evidence of mutagenicity in respiratory cells following inhalation exposure is lacking. Results of the in vivo studies described here are

consistent with the hypothesis that some forms of amphibole asbestos act through a MOA dependent on cellular toxicity. This conclusion is largely based on the observations that cytotoxicity and reparative proliferation occur following subchronic exposure and that bronchiolar tumors are produced at exposure levels that produce cytotoxicity and reparative proliferation. However, dose-response data in laboratory animal studies for damage/repair and tumor development are limited because of the lack of inhalation studies using multiple doses of fibers that exist. Although evidence is generally supportive of a MOA involving chronic inflammation or cellular toxicity and repair, there is insufficient evidence to support these hypotheses; thus, a linear approach is used to calculate the inhalation cancer unit risk in accordance with the default recommendation of the 2005 *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a). It is possible that multiple MOAs discussed above, or an alternative MOA, may be responsible for tumor induction.

Table 4-23. Hypothesized modes of action for carcinogenicity of Libby Amphibole asbestos in specific organs

Potential MOA	Evidence for MOA	Limitations/evidence against MOA	Weight of evidence
Lung cancer			
Chronic inflammation	Inflammatory response demonstrated at the site of fiber deposition and has been linked to genotoxicity and mutagenicity.	Limited analysis of inflammation/tumor site concordance. Genotoxicity is commonly assumed to contribute to carcinogenesis. Inflammation can occur without progressing to cancer.	Some inconclusive evidence for this MOA.
ROS	ROS known to be produced following exposure to multiple types of fibers. ROS are associated with DNA damage, lipid peroxidation, and chronic inflammation.	ROS lead to DNA adduct formation, which in turn can lead to mutation. Limited studies have examined the production of ROS following exposure to LAA.	Suggestive evidence for this MOA for LAA (strong for other fiber types).
Lung cancer—genotoxicity			
Direct	Fibers directly interact with spindle apparatus and can interfere during mitosis leading to clastogenicity.	Ames assay inconclusive for fiber analysis (cell type unable to show ROS production and then possible mutations).	Suggestive evidence for this MOA for LAA (strong for other fiber types).
Indirect	Fibers lead to ROS production, which leads to DNA damage.	ROS lead to DNA adduct formation, which in turn can lead to mutation. Limited studies have examined the production of ROS following exposure to LAA (cell type unable to show ROS production).	Suggestive evidence for this MOA for LAA (strong for other fiber types).
Cytotoxicity and cellular proliferation	Increased cellular proliferation can increase the chance of cancer by increasing the population of mutations. Many fibers activate signaling pathways that lead to cellular proliferation.	Limited analysis of cell types/target tissues where cell proliferation occurs without chronic inflammation.	Suggestive evidence for this MOA for asbestos fibers.

Table 4-23. Hypothesized modes of action for carcinogenicity of Libby Amphibole asbestos in specific organs (continued)

Potential MOA	Evidence for MOA	Limitations/Evidence against MOA	Weight of evidence
Mesothelioma			
Chronic inflammation	Inflammatory response demonstrated at the site of fiber deposition and has been linked to genotoxicity and mutagenicity.	Limited analysis of inflammation/tumor site concordance. Genotoxicity is commonly assumed to contribute to carcinogenesis. Inflammation can occur without progressing to cancer.	Insufficient evidence for this MOA.
ROS	ROS known to be produced following exposure to multiple types of fibers. ROS are associated with DNA damage, lipid peroxidation, and chronic inflammation.	Limited analysis in this target tissue. ROS lead to DNA adduct formation which in turn can lead to mutation. Limited studies have examined the production of ROS following exposure to LAA.	Insufficient evidence for this MOA.
Mesothelioma—genotoxicity			
Direct	Fibers directly interact with spindle apparatus and can interfere during mitosis, leading to clastogenicity.	Limited analysis in this target tissue. Ames assay inconclusive for fiber analysis (cell type unable to show ROS production followed by possible mutations).	Insufficient evidence for this MOA.
Indirect	Fibers lead to ROS production, which leads to DNA damage.	Limited analysis in this target tissue. ROS lead to DNA adduct formation which in turn can lead to mutation. Limited studies have examined the production of ROS following exposure to LAA.	Insufficient evidence for this MOA.
Cytotoxicity and cellular proliferation	Increased cellular proliferation can increase chance of cancer by increasing the population of mutations. Many fibers activate signaling pathways that lead to cellular proliferation.	Limited analysis in this target tissue. Limited analysis of cell types/target tissues where cell proliferation occurs without chronic inflammation.	Insufficient evidence for this MOA.
Lymphatic system and other organs			
Data not available	Data not available	Limited analysis in these target tissues.	Insufficient evidence for any MOA.

4.6.2.5. *Application of the Age-Dependent Adjustment Factors*

As described above, the MOA for LAA is unknown. The weight of evidence 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 is not recommended.

4.7. SUSCEPTIBLE POPULATIONS

Certain populations may be more susceptible to adverse health effects from exposure to LAA. Because the adverse health effects resulting from exposure to LAA have been primarily studied in occupational cohorts of adult white men (see Sections 4.1.1 and 4.1.3), there is limited information on the effects to a broader population. A few studies, however, have examined health effects resulting from nonoccupational exposure in other age groups, genders (i.e., females), and races or ethnicity groups. The data from these studies could inform whether any differential risk exists for these groups (see Sections 4.1.2 and 4.1.4). However, note that distinguishing true differences from chance variation in effect estimates is related to the sample size and statistical power, which is usually limited in these studies. In addition, genetic polymorphisms, preexisting health conditions, and differences in nutritional status may alter an individual's response to LAA. Finally, coexposures to other substances (e.g., tobacco smoke or particulate matter) may increase an individual's risk of adverse health effects from exposure to LAA. When data are available, each of these factors is discussed below with respect to increased susceptibility to cancer and noncancer effects from exposure to LAA. When information specific to LAA is not available, the general literature on the toxicity of mineral fibers is briefly referenced.

There are also factors that may influence one's exposure potential to asbestos based on life stage or other characteristics. For example, children spend more hours outside and may engage in activities which impact exposure potential compared to adults (U.S. EPA, 2006b; NRC, 1993). Because life stage and activity patterns can increase the potential for health effects from exposure, these factors define who may be more susceptible to health effects due to greater exposure. Section 2.5 discusses this exposure potential, including how children, workers, household contacts, and residents may be exposed to LAA.

4.7.1. Influence of Different Life Stages on Susceptibility

Individuals at different life stages differ from one another physiologically, anatomically, and biochemically. Individuals in early and later life stages differ markedly from adulthood in terms of body composition, organ function, and many other physiological parameters, which can influence the toxicokinetics and toxicodynamics of chemicals and their metabolites in the body (Guzelian et al., 1992). This also holds true for mineral fibers, including asbestos fibers (see Section 3). This section presents and evaluates the literature on how individuals in early or later life stages might respond differently and thus potentially be more susceptible to adverse health effects of LAA exposure.

4.7.1.1. *Life-Stage Susceptibility*

Humans in early life stages (i.e., conception through adolescence) can have unique susceptibilities compared to those in later life stages because they undergo rapid physiological changes during critical periods of development (Selevan et al., 2000). Furthermore, young people are often exposed to xenobiotics via unique exposure pathways [i.e., transplacental transfer and breast milk ingestion; (U.S. EPA, 2006b; NRC, 1993)]. The nature of these alternate exposure pathways, and the lack of studies that accurately document exposure levels and outcomes in the very young, contribute to the difficulty in assessing the relative susceptibility of early life stage exposure to amphibole asbestos.

No in utero exposure data exist for LAA but limited observations in stillborn infants indicate transplacental transfer of tremolite (Haque et al., 1998; Haque et al., 1996) and other asbestos and nonasbestos fibers does occur (Haque et al., 1998; Haque et al., 1996; Haque et al., 1992; Haque et al., 1991). Transplacental transfer of asbestos was also demonstrated in animals following maternal exposure by gavage (Haque et al., 2001) or injection [(Haque and Vrazel, 1998; Cunningham and Pontefract, 1974); see Section 3]. These studies did not evaluate the sources or levels of exposure, and injection studies are a less relevant route of exposure compared to inhalation. Based on these studies, LAA fibers may be transferred through the placenta, resulting in prenatal exposure at any stage of fetal development.

A number of studies have attempted to determine the impact of in utero and early life exposure on the developing child. Those analyses performed in the very young include reports of stillbirth (Haque et al., 1998; Haque et al., 1996) and death among infants and young children (age 1−27 months) due to sudden infant death syndrome and bronchopulmonary dysplasia (Haque and Kanz, 1988). These studies found higher levels of asbestos in the lungs of those who died compared to unexposed individuals. In an infant study, the authors speculate that there was either a preexisting abnormal lung physiology in these children that contributed to a reduced ability to clear fibers from the lung, or the children had an increased exposure to asbestos (Haque and Kanz, 1988). Those studies conducted in older children include reports of pleural and diaphragmatic calcifications (Epler et al., 1980) and altered immune and respiratory conditions (Shtol' et al., 2000). Although the data are suggestive of increased sensitivity in infants, no definitive conclusion can be reached.

In experimental animal studies, the effects of in utero and early life exposure to asbestos are equivocal. Rats' offspring that were exposed to tremolite had decreased body-weight gain at weaning and 8-weeks old compared to controls (NTP, 1990b; McConnell et al., 1983a). This finding was observed in similar studies with other forms of asbestos (NTP, 1990a, 1988, 1985; McConnell et al., 1983a) but not replicated in others (McConnell et al., 1983b; NTP, 1983). Embryonic toxicity was noted in a few experimental animal studies. Crocidolite injected into pregnant mice resulted in altered limb differentiation in cultured embryos [(Krowke et al., 1983) abstract], and chrysotile suspended in drinking water and given to pregnant mice resulted in

decreased postimplantation survival in cultured embryos (Schneider and Maurer, 1977). However, chrysotile ingested via drinking water did not affect embryonic survival in vivo in pregnant mice (Schneider and Maurer, 1977). Altogether, the data provide no clear evidence for increased susceptibility following early life or in utero asbestos exposure.

Several studies have examined the susceptibility of asbestos exposure on young children, including how fiber deposition is affected by the physiological differences in children's lungs. Evidence suggests that fiber deposition is increased in the lungs of children compared with adults (Bennett et al., 2008; Isaacs and Martonen, 2005; Asgharian et al., 2004; Phalen and Oldham, 2001; Oldham et al., 1997; Schiller-Scotland et al., 1994; Phalen et al., 1985). Nasal deposition of particles was lower in children compared to adults—particularly during exercise (Becquemin et al., 1991). The lung and nasal depositional differences are partially due to structural differences across life stages that change the depositional pattern of different fiber sizes, possibly altering the site of action, and resulting in differential clearance and subsequent health effects. However, it is unclear whether the lung surface, body weight, inhalation volume, or exposure patterns are most determinative of dose.

There are a few studies analyzing noncancer outcomes in children exposed to LAA. A Libby medical screening program collected data on 7,307 participants, including 600 children aged 10−17 years, which represents 8.2% of the cohort (Peipins et al., 2003). Pulmonary function tests showed that none of these children had moderate or severely restricted lung function (ATSDR, 2002, 2001b). This program also studied chest radiographs for those 18 years or older (Noonan et al., 2006; Peipins et al., 2003; ATSDR, 2001b), but x-rays were not conducted on children. Among 1,003 adolescents and young adults (ages 10 to 29) who were ≤age 18 in 1990 when the mining/milling operations closed (Vinikoor et al., 2010), there was little variation in prevalence of shortness of breath, physician-diagnosed lung disease, or abnormal pulmonary function tests (restrictive, obstructive, or mixed, based on FEV_1 and FVC values) across the exposure categories. This analysis does not directly address the issue of susceptibility by age, however, because a comparison with people exposed only at older ages is not included.

Based on limited studies described below, it is possible that early life stage exposure may increase the risk of noncancer outcomes in adulthood. Altered immunity (Zerva et al., 1989) and asbestosis (Voisin et al., 1994) were observed in adults following tremolite exposure during childhood. No other studies of noncancer outcomes in early life stages of humans or experimental animals exposed to LAA have been reported. Thus, additional research is needed to establish the clinical significance of these findings and to expand understanding of the progression of the adverse health effects in the community.

To address the potential for increased susceptibility to cancer from early lifetime exposures, one needs to consider if there is evidence of differential health effects such as increased potency from early lifetime exposure, changes in latency based on the age of exposure,

or cancers observed with early lifetime exposures not seen with adult exposures. There are no published reports that can directly answer these questions for exposure to LAA. Few cancers occurring in childhood have been documented in children exposed to any form of asbestos. Examples of cases include a 17-year-old exposed to chrysotile and tremolite (Andrion et al., 1994) and a 3-year-old exposed to chrysotile (Lieben and Pistawka, 1967), both of whom developed mesothelioma. Notably, childhood mesothelioma may have an etiology that is different from that of the disease seen in adults, further confounding interpretation of these data (Cooper et al., 1989).

Studies involving populations exposed to other types of asbestos have yielded equivocal results on the carcinogenic effects following exposures occurring earlier in life, and few evaluate very early life exposures. One study in the United Kingdom described occupational exposure to chrysotile, crocidolite, and amosite for a group of 900 women. First exposure from ages 15−24 years led to a higher relative mortality risk for lung and pleural cancer compared with women who were first exposed at older ages (SMR 30 based on 12 observed and 0.4 expected, SMR 8 based on 4 observed and 0.5 expected, and SMR 6.7 based on 6 observed and 0.9 expected in the first exposure at ages 15−24, 25−34, and ≥35 years, respectively; (Newhouse et al., 1972). In a study in Wittenoom, Western Australia, 27 individuals were diagnosed with mesothelioma who had been environmentally exposed to crocidolite (i.e., residents of the town but not directly employed in the area's crocidolite mining and milling industry); 11 of these subjects were <15 years old at the time of exposure (Hansen et al., 1998). One-third of all the subjects were younger than 40 years old when diagnosed, but the authors found no increase in mesothelioma mortality rates when analyzed by age at first exposure. However, risk was significantly increased based on time from the first exposure, duration of exposure, and cumulative exposure (Hansen et al., 1998). Additional studies of this cohort found that the mesothelioma mortality rate was lower for those first exposed (based on age residence in the area began) to crocidolite at ages <15 years [*n* = 24; mesothelioma mortality rate 47 per 100,000 person-year) compared with those first exposed at ages ≥15 years (*n* = 43; mesothelioma mortality rate 112 per 100,000 person-year; (Reid et al., 2007)]. The hazard ratio for age at first residential exposure of ≥15 years compared with <15 years was 3.83 (95% CI: 2.19, 6.71), adjusting for cumulative exposure, gender, and an interaction term for gender and cumulative exposure. Altogether, these studies do not clarify whether exposure during childhood yields different adverse health effects compared with exposure during adulthood.

Relatively few studies have examined the effects of asbestos exposure in juvenile animals. Oral exposure to nonfibrous tremolite did not increase tumors in the offspring of rats compared to controls (NTP, 1990b; McConnell et al., 1983a). Similar studies of other forms of asbestos reported an increase of various neoplasms in the offspring (NTP, 1990a, 1988, 1985; McConnell et al., 1983b; McConnell et al., 1983a), but another study reported none (NTP, 1983). No cancer bioassays have been performed in juvenile animals exposed to LAA. Based on these

very limited and inconclusive studies on other forms of asbestos, no conclusions can be drawn about differential risk of adverse health effects after early life stage exposure to LAA compared to exposure during adulthood. It is unknown whether early life stage exposure compared to adult exposure increases susceptibility for adult cancers, as measured by increased incidence, severity, or disease progression, or by decreased latency.

Later life stage is generally defined as ≥65 years old. Because pulmonary function (volume and rate of breathing) decreases with age (Weiss, 2010), increased deposition of fibers in the lung from exposures in later life stages is unlikely. Older adults could be more susceptible to the effects of LAA due to the gradual age-related decline in physiological processes. For instance, clearance of fibers from the lung might be reduced because cough reflex and strength of older adults is less effective and the cilia are less able to move mucus out of the airway (U.S. EPA, 2006a). Additionally, decreased immune function, increased genetic damage, and decreased DNA repair capacity can result in increased susceptibility with age (U.S. EPA, 2006a). These age-associated alterations could decrease fiber-induced DNA damage repair but might also reduce the incidence of fiber-induced DNA damage due to decreased phagocytosis or inflammation. Specific data pertaining to age-varying effects of LAA on these processes are not available.

Because the risk of many types of noncancer effects increases with age, an increasing rate of specific diseases with increasing age can be expected among individuals exposed at some point in their lives to LAA. Radiographic tests among those exposed to LAA show that older age, which in some occupational settings may be highly correlated with time since first exposure (TSFE), is one of the factors most associated with pleural or interstitial abnormalities (Rohs et al., 2008; Horton et al., 2006; Muravov et al., 2005; Peipins et al., 2003; ATSDR, 2001b; Amandus et al., 1987a; McDonald et al., 1986b; Lockey et al., 1984). Abnormal radiographs also increase with age in general population studies (Pinsky et al., 2006). In a community health screening study, an increased risk of rheumatoid arthritis among individuals ages ≥65 years was observed in relation to several measures reflecting exposure to LAA [e.g., worked for W.R. Grace, used vermiculite for gardening; (Noonan, 2006)]. However, the available studies do not provide a basis for evaluating the timing of the exposure in relation to these outcomes. No conclusions can be drawn about differential risk of noncancer after later life stage exposure to LAA compared to exposure earlier in life.

No studies assessing the carcinogenic effect of exposures occurring in older age groups are available for LAA or other amphiboles. Note that health effects observed among individuals exposed to LAA are likely to increase with age due to the long latency period for the exposure response for asbestos and lung cancer and other chronic diseases. However, this type of observation would not directly address the question of whether exposures at older ages have a stronger or weaker effect compared with exposures at younger ages.

4.7.2. Influence of Gender on Susceptibility

A discussion of gender-related differences in risk from asbestos exposure raises several important issues, such as gender-related differences in exposure patterns, physiology, and dose-response (Smith, 2002). For example, nasal breathing filters out particles, and men tend to breathe less through their nose during exercise than women do (Bennett et al., 2003). Bennett et al. (1996) showed a gender difference in fractional deposition (defined as the ratio of particles not exhaled to total particles inhaled) of particles 2 μm in mass median aerodynamic diameter. This particle diameter is within the range of LAA particles reported in Table 2-2. This study found that, in general, women had a greater retention of particles compared to men because men had higher ventilation rates compared to women; however, the overall deposition rate was higher in the men (Bennett et al., 1996).

Most occupational studies for LAA have examined the effects of exposure only in men (Moolgavkar et al., 2010; Sullivan, 2007; McDonald et al., 2004; Amandus et al., 1988; Amandus et al., 1987b; Amandus and Wheeler, 1987; McDonald et al., 1986a; McDonald et al., 1986b). There is limited information specifically on women exposed to LAA. In the Libby, MT community studies, no gender-related trends in mortality due to lung or digestive cancer were observed (ATSDR, 2000). These limited data do not provide a basis for drawing conclusions regarding gender-related differences in adverse health effects from LAA.

4.7.3. Influence of Race or Ethnicity on Susceptibility

Race and ethnicity often are used in medical and epidemiological studies to define various groups of the population. These categories could be surrogates for differences in exposure (e.g., occupation, socioeconomics, behavior) or biology (e.g., physiology, genetics), in which case these factors may play a role in susceptibility as well. Nasal structure and lung architecture can influence the depositional patterns for both particles and fibers. One study of 18 Caucasians (ages 8 to 30 years) and 14 African Americans (ages 8 to 25 years) reported increased ventilation rates during exercise in the African Americans [matched on gender, age, height, and weight; (Cerny, 1987)]. Another study (11 Caucasians and 11 African Americans, ages 18 to 31 years) reported decreased nasal deposition efficiency (for particle sizes of 1−2 μm, which is in the range of those for LAA reported in Table 2-2) in African Americans compared to Caucasians (Bennett and Zeman, 2005). Furthermore, nasal breathing during exercise occurred less in Caucasians compared to African Americans in this study (Bennett et al., 2003).

Of the occupational and residential studies for LAA, the vast majority of subjects with known race were white, precluding the ability to conduct an analysis of racial and ethnicity-related differences in the mortality risks within the Libby worker cohort. In a study of occupational exposure to chrysotile asbestos in a textile factor, lung cancer mortality risk in relation to exposure was lower in nonwhite males (0.84, 95% CI: 0.52−1.27) compared to white males (2.34, 95% CI: 1.94−2.79), although a statistically significant increase in SMR was

observed for nonwhite males at high exposure levels [≥120 fibers-yr/mL; (Hein et al., 2007)]. This observed difference could be due to a lower prevalence of smoking among nonwhite compared with white males (Hein et al., 2007).

4.7.4. Influence of Genetic Polymorphisms on Susceptibility

XRCC1 is a DNA damage repair gene. A recent study demonstrated that *XRCC1*-deficient cells exposed to LAA or crocidolite asbestos demonstrated increased levels of micronuclei induction (Pietruska et al., 2010). Two other studies examined *XRCC1* polymorphisms in relation to disease risk with other types of asbestos exposure. Zhao et al. (2006) found no association between *XRCC1* polymorphisms and asbestosis in asbestos-exposed workers. A study by Dianzani et al. (2006), however, did find an association between *XRCC1* and asbestos-induced lung disease in a population exposed to asbestos pollution. Further work is necessary, with clear definitions of patient populations and their exposure levels, so that these studies and others can be compared to determine if *XRCC1* polymorphisms increase susceptibility to adverse health effects following exposure to LAA.

Superoxide dismutases are free radical scavengers that dismutate superoxide anions to oxygen and hydrogen peroxide. SODs are expressed in most cell types exposed to oxygen. Several common forms of SODs occur and are named by the protein cofactor: copper/zinc, manganese, iron, or nickel. A recent study observed no significant alterations in levels of intracellular SOD following a 3-hour exposure to LAA in mice (Blake et al., 2007). Other studies in humans and mice have examined SOD expression in relation to other types of asbestos exposure. Manganese SOD activity was elevated in biopsies of human asbestos-associated malignant mesothelioma, although no genotypic differences were found to be related to this change in activity (Hirvonen et al., 2002). Other studies have focused on the role of extracellular superoxide dismutase (EcSOD) and asbestos-induced pulmonary disease (Kliment et al., 2009; Gao et al., 2008; Fattman et al., 2006; Tan et al., 2004). These studies have suggested a protective effect of EcSOD, because mice that lack this form of SOD have increased sensitivity to asbestos-induced lung injury (Fattman et al., 2006). Familial studies showing an unusually high incidence of mesothelioma suggest that genetic factors might play a role in the etiology of mesothelioma (Ugolini et al., 2008; Huncharek, 2002; Roushdy-Hammady et al., 2001), although whether a genetic factor or a common environmental element leads to the similar responses in these families is difficult to determine. Increased interest in the role of genetic factors in asbestos-related health outcomes has led to several analytical studies on specific genetic polymorphisms. A review of 24 published reports (19 studies) discusses the current state of knowledge regarding genetic susceptibility associated with asbestos-related diseases (in particular, malignant pleural mesothelioma). Results from several studies demonstrated an association between asbestosis-related diseases and *GSTM1*-null polymorphism, whereas results for other polymorphisms were conflicting (Neri et al., 2008). Some polymorphisms discussed in

Neri et al. (2008) are in genes for *N-acetyl-transferase 2; glutathione-S-transferases (GSTs); SOD; CYP1A1, CYP2D6; neurofibromatosis 2 (Nf2); p53;* and *XRCC1*. Although occupational asbestos exposure was assessed, the type of asbestos is generally unknown in these studies.

Limited animal studies have examined the role of genetic variations related to asbestos exposure, including specific signaling pathways (Shukla et al., 2007), DNA damage repair (Lin et al., 2000; Ni et al., 2000), and tumor suppressor genes (Vaslet et al., 2002; Kleymenova et al., 1997; Marsella et al., 1997). Genetic alterations of particular interest for mesothelioma include those involved in tumor suppression (*p53, Nf2*) and oxidative stress (*SOD, GSTs*). *Nf2* and *p53* are frequently altered in mesotheliomas, but no consistent mutations have been found (Cheng et al., 1999; Mayall et al., 1999; Bianchi et al., 1995). Alterations in expression of antioxidant enzymes like SOD and GST in mesothelioma can yield cells more resistant to oxidative stress as compared to normal cells due to increased antioxidant activity (Ramos-Nino et al., 2002; Rahman and MacNee, 1999). No studies that examine the role of cell-cycle control genes were found following exposure to LAA. Additionally, no information on other genetic polymorphisms in relation to disease risk among those exposed to LAA was identified in the available literature.

4.7.5. Influence of Health Status on Susceptibility

Preexisting health conditions could potentially alter the biological response to asbestos exposure. Mesothelioma risk has been hypothesized to be related to immune impairment (Bianchi and Bianchi, 2008) and Simian virus 40 (SV40) exposure in humans (Carbone et al., 2007; Kroczynska et al., 2006; Cristaudo et al., 2005; Foddis et al., 2002; Bocchetta et al., 2000; Mayall et al., 1999). Coexposure to asbestos and SV40 has been associated with p53-related effects in vitro (Foddis et al., 2002; Bocchetta et al., 2000; Mayall et al., 1999), and cell signaling aberrations in vivo (Kroczynska et al., 2006; Cristaudo et al., 2005). However, the influence on cancer risk is unknown, as these lines of research are not fully developed and have not been applied specifically to LAA.

Obesity can compromise inhalation exposure, as increased particle deposition in the lungs of overweight children (Bennett and Zeman, 2004) and adults (Graham et al., 1990) has been observed. Individuals with respiratory diseases could have compromised lung function that alters inhalation exposure to LAA. For example, individuals with chronic obstructive pulmonary disease (COPD) have increased inhalation volume (Phalen et al., 2006) and increased fine particle deposition (Phalen et al., 2006; Bennett et al., 1997; Kim and Kang, 1997) and retention (Regnis et al., 2000). Similarly, studies have reported an increase in coarse particle (aerodynamic diameter >5 μm) deposition in individuals with cystic fibrosis (Brown and Bennett, 2004; Brown et al., 2001). For people exposed to LAA, an increased risk for interstitial lung abnormalities was observed for those with a history of pneumonia (Peipins et al., 2003). In another study, bronchial asthma was examined as a potential confounding variable for

asbestos-related effects on pulmonary function, although no confounding was observed (Whitehouse, 2004).

4.7.6. Influence of Lifestyle Factors on Susceptibility

Smoking can impair clearance of particles from the lung (Camner, 1980; Cohen et al., 1979) and increase deposition of asbestos fibers (Sekhon et al., 1995; McFadden et al., 1986). These effects could lead to the retention of more inhaled asbestos fibers and for a longer period of time in smokers compared to nonsmokers, even when controlling for initial exposure. Evidence of smoking-related susceptibility to pulmonary effects of asbestos was reported by Christensen and Kopylev (2012) using data from the O.M. Scott, Marysville, OH plant cohort described by Rohs et al. (2008). The amount of LAA exposure required to elicit the same increase in risk of localized pleural thickening was considerably lower (sixfold) for smokers compared with nonsmokers.

No studies were identified that examined lifestyle factors specifically with respect to LAA and cancer susceptibility. Lifestyle factors such as exercise, nutritional status, and smoking habits could affect the biological effects of asbestos exposure through various mechanisms. For example, those with more physically demanding jobs or those who regularly engage in vigorous exercise might experience increased lung deposition from fine particles or fibers compared to those with a more sedentary lifestyle (Phalen et al., 2006; Becquemin et al., 1991). Randomized controlled trials of vitamin supplementation (beta-carotene and retinol) have been conducted for asbestos-related lung cancer, but results do not support a protective effect (Cullen et al., 2005).

For lung cancer, a synergistic relationship between cigarette smoking and asbestos exposure has been demonstrated (Wraith and Mengersen, 2007; Hammond et al., 1979; Selikoff and Hammond, 1979). Research has suggested that asbestos fibers might also enhance the delivery of multiple carcinogens in cigarette smoke, and that cigarette smoking decreases the clearance mechanisms in the lungs and could, therefore, lead to an increase in fiber presence in the lungs (Nelson and Kelsey, 2002). Smoking likely causes genetic alterations associated with lung cancer (Landi et al., 2008) that might increase the carcinogenic risk from exposure to asbestos. Benzo[a]pyrene, a component of tobacco, also has been observed to enhance the carcinogenic effects of asbestos (Loli et al., 2004; Kimizuka et al., 1987; Mossman et al., 1984; DiPaolo et al., 1983; Mossman et al., 1983; Reiss et al., 1983).

4.7.7. Susceptible Populations Summary

A very limited amount of information is available on exposure to LAA early in life to determine if early exposure could lead to increased risk of asbestos-induced disease later in life. Due to the long latency period of some diseases in relation to asbestos exposure in general, adverse effects are more likely to be observed with an increase in age or, more specifically, with increased time since first exposure. Further, asbestos exposure during specific life stages may

lead to alternate exposure pathways and health outcomes, but there are limited studies assessing the effect of exposure to amphibole asbestos by specific life stage. In the absence of chemical-specific data to evaluate differences in susceptibility by specific life stage, 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 is not recommended (see Section 4.6.2.4 and 4.6.2.5). The number of women who have been occupationally exposed to LAA is very small, and health risks have not been evaluated specifically for this group. Differences between men and women in residential sources and types of exposure (e.g., types of activities done in the household) also preclude the possibility of drawing conclusions regarding the relative susceptibility of women compared with men to health effects of exposure to LAA. Similarly, sufficient data are not available to draw conclusions regarding racial or ethnic variation in susceptibility to diseases caused by exposure to LAA. In addition, the potential modifying effects of genetic polymorphisms, preexisting health conditions, nutritional status, and other lifestyle factors have not been studied, specifically as related to exposure of LAA and health outcomes.

5. EXPOSURE-RESPONSE ASSESSMENT

5.1. ORAL REFERENCE DOSE (RfD)

An oral RfD was not derived. Oral exposure was not assessed because inhalation is the primary route of concern and oral data for Libby Amphibole asbestos[20] (LAA) is lacking.

5.2. INHALATION REFERENCE CONCENTRATION (RfC)

An RfC is defined as "an estimate (with uncertainty spanning perhaps an order of magnitude) of an exposure (including sensitive subgroups) that is likely to be without an appreciable risk of adverse health effects over a lifetime" (U.S. EPA, 2002). Consequently, studies that relate these adverse health effects to exposure levels are necessary for RfC derivation. Preferred study characteristics for RfC derivation include adequate exposure-response information, ideally with quantitative exposure estimates to distinguish exposure levels in the study subjects, and adequate duration of follow-up to identify health effects of interest.

Overview of the Methodological Approach

The noncancer effects which were evaluated in populations with exposure to LAA (see Sections 4.1.2 and 4.1.3) are pulmonary effects (including asbestosis, pleural thickening [localized or diffuse], and other nonmalignant respiratory disease), cardiovascular disease-related mortality, and autoimmune effects. Localized pleural thickening (LPT) was deemed the most sensitive and was thus selected as the critical effect to derive the RfC (see Section 5.2.2.3). A benchmark response (BMR) of 10% extra risk was selected for exposure-response modeling (see Section 5.2.2.5.

RfCs are based on human data when appropriate epidemiologic studies are available. The general approach to developing an RfC from human epidemiologic data is to quantitatively evaluate the exposure-response relationship for that agent to derive a specific estimate of its effect on the risk of the selected outcome in the studied population. For the current assessment, the first step was to identify the most appropriate data set available to quantitatively estimate the effects of LAA exposure on pleural effects. Studies of three different cohorts provide such quantitative exposure-response information. Two are of occupationally exposed cohorts. The first one is Libby Workers (Larson et al., 2012a) and the second one is Marysville workers (Rohs et al., 2008). The third consisted of community members with nonoccupational exposure, who resided around the Western Minerals plant in Minneapolis (Alexander et al., 2012). Upon

[20]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.

evaluating these three cohorts, the Marysville workers were selected as the most appropriate for derivation of the RfC. The Libby workers had generally higher levels of occupational exposure and additional, unquantified exposures outside of the workplace (i.e., residential exposures). While data on a critical predictor of the risk of pleural thickening (the time since first exposure [TSFE]) was available for the occupational exposures, information on TSFE for the residential exposures from living in Libby, MT prior to working in the mining or related operations is not known. Substantial uncertainty also exists in the exposure estimates for the Minneapolis study, and although some information on residential history was used by the investigators, it is unclear whether this information applied just to the residence or whether there was information on TSFE for the different exposure routes [see (Kelly et al., 2006)].

Among the Marysville workers, there were differences in the availability of exposure and health outcome data over time. No industrial hygiene measurements were available before 1972. Health examinations were performed at two time points, 1980 and 2002−2005, using different x-ray reading protocols and different film readers. Thus, the subgroup of workers with the highest quality exposure and outcome evaluation information, was determined to be those workers who were hired in 1972 or later, and who had health examinations performed in 2002−2005; this group was selected as the primary analytic data set for derivation of the RfC (see Section 5.2.2.2). Once the relevant data describing a well-defined group of individuals along with their exposures and health outcomes were selected, a suite of appropriate statistical model forms was evaluated. Before performing any modeling, biological and epidemiological features were considered to determine a priori which variables and which models would be most suitable for the given exposure and health outcome (see Section 5.2.2.6.1). Based on these considerations, the Dichotomous Hill model was considered to be the most flexible and potentially most suitable model form; however, all model forms suitable for dichotomous epidemiological data were examined. Each model was evaluated for adequate fit to the data, with each person's individual-level exposures and outcomes modeled using a variety of exposure metrics. Appropriate covariates, which may be important predictors of LPT risk, were evaluated for potential confounding in the statistical model.

In the primary analytic data set (the subcohort of workers hired in 1972 or later), all univariate models examined had adequate fit and for each model form, mean exposure was shown to have the best relative fit (compared with either cumulative or residence time-weighed exposure metrics). Among the model forms, the relative fits were comparable, and thus the Dichotomous Hill model (with plateau fixed at 85%) using the mean exposure metric was selected as the primary model for RfC derivation. When evaluating nonexposure-related covariates, none were found to fit the criteria for a confounder (i.e., they were not associated with both the outcome and the exposure) and were not significant predictors of LPT risk when included in the final model. Time since first exposure, one of the key covariates evaluated, was associated with the exposure in the primary analytic data set but not the outcome. This is likely

because there was a relatively narrow range of TSFE values (i.e., low variability) in the primary analytic data set. However, based on the epidemiological literature, TSFE is expected to be a major predictor of LPT risk and thus an important variable in evaluating the exposure-response relationship with LAA. Because inclusion of TSFE in the model did not improve model fit (and it was not a significant predictor), alternative strategies were explored to incorporate the effect of TSFE into the exposure-response model. EPA decided to use a hybrid modeling strategy. First, the effect of TSFE was estimated in a larger subset of the Marysville workers (all those with health evaluations in 2002−2005, regardless of hire date) with a broader range of TSFE values, using the same model as for the primary analytic data set. Next, this estimated effect was carried over to the model for the primary analytic data set (workers hired in 1972 or later with health examinations in 2002−2005) as a fixed regression coefficient, and the benchmark concentration and lower limit of the benchmark concentration (BMCL) estimated.

The BMCL from the "hybrid" modeling approach was used as the point of departure. Uncertainty factors were then applied to derive an RfC (see Section 5.2.3). Alternative analyses are presented in Section 5.2.4 and 5.2.5 with a summary in Section 5.2.6. Uncertainties in this noncancer assessment are described in detail in Section 5.3.

5.2.1. Choice of Principal Study

5.2.1.1. *Candidate Studies*

While there are studies of health effects in humans, no studies in laboratory animals on the inhalation route of exposure are suitable for derivation of an RfC because the available animal studies lack adequate LAA exposure-response information and are of a short-term duration.

Multiple studies have identified several noncancer health effects in humans that could be considered as potential critical effects for the derivation of an RfC. The noncancer health effects range in severity from mortality to pleural abnormalities. Five mortality studies of cohorts of workers who mined, milled, and processed Libby vermiculite identified increased risk of mortality from noncancer causes including nonmalignant respiratory disease—especially asbestosis and chronic obstructive pulmonary disease (COPD) (Larson et al., 2010b; Sullivan, 2007; McDonald et al., 2004; Amandus and Wheeler, 1987; McDonald et al., 1986a)—as well as cardiovascular disease (Larson et al., 2010b). Because an RfC is intended to be a level that is likely to be without appreciable risk of deleterious effects, these mortality studies were not considered as candidates for RfC derivation because other human studies exist that provide evidence of an association between LAA and less severe outcomes generally occurring at lower levels of exposure, such as parenchymal and pleural abnormalities. More detailed discussion of the choice of the critical effect for the RfC is presented in Section 5.2.2.3 and Appendix I.

Studies conducted among two cohorts of occupationally exposed workers have shown radiographic evidence of health effects on the lung and pleura (a thin tissue surrounding the lung

and lining the chest cavity). These effects include pleural thickening and fibrosis of the lung (Larson et al., 2012a; Larson et al., 2012b; Larson et al., 2010b; Rohs et al., 2008; Amandus et al., 1987a; McDonald et al., 1986b; Lockey et al., 1984). Studies of exposed community members in Libby, MT and Minneapolis, MN have also reported evidence of health effects on the lung and pleura [(Alexander et al., 2012; Weill et al., 2011; Muravov et al., 2005; Peipins et al., 2004b; Whitehouse, 2004; Peipins et al., 2003); see Section 4.1.2].

Although data exist that define exposures from some activities in the Libby, MT community studies (see Section 2.3), the available exposure data were insufficient to estimate exposure at the individual level. Only studies that include exposure measurement data allowing estimation of individual exposures and identify appropriate health effects are considered for RfC derivation (Alexander et al., 2012; Larson et al., 2012a; Rohs et al., 2008; Amandus et al., 1987a; McDonald et al., 1986b; Lockey et al., 1984). Among these six candidate principal studies (see Figure 5-1), one study was of the community surrounding a vermiculite processing facility in Minneapolis, MN (Alexander et al., 2012), three were occupational studies of exposed workers in Libby, MT (Larson et al., 2012a; Amandus et al., 1987a; McDonald et al., 1986b), and two were studies in workers from the Marysville, OH facility (Rohs et al., 2008; Lockey et al., 1984). The studies by Larson et al. (2012a) and Rohs et al. (2008) represent the most recent evaluations of the occupational studies of exposed workers in Libby, MT and Marysville, OH workers, respectively, and were considered as candidate principal studies for the derivation of the RfC, along with the study of the Minneapolis community by Alexander et al. (2012).

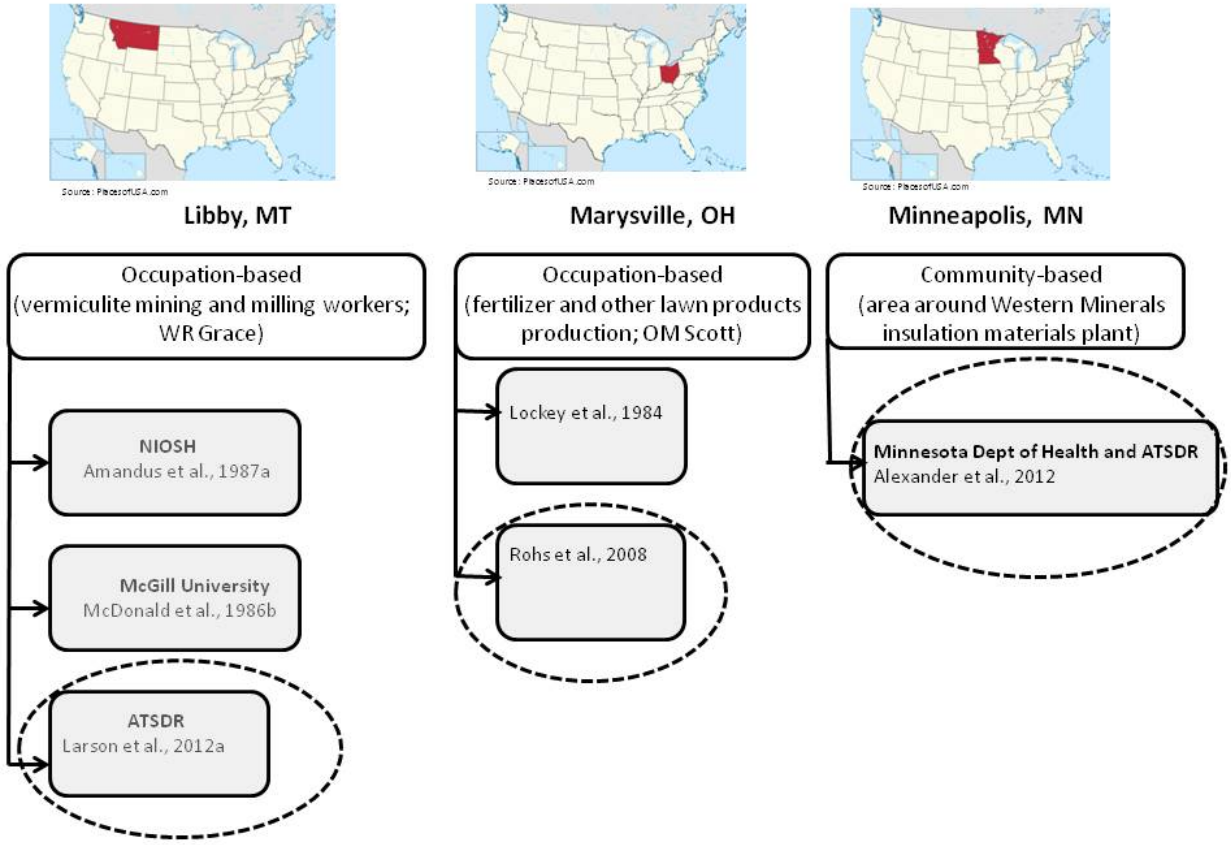

Figure 5-1. Candidate studies for derivation of the reference concentration (RfC) in three different study populations, with the most recent study of each population circled.

Each study has adequate reporting of the studied populations, methods of assessment of health outcome(s) of interest, and statistical analyses. Each study also demonstrated associations between exposure to LAA and radiographic signs of nonmalignant respiratory effects, specifically pleural thickening (circumscribed and/or localized and/or diffuse) and small interstitial opacities (indicative of parenchymal damage) (ILO, 2002, 1980, 1971). Table 5-1 summarizes the candidate principal studies. See Section 4.1.1 for detailed study information and results.

Table 5-1. Summary of candidate principal studies on LAA for reference concentration (RfC) derivation

	Libby, MT Larson et al. (2012a)	Marysville, OH Rohs et al. (2008)	Minneapolis, MN Alexander et al. (2012)
Study population	Occupationally exposed (*n* = 336) 93.2% male, median age 55.6 (interquartile range 47.4–65.8) yr	Occupationally exposed (*n* = 280) 94.3% male, mean age 59.1 (age range 44–87) yr	Community residents not occupationally exposed (*n* = 461) 52.3% male, median birth yr 1951−1960 (19.3% born ≤1940, 18.4% born ≥1960)
Time of health assessment	2000−2001	2002−2005	2001−2003
Health outcome assessment	Films independently read by two readers using 1980 ILO standards, with a third reader if the two primary readers disagreed Film quality not reported Spirometry Self-reported respiratory symptoms	Films independently read by three board-certified radiologists (B Readers) using 2000 ILO standards Seven employees had unreadable films and are not included in the cohort of 280 participants	Films independently read by two readers using 2000 ILO standards, with a third reader if the two primary readers disagreed Seven participants had unreadable films
Health outcomes evaluated	(1) Parenchymal changes (small interstitial opacities ≥1/0) (2) Pleural changes: LPT[a] ("presence of circumscribed plaque on the chest wall [as indicated on the International Labor Office form] or diaphragm without the presence of DPT or parenchymal abnormalities"); DPT (as indicated by ILO form and accompanied by costophrenic angle obliteration) (3) Self-reported symptoms (shortness of breath, excess cough, chronic bronchitis) (4) Spirometry: FVC, FEV_1, FEV_1/FVC ratio, and obstructive spirometry (defined as FVC ≥ lower limit of normal and FEV_1/FVC < lower limit of normal) and restrictive (defined as FVC < lower limit of normal and FEV_1/FVC > lower limit of normal)	(1) Parenchymal changes (irregular interstitial opacities, profusion score >1/0) (2) Pleural changes: LPT (any thickening, with or without calcification, excluding solitary costophrenic angle blunting); DPT (any pleural thickening, including costophrenic angle blunting, with or without calcification)	(1) Parenchymal changes (2) Pleural changes[b]: pleural plaques, DPT

Table 5-1. Summary of candidate principal studies on LAA for reference concentration (RfC) derivation (continued)

	Libby, MT Larson et al. (2012a)	Marysville, OH Rohs et al. (2008)	Minneapolis, MN Alexander et al. (2012)
Exposure Assessment	1945−1993 Industrial hygiene measurements and work history (JEM); measurements made using midget impinger (pre-1970) and PCM (post-1970)	1963−1980[c] Industrial hygiene measurements and work history (JEM); measurements made using PCM (1971 onwards)	1980−1989 Emissions-based modeling and self-reported activities; based on air dispersion modeling based on stack emissions and activity-based sampling
Exposure levels	Median: 3.6 fibers/cc-yr (IQR: 0.4−15.8)	Mean (standard deviation): 2.48 fibers/cc-yr (4.19)	Median: 2.42 fibers/cc-yr (cases) and 0.59 fiber/cc-yr (noncases)

[a]Although ILO 1980 guidelines were used, modifications were made such that the radiographic abnormalities were equivalent to ILO 2000 guidelines.
[b]Radiographic abnormalities were evaluated together as a group, and LPT was not modeled separately. However, in the lower exposure group, all 17 cases had pleural plaques (either alone or with another abnormality; personal communication from Bruce Alexander, 7 June 2013).
[c]Dates used in analysis by Rohs et al. (2008) are reported to be based on ATSDR (2005).
JEM = job-exposure matrix; IQR = interquartile range; PCM=phase contrast microscopy.

5.2.1.2. *Evaluation of Candidate Studies and Selection of Principal Study*

The candidate studies were further evaluated in terms of quality attributes that would support their use as a principal study in the derivation of an RfC. When selecting among candidate principal studies, several factors, summarized in Table 5-2, are generally considered.

Table 5-2. Summary of rationale for identifying candidate principal studies on LAA for reference concentration (RfC) development

Attribute	Preferred characteristics for candidate principal studies for the Libby Amphibole asbestos RfC
Relevance of exposure paradigm	Studies of subchronic or chronic duration are preferred over studies of acute exposure duration because they are most relevant to environmental exposure scenarios (potentially including both continuous exposure from ambient conditions and episodic activity-related exposures). When available studies observe occurrence of effect at both lower and higher doses, relatively low exposure intensities that may represent conditions more similar to environmental exposures are preferred as there may be less uncertainty in extrapolation of the results to lower exposure levels.
Study design characteristics	Sufficient follow-up time for outcomes to develop (this can depend on the health outcome being addressed). Study size and participation rates that are adequate to detect and quantify health outcomes being studied (without influential biases in study population selection) are preferred. Use of a study design or analytic approach that adequately addresses the relevant sources of potential confounding, including age, gender, smoking, and exposure to other risk factors (such as non-Libby asbestos).
Measurement of exposure	Emphasis is placed on the specificity of exposure assessment in time and place with a preference for greater detail where possible. Exposure measurements that are site and task specific provide generally preferred exposure information. Where available, individual-level measurements are generally preferred. Measurement techniques that are more specific to the agent of concern are preferred over less specific analytical methods. Better characterization of fibers is preferred. For asbestos fibers, transmission electron microscopy (TEM) analysis, which can identify the mineral fibers present, provides the most specific information; PCM identifies fibers as defined by that method (NIOSH 7400), and thus, is useful but does not confirm the mineral nature of the counted fibers. Total dust measurements are the least informative of those available. Stronger studies will often be based upon knowledge of individual work histories (job titles/tasks with consideration of changes over time); however, appropriate group-based exposure estimates may also be relevant. Exposure reconstruction and estimating exposures based on air sampling from other time periods and/or operations are less preferred methods of exposure estimation. Fibrosis in the pleural tissues needs time to develop and become visible on an x-ray (Larson et al., 2010a). It has been shown that the prevalence of fibrotic lesions progresses as a function of time (Rohs et al., 2008) and can appear long after the initial exposure (Lilis et al., 1991). Many investigations of the exposure-response relationship for pleural plaques has found that time since first exposure (TSFE) is a significant explanatory variable (Paris et al., 2009; Paris et al., 2008; Järvholm, 1992). Stronger studies will have data on TSFE for the relevant exposures.

Table 5-2. Summary of rationale for identifying candidate principal studies on LAA for reference concentration (RfC) development (continued)

Attribute	Preferred characteristics for candidate principal studies for the Libby Amphibole Asbestos RfC
Measurement of effect(s)	Emphasis is placed on the more sensitive health outcome endpoints that are available. For the parenchymal and pleural effects considered here, the radiographic abnormalities are more sensitive than the corresponding mortality causes. An RfC is intended to be a level at which no category of adverse health outcome would occur. Pleural and parenchymal abnormalities assessed using good-quality radiographs or high-resolution computed tomography and independently evaluated by multiple qualified readers according to ILO standards. Evaluation of radiographs should not be influenced by knowledge of exposure status.

Two of the studies were conducted in occupationally exposed populations (Larson et al., 2012a; Rohs et al., 2008), while the third was conducted in community residents without occupational exposure (Alexander et al., 2012). Each of the studies provided estimates of cumulative LAA exposure (in fibers/cc-yr). However, there were differences in exposure sources and intensity. Of the two occupational studies, one (Larson et al., 2012a) occurred in a setting where both occupational and nonoccupational exposures were relevant due to the close proximity of the local vermiculite mining and milling operations to the Libby, MT community. Nonoccupational exposures in the Libby, MT community were not quantified and thus were not accounted for in the overall estimates of individual exposure. In the other study (Rohs et al., 2008), exposures were generally lower and considered to be limited to the occupational setting because most of the employees showered and changed into civilian clothes at the end of the work shift. Therefore, nonoccupational exposure in the Marysville workers was assumed to be minimal. However, in both cases, the exposure estimates for earlier years are subject to uncertainty. For example, data on job and department were missing for the majority of the workers in the Libby facility hired before 1960 (Larson et al., 2012a). In the Marysville facility, no fiber measurements exist before 1972 (Rohs et al., 2008), although exposure estimates for this period were constructed based on measurements taken in subsequent years (see Appendix F). The third study, by Alexander et al. (2012), was conducted among Minneapolis community residents (including a higher proportion of women compared to the other studies). The researchers attempted to estimate individual community members' exposure based on facility emissions and the individual's specific activities that were considered to be related to exposure (e.g., installing or removing vermiculite insulation or playing in or around waste piles). However, exposure estimates were constructed from modeled emissions based on very sparse data from the facility's discharge stacks and activity-based exposure reconstruction, and as a result are considered to have greater uncertainties.

As noted in Table 5-2, relatively lower exposure levels are advantageous for developing an RfC (given sufficient numbers of individuals with the health effect of interest) due to uncertainties inherent in extrapolating from high-intensity (e.g., occupational) exposure levels to low-intensity (e.g., environmental) exposure levels. A limitation of the studies conducted among workers at the Libby facility is that the exposure levels experienced for some job codes are high compared with those in the other two studies (see Table 5-1; e.g., based on the interquartile range (IQR) of exposure from the 25th percentile value of 0.4 fiber/cc-yr to the 75th percentile value of 15.8 fibers/cc-yr, 25% of participants had cumulative exposures above 15.8 fibers/cc-yr). Another limitation of these studies for conducting exposure-response analysis for LPT is that many of the Libby workers were likely to have also been residents in Libby both before and during their employment at the mining and related operations, so their actual TSFE to any LAA exposure may be longer than their TSFE to occupational exposure to LAA. Therefore, data on this important variable is uncertain. Thus, the Libby workers study (Larson et al., 2012a) is less preferable for RfC derivation. The other two studies (Alexander et al., 2012; Rohs et al., 2008) had generally lower exposure levels in comparison; however, greater uncertainty exists in the exposure estimates for the Minneapolis cohort because few measurements of facility emissions into the ambient air (Adgate et al., 2011). Indeed, the authors estimate that the numerical uncertainty in exposure estimates is likely to be at least an order of magnitude, perhaps much greater. Further, it is unclear whether TSFE is well characterized for the nonoccupational exposures in the Minneapolis cohort. In contrast, the study of workers at the O.M. Scott plant in Marysville, OH (Rohs et al., 2008) used exposure estimates based on extensive industrial hygiene sampling data, individual worker histories, and employee focus interviews. Thus, Rohs et al. (2008) is the preferred study for derivation of the RfC.

5.2.2. Methods of Analysis

5.2.2.1. *Exposure Assessment*

EPA collaborated with a research team at the University of Cincinnati 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 unavailable for previous studies conducted in this cohort (Rohs et al., 2008; Lockey et al., 1984). Exposure estimates for each worker in the O.M. Scott Marysville, OH plant were developed based on the arithmetic mean of the available industrial hygiene data from the plant. The exposure assessment procedure is described in Appendix F. 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).

5.2.2.2. *Data Sets for Modeling Analyses*

Section 5.2.1.2 describes the selection of the Rohs et al. (2008) cohort as the principal study. As explained below, EPA further considered the differential quality of exposure data for different years within this data set and concluded that estimation of an RfC would be improved if the primary data set for exposure-response modeling was restricted to the subset of workers hired in 1972 and later, when higher quality exposure information was available.

As described in Section 5.2.1.2, the Marysville workers evaluated by Rohs et al. (2008) formed the principal analytic group for derivation of the RfC, with exposure information updated and augmented by the University of Cincinnati in collaboration with EPA. As noted in Section 4.1.1.2.2 and Appendix F, the more reliable exposure estimates are considered to be those from 1972 and later, as these data were based on analytical measurements. Therefore, the primary modeling to derive a point of departure (POD) was conducted among the subgroup of workers evaluated by Rohs et al. (2008) that began work in 1972 or later and had no previous occupational exposure to asbestos (119 workers: 13 cases of localized pleural thickening and 106 unaffected individuals). However, information from workers who were hired before 1972, as well as from workers who were evaluated only in the earlier study by Lockey et al. (1984), were also considered in separate analyses (details and results of the analysis are in Appendix E). In each case, to avoid any potential bias from previous unmeasured occupational exposure to asbestos, only the data from those who did not report any previous occupational exposure to asbestos were used.

Table 5-3 and Figure 5-2 present summary characteristics for the three analytic groups. The first is the combined information for the 1980 (Lockey et al., 1984) and 2002−2005 (Rohs et al., 2008) evaluations, comprising all workers without previous exposure to asbestos; a detailed description of how these data were combined is in Appendix E. The second group is all workers evaluated in 2002−2005 without previous exposure to asbestos (as described by (Rohs et al., 2008). The third group is a subset of the workers evaluated in 2002−2005, hired in 1972 or later, without previous exposure to asbestos (primary analytic group). For the groups comprising only individuals evaluated in 2002−2005, exposure estimates covered the period from start of work through the date of job stop or at the time vermiculite ceased to be used in 2000, whichever occurred earlier.

Table 5-3. Characteristics of workers at the O.M. Scott plant in Marysville, OH

	All individuals evaluated in 1980 and/or in 2002−2005[a]		Individuals evaluated in 2002−2005		Individuals evaluated in 2002−2005, hired in 1972 or later	
Demographic characteristics	***n***	**%**	***n***	**%**	***n***	**%**
Total (*n*)	434	100	252	100	119	100
Gender						
Male	403	92.86	236	93.65	106	89.08
Female	31	7.14	16	6.35	13	10.92
Smoking status[b]						
Never smoker	157	36.60	95	37.70	48	40.34
Ever smoker	272	63.40	157	62.30	71	59.66
Current	114	26.57	39	15.48	29	24.37
Former	158	36.83	118	46.83	42	35.29
	Mean (SD)	**Median (25^{th}–75^{th} percentiles)**	**Mean (SD)**	**Median (25^{th}–75^{th} percentiles)**	**Mean (SD)**	**Median (25^{th}–75^{th} percentiles)**
Age at x-ray (yr)	50.73 (14.88) Range: 19−86	52 (43−60)	58.66 (10.53) Range: 42−86	56 (50−66)	52 (7.1) Range: 42−82	50 (47−55)
Time since first exposure (yr)	24.42 (13.59) Range: 0.42−47.34	25.96 (11.75−34.77)	34.40 (7.12) Range: 23.14−47.34	33.51 (28.70−38.47)	28.24 (2.54) Range: 23.14−32.63	28.39 (25.81−30.29)
Exposure duration (yr)—duration of exposed time (i.e., accounting for gaps)	18.93 (11.44) Range: 0.41−44.00	20.75 (8.75−27.41)	24.96 (10.17) Range: 0.67−44.00	26.46 (19.75−32.17)	18.23 (8.61) Range: 0.67−29.00	21.75 (9.50−25.59)
Body mass index[b]	30.80 (6.25) Range: 17.30−61.97	29.44 (26.93−33.33)	30.80 (6.25) Range: 17.30−61.97	29.44 (26.93−33.33)	31.30 (6.90) Range: 20.08−61.97	30.11 (27.23−33.85)
Cumulative exposure (fibers/cc-yr)	7.9232 (17.9598) Range: 0.003−96.91	1.1252 (0.3414−3.7684)	8.75 (19.12) Range: 0.005−96.91	1.26 (0.51−5.20)	1.439 (2.5479) Range: 0.005−17.33	0.5048 (0.2188−1.5519)
Mean exposure (fibers/cc)	0.3733 (0.7942) Range: 0.007−4.34	0.0566 (0.0267−0.2364)	0.31 (0.65) Range: 0.007−4.10	0.05 (0.02−0.20)	0.0716 (0.1239) Range: 0.007−0.77	0.0234 (0.0133−0.074)
Residence time-weighted (RTW) exposure (fibers/cc-yr^2)[c]	193.3093 (519.3874) Range: 0.0007−3500.66	19.4767 (4.2550−78.0944)	294.38 (687.95) Range: 0.12−3,500.66	34.31 (11.07−154.36)	33.7415 (69.2231) Range: 0.12−474.01	10.2075 (3.9055−29.1246)

Table 5-3. Characteristics of workers at the O.M. Scott plant in Marysville, OH (continued)

[a]See Appendix E for details of how the individual health outcome data for all workers who participated in the Lockey et al. (1984) study and the follow-up study by Rohs et al. (2008) were combined.
[b]Data on smoking status were missing for five individuals in the full cohort. Data on body mass index (BMI) was unavailable for 216 individuals in the full cohort, 34 individuals examined in 2002−2005, and 21 individuals examined in 2002−2005 who were hired in 1972 or later.
[c]RTW exposures are calculated using midpoint of each work season.

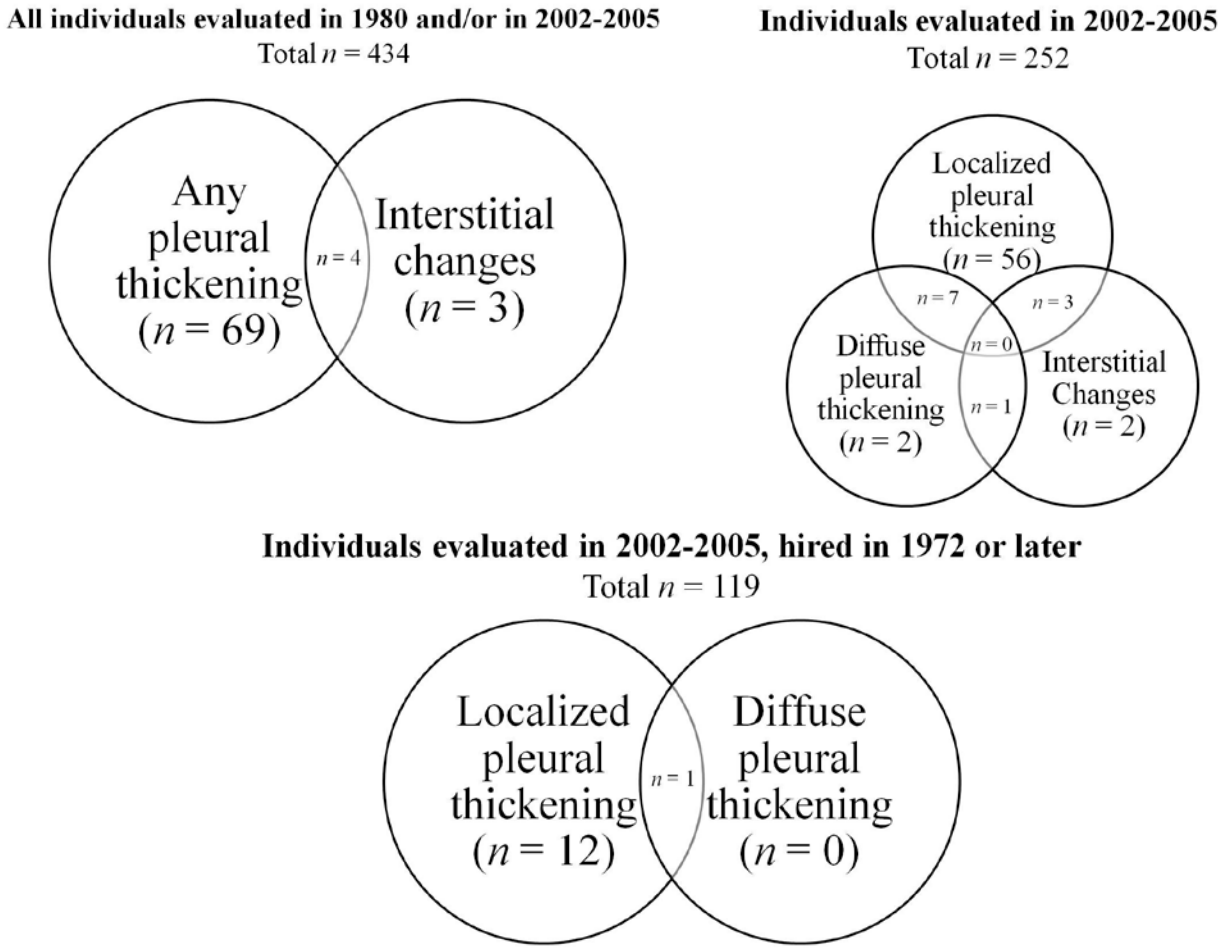

Figure 5-2. Radiographic outcomes among Marysville, OH workers. Only the data from those who did not report any previous occupational exposure to asbestos were used. Numbers of individuals in each category are exclusive (e.g., there are 69 individuals among the total $n = 434$ with pleural thickening only, and an additional four individuals have pleural thickening in addition to interstitial changes).

As stated previously, fiber measurements started in the Marysville plant in 1972, and exposures before this time were estimated by University of Cincinnati scientists, based on focus group interviews with 15 long-term former workers and the times when engineering changes were made to control dust in the facility (see Appendix F). Exposure estimates for the period before 1972 can be considered less certain compared with those estimates more directly based on industrial hygiene data. The University of Cincinnati analysis assumed that early exposure levels in the plant are twice those measured in 1972 (see Appendix F). The greater uncertainty of the pre-1972 exposure estimates led to EPA's decision to focus the analysis on the group of workers hired in 1972 or later. Although it is generally true that the use of more data is an advantage for statistical analyses because it allows for the computation of more statistically precise effect estimates, this increased precision can be offset by a negative impact on the accuracy of the effect estimate if an increase in sample size is accompanied by greater exposure misclassification or other biases.

In summary, the primary analytic group was the Marysville workers evaluated by Rohs et al. (2008) who were hired in 1972 or later; however, additional information from workers hired before that date was also used in modeling and sensitivity analyses.

5.2.2.3. *Selection of Critical Effect*

A critical effect is defined as "The first adverse effect, or its known precursor, that occurs to the most sensitive species as the dose rate of an agent increases" (U.S. EPA, 2011). Three endpoints are suitable for consideration as critical effects for the derivation of an RfC for LAA where health effects data and exposure information are available in the principal study (Rohs et al., 2008): (1) parenchymal changes viewed as small interstitial opacities in the lung, (2) localized pleural thickening (LPT), or (3) diffuse pleural thickening (DPT) as defined in ILO (2000). Each of these represents persistent changes to normal tissue structure.

Small interstitial opacities (asbestosis) are widely accepted as adverse; the American Thoracic Society (ATS) states that "asbestosis is usually associated with dyspnea, bibasilar rales, and changes in pulmonary function: a restrictive pattern, mixed restrictive-obstructive pattern, and/or decreased diffusing capacity" (ATS, 2004). Similarly, DPT is also widely accepted as adverse, with the ATS stating that "decrements associated with diffuse pleural thickening reflect pulmonary restriction as a result of adhesions of the parietal with the visceral pleura. Restrictive impairment is characteristic, with relative preservation of diffusing capacity (pattern of entrapped lung)" (ATS, 2004).

Statements from the consensus groups vary as to whether pleural plaques impact lung function. Regarding pleural plaques, the ATS notes that this endpoint is also associated with decrements in lung function:

> Although pleural plaques have long been considered inconsequential markers of asbestos exposure, studies of large cohorts have shown a significant reduction in lung function attributable to the plaques, averaging about 5% of FVC, even when interstitial fibrosis (asbestosis) is absent radiographically…The presence of circumscribed plaques can be associated with restrictive impairment and diminished diffusing capacity on pulmonary function testing, even in the absence of radiographic evidence of interstitial fibrosis.(ATS, 2004).

However, the statement goes on to note that findings of significant pulmonary deficits are not consistent, and that "most people with pleural plaques alone have well-preserved lung 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%). Therefore, EPA undertook a systematic review to evaluate the magnitude and extent of the pulmonary function deficits associated with pleural plaques and LPT, described in Appendix I. The review demonstrates that these deficits can be considered adverse. LPT is a pathological change associated with decreased pulmonary function, and thus is considered an appropriate adverse effect for deriving the RfC (see Section 5.2.2.3 and Appendix I). Based on the association of LPT with pulmonary function decrease, LPT is an appropriate health effect for derivation of an RfC. Because interstitial opacities, DPT, and LPT are all appropriate candidate endpoints, the critical effect was chosen as that which is the first to appear, or which occurs at the lowest levels of exposure. A summary of the systematic review of the pleural plaque data is discussed below.

Larson et al. (2012a) evaluated the timing of appearance and exposure levels at which pleural and parenchymal abnormalities occur on chest radiographs of vermiculite workers at the Libby facility relative to hire date (i.e., time since first occupational exposure). In this retrospective analysis, the study authors reported that the health endpoint with the shortest median time to appearance was circumscribed pleural plaques with a median latency of 8.6 years, compared to median latency times of 27.0 years for DPT and 18.9 years for parenchymal changes (small interstitial opacity profusion of 1/0 or greater). Although all workers experienced generally high exposure, cumulative fiber levels were lowest for those with circumscribed pleural plaques (median of 44.1 fibers/cc-yr), compared to those with DPT (median of 317.8 fibers/cc-yr), and highest for those with parenchymal changes (median of 235.7 fibers/cc-yr for those with major profusion category 1 abnormalities, 678.4 for category ≥2/1, and 1,303.4 for category ≥3/2). Similarly, Rohs et al. (2008) found that for all workers in that study, on average the cumulative fiber exposure for those workers with LPT only (3.45 fibers/cc-yr) was lower compared to those with DPT only (8.99 fibers/cc-yr) or with any

interstitial changes (alone or with either LPT or DPT; 11.86 fibers/cc-yr). These results indicate that LPT may be the most sensitive of the effects examined, as the radiographic outcome most likely to occur soonest after first occupational exposure, and the outcome most likely to appear at relatively lower cumulative exposure levels. The clinical perspective suggests that LPT do not clinically impair lung function for most people. This perspective was stated by the American College of Chest Physicians (Banks et al., 2009) regarding the 2004 ATS statement: "Data were cited showing that large studies of workers with pleural plaques had approximately a 5% mean decline in FVC compared to asbestos workers without pleural plaques. In this report, the experts concluded that the presence of pleural plaques did not decrease lung function to a significant extent"—that is, they concluded that the observed decrements were not clinically significant to an individual patient. EPA's systematic review of the literature and formal meta-analysis found decrements in the same range—statistically significant decreases in mean FVC of 4.09% (4.08% when studies without limitations are used) and in FEV_1 of 1.99% (3.87% when studies without limitations are used). In addition, although few of the studies evaluated reported results for diffusing capacity (as evaluated by DL_{CO}, the diffusing capacity of the lung for carbon monoxide), these studies did observe statistically significant or nearly significant decreases between those with no radiographic abnormalities and those with LPT or pleural plaques and without any evidence of other radiographic abnormalities.

As stated by ATS (2004), the majority of individuals with pleural plaques may have well-preserved lung function. However, for individuals who are already at the lower end of the "normal" range of function, already have compromised function, or have increased vulnerability or susceptibility due to other factors (such as chronic disease, other environmental exposures, smoking, etc.), even a relatively small decrease in lung function can be important, but once averaged into the whole study population (i.e., looking at only average changes in the whole group) the sensitive individuals' contribution to the population-wide change in mean pulmonary function measures is muted.

Accordingly, there is a difference in considering what may be significant from a clinical perspective compared to an epidemiological perspective. The clinician's focus is the individual patient, and decisions made in that context (i.e., benefits/risks of medical treatments or tests). In contrast, the population-level (risk assessment) perspective considers any changes in the population distribution of pulmonary function and the potentially increased risks of adversity to subpopulations of the general population. When considering an entire population with a distribution of lung function parameters, even small changes in the mean of that distribution means that a much larger proportion of the exposed population is shifted down into the lower "tail" of the lung function distribution. This line of thinking is well understood in the recent examples of lead and IQ (U.S. EPA, 2013a) and respiratory function and ozone (U.S. EPA, 2013b). Early childhood exposure to lead can lead to decrements in intelligence as measured by IQ. Depending on the exposure level to lead, a mean deficit of 2 IQ points would not be

measurable nor lead to a clinical finding of harm in individuals, but from a epidemiologic or population-level perspective, a downward shift in a portion of the entire IQ distribution by 2 IQ points would be expected to push many individuals already in deficit further into a more clearly "adverse" state. Similarly, even small decrements in lung function on the population level could push "borderline" individuals into a state of clinically significant decreased lung function.

In addition, ATS (2004) stated "The presence of plaques is associated with a greater risk of mesothelioma and of lung cancer compared with subjects with comparable histories of asbestos exposure who do not have plaques." While references provided in the ATS (2004) statement (Hillerdal and Henderson, 1997; Hillerdal, 1994) do not directly support the ATS (2004) statement, a recent large (5,287 retired workers, 17 mesothelioma cases) study (Pairon et al., 2013) found a statistically elevated risk of mesothelioma in a group with plaques (parietal and diaphragm) compared to a no-plaques group, using computer tomography (CT). The study authors found that, after adjusting for cumulative exposure index and TSFE, the risk of mesothelioma in the plaques (parietal or diaphragm) group was statistically elevated (hazard rate (HR) = 6.8, 95% CI: 2.2−21.4) compared to the risk of mesothelioma in the exposed workers without pleural plaques.

In the Marysville workers evaluated in 2002−2005, differences in exposure patterns are also apparent among outcome groups (see Table 5−4). Exposure to LAA was lower among those with no radiographic abnormalities compared to those with LPT and those with DPT and/or interstitial opacities. Of the candidate critical effects, LPT has the shortest TSFE, and is more likely to appear at lower levels of LAA exposure. LPT is associated with adverse decrements on pulmonary function. Thus, LPT is selected as the critical effect from among the noncancer radiographic endpoints evaluated in the principal study for RfC derivation.

Table 5-4. Characteristics of workers at the O.M. Scott plant in Marysville, OH, with health evaluations in 2002−2005 who did not report any previous occupational exposure to asbestos

	No radiographic abnormalities	All LPT cases (with or without DPT/interstitial changes)	LPT cases without DPT/interstitial changes	LPT cases with DPT/interstitial changes	DPT/interstitial changes cases, without LPT
N	181	66	56	10	5
Time (years) since first exposure (TSFE), range	23.14−47.34	24.46−47.30	24.46−47.30	31.52−42.22	36.15−45.56
TSFE, median (interquartile range, IQR)	31.14 (27.56−36.30)	38.21 (34.38−45.81)	37.41 (34.36−45.53)	42.03 (37.58−46.22)	37.22 (37.16−45.04)
Mean exposure (fibers/cc), range	0.0067−3.7396	0.0068−4.1000	0.0068−2.6230	0.0571−4.1000	0.0692−3.0463
Median (IQR)	0.0372 (0.0167−0.0943)	0.1634 (0.0431−0.7532)	0.0953 (0.0421−0.3958)	1.9197 (0.6623−2.2848)	0.2378 (0.0954−1.7186)
Cumulative exposure (fibers/cc-yr), range	0.0050−95.0386	0.0233−96.9072	0.0233−96.5450	1.9080−96.9072	1.7986−81.4815
Median (IQR)	1.0188 (0.3162−2.0743)	4.5210 (1.3355−22.9072)	3.1710 (1.2472−10.0445)	47.3994 (22.9072−61.4999)	3.6659 (2.2890−28.2097)
Residence time-weighted (RTW) exposure (fibers/cc-yr^2), range	0.1196−3468.28	0.5313−3,500.66	0.5314−3477.33	65.3771−3500.66	62.7209−3,011.68
Median (IQR)	23.7297 (7.6204−50.7792)	127.4075 (36.5668−770.4642)	88.2670 (34.8638−302.5802)	1,693.86 (770.4642−2365.89)	120.5295 (74.3389−944.9676)

Table 5-4 and Figure 5-2 both highlight a complexity in that these radiographic changes are not mutually exclusive—individuals may have one or more changes simultaneously, in any combination. Among the 66 individuals with LPT, 10 also had DPT or interstitial opacities, and these 10 individuals are noticeably different with regards to TSFE and exposure compared to LPT cases without other radiographic changes, consistent with the results of Larson et al. (2012a). When restricting to the subgroup of individuals hired in 1972 or later, there are 106 individuals with no radiographic abnormalities, 12 individuals with LPT only, and one individual with both LPT and DPT. The individual with both LPT and DPT had a TSFE of 31.52 years, similar to the median TSFE of 29.71 years among the 12 individuals with LPT only. However, this individual had higher estimated mean exposure (0.46 fiber/cc, compared to a median of 0.08 fiber/cc) and cumulative exposure (9.13 fibers/cc-yr, compared to a median of 1.82 fibers/cc-yr), compared to the other 12 LPT cases. The primary analysis considers as the critical effect all LPT cases together, contrasted to those without radiographic abnormalities, but

the effect of separating out those with multiple radiographic outcomes is examined in the sensitivity analyses (see Section 5.3.5).

In addition, an alternative critical effect of "any pleural thickening" (APT) is considered. Note that in the case of the subcohort of workers evaluated in 2002−2005 and hired in 1972 or later, this definition is equivalent to a critical effect of LPT because no individuals had DPT alone.

5.2.2.4. *Selection of Explanatory Variables to Include in the Modeling*

As with the mode of action (MOA) for carcinogenicity, the MOA for LPT and the results of other asbestos epidemiology studies could potentially inform noncancer modeling decisions and suggest exposure metrics to use in modeling. The following text discusses the plausibility of exposure metrics proposed in the MOA/epidemiology literature.

As noted in Section 4.4, important considerations in evaluating the available mechanism and MOA data are fiber characteristics, route of exposure, dose metric, as well as study design and interpretation. Specific fiber characteristics impact the fiber toxicokinetics (reviewed in Section 3), and in turn, the biologic response to fibers. Fiber dimensions play a role in translocation, a clearance mechanism that may lead to inhaled fibers moving from the lung to the pleura. Data gaps still remain to determine specific mechanisms involved in LAA-induced pleural disease. The review of studies in Section 4.4 clearly highlights the need for more controlled studies examining LAA in comparison with other forms of asbestos and for examining multiple endpoints—including reactive oxygen species (ROS) production and proinflammatory gene expression alterations—to improve understanding of mechanisms involved in noncancer health effects. Although research demonstrates that the LAA has biologic activity consistent with the inflammatory action and cytotoxic effects seen with other forms of asbestos, the conclusion of Section 3 of this assessment is that the data are not sufficient to establish an MOA for the pleural and/or pulmonary effects of exposure to LAA.

A general understanding of the biology and the epidemiology of LPT can still inform the modeling as to which explanatory variables should be considered in the models, how the variables should be considered or statistically parameterized, and whether they should be retained in the model. From a general understanding of the respiratory effects of asbestos, the intensity of exposure (i.e., concentration), the duration of exposure, and the timing of exposure in relation to subsequent diagnosis of LPT (i.e., TSFE) have been shown to be univariate predictors of pleural plaques in multiple epidemiologic studies as discussed below and, therefore, merit specific consideration in this modeling effort.

Timing of exposure

Fibrosis in the pleural tissues needs time to develop and become visible by x-ray (Larson et al., 2010a). It has been shown that the prevalence of fibrotic lesions progresses as a function

of time (Rohs et al., 2008) and can appear long after the initial exposure (Lilis et al., 1991). Many investigations of the exposure-response relationship for pleural plaques has found that TSFE is a significant explanatory variable (Paris et al., 2009; Paris et al., 2008; Järvholm, 1992). This suggest that TSFE should be considered as a potential explanatory variable in the modeling.

It is important to understand that even when an individual explanatory variable may be an important univariate predictor of the risk of LPT, in more complex modeling with two or more explanatory variables, the relationship observed in univariate modeling may no longer hold. One reason for this is that two variables can be highly correlated in many occupational cohorts, thus, the regression modeling may indicate that, for the data at hand, there is more unique information to explain the risk of LPT in one variable than in the other.

Intensity of exposure

A general understanding of toxicology suggests that, for a given duration of exposure, exposure at higher intensities (concentrations) will likely result in higher burdens of fibers in the alveolar region of the lung, and potentially in the pleural tissue as well. Therefore, for a given duration of exposure, there is a reasonable expectation that people exposed at higher intensities of LAA would experience greater risk of being diagnosed with LPT than people exposed at lower exposure intensities. Similarly, from general principles, at a given intensity of exposure, greater duration of exposure results in higher tissue concentrations of fibers. Epidemiologic evidence from a large cohort of asbestos-exposed workers has reported that exposure intensity (concentration) can be an important predictor of being diagnosed with pleural plaques — even in a multivariate model along with TSFE (Paris et al., 2009; Paris et al., 2008). As noted in Section 4.1.2.1.1.1, LPT was introduced as a term in the 2000 ILO guidance. LPT includes plaques on the chest wall and at other sites (e.g., diaphragm). Plaques on the chest wall can be viewed either face-on or in profile. A minimum width of about 3 mm is required for an in-profile plaque to be recorded as present according to the 2000 ILO guidance. Järvholm (1992) fit a mathematical model for the incidence of pleural plaques based on concentration and TSFE, which the author considered to have a biological interpretation. This suggests that exposure intensity should be considered as a potential explanatory variable in the modeling.

Duration of exposure

Important characteristics of amphibole fibers are their biodurability and biopersistence. Due to the slow clearance of amphibole fibers from the lung, the fiber burden in the alveolar region of the lung is expected to increase for a given exposure intensity as the duration of exposure increases. This may be true of the pleural tissues as well—but little scientific information is available on the time course of potential fiber accumulation in pleura. Amphibole fibers may remain biologically active for many years while the fibers are in residence in the tissues, although this biological activity may vary with time. For example, depending on the

composition and structure of the fiber, certain fibers may cease to have surface activity in biological media, or may have different biological activity in this media (Pezerat, 2009). Further, some asbestos fibers can become covered with an iron-protein coat in the lungs of exposed individuals [i.e., forming ferruginous bodies; (Dodson et al., 1993; Churg and Warnock, 1981)]. The biological effect of this coating is unclear, but may alter the activity of the fibers. Epidemiologic evidence from studies of asbestos-exposed workers [e.g., Clin et al. (2011)] indicates that cumulative exposure, a metric of exposure that encompasses both exposure intensity as well as duration, can be an important predictor of the probability of being diagnosed with pleural plaques. This suggests that duration of exposure should be considered in modeling. Cumulative exposure (as an expression of concentration and duration) should be considered as a potential explanatory variable in the modeling. Therefore, modeling results using both exposure intensity, C, and cumulative exposure, CE, as the exposure metric are considered. Another exposure metric related to both exposure intensity and duration is called residence time-weighted exposure, a metric of exposure that can be used to more heavily weigh earlier exposures. Residence time-weighted exposure is also considered for modeling.

Other explanatory variables

Other explanatory variables of interest include those that may be confounders of the explanatory variables' statistical relationships with the risk of LPT. These include body mass index (BMI), age, and smoking (complete list from the table of potential confounders). Each of these was assessed as a potential confounder prior to modeling the main explanatory variables of interest.

5.2.2.5. *Selection of the Benchmark Response*

Selecting a benchmark response (BMR) involves making judgments about the statistical and biological characteristics of the data set and about the applications for which the resulting benchmark concentration (BMCs)/lower limit of the BMC (BMCLs) will be used. An extra risk of 10% is recommended as a standard reporting level for quantal data. Biological considerations may warrant the use of a BMR of 5% or lower for some types of effects (e.g., frank effects), or a BMR greater than 10% (e.g., for early precursor effects) as the basis of the POD for a reference value (U.S. EPA, 2012).

LPT is a persistent change to normal tissue structure and is associated with a decrement in lung function on a population level (~5 and ~2.5% decrements in percentage predicted FVC and FEV_1, respectively). Larson et al. (2012a) showed a statistically significant increased risk of people with LPT having "restrictive spirometry" and concluded that this abnormality may result in lung function impairment. However, the available data do not lead EPA to conclude LPT should be considered a frank effect and thus EPA selects a BMR of 10% extra risk for this endpoint.

As noted in Section 5.2.3.1, an alternative critical effect of APT was also considered as an alternative analysis. For this outcome, a BMR of 10% was also used, given that (as shown in Figure 5-2) a significant majority of cases were LPT.

5.2.2.6. *Exposure-Response Modeling*

LPT was selected as the critical effect based on the adverse health effects associated with pleural thickening specific to this diagnosis (ILO, 2002). Note that for the primary analytic data set (workers evaluated in 2002−2005 and hired in 1972 or later), the number of individuals with LPT is the same as the number with either "any pleural thickening" or "any radiographic change" (i.e., there is no difference in the number of cases or the estimates of risk) because the single case with DPT also had LPT (and thus is included as an LPT case) and no cases of interstitial abnormalities occurred. However, in the larger cohort of workers (all workers, and those evaluated in 2002−2005 regardless of hire date), there were individuals with these more severe outcomes as well as LPT (see Figure 5-2).

The exposure-response relationship was modeled as described below, and PODs were estimated using BMC methodology. For inhalation data, the BMC is defined as the exposure level that results in a specified BMR. The RfC is derived from the lower 95% confidence limit of the BMC, referred to as the BMCL, which accounts for statistical uncertainty in the model fit to the data. All analyses were performed using SAS® statistical software v. 9.3. BMCLs were obtained by the profile likelihood method as recommended by Crump and Howe (1985) using the nonlinear mixed modeling procedure (PROC NLMIXED) in SAS (Wheeler, 2005).

5.2.2.6.1. ***Considerations of appropriate model forms and explanatory variables.*** The process and considerations for exposure-response modeling of the Marysville data were guided by EPA's 2012 Benchmark Dose Technical Guidance (U.S. EPA, 2012). As outlined in that document, there are several stages of exposure-response modeling. Once the appropriate data set(s), endpoint(s), explanatory variables(s), and BMR are determined, the next step is to choose an appropriate statistical model form or set of model forms to evaluate (e.g., logistic, probit, Dichotomous Hill, etc.). Among this set of models, the overall model fit and the fit in the region of the BMR are evaluated to determine which models adequately represent the data. Finally, one or more models are selected from the group of adequately fitting models to derive a POD for the reference value. Regarding the selection of models to evaluate, the Benchmark Dose Technical Guidance (see p. 26) states: "The initial selection of a group of models to fit to the data is governed by the nature of the measurement that represents the endpoint of interest and the experimental design used to generate the data. In addition, certain constraints on the models or their parameter values sometimes need to be observed and may influence model selection." In the Marysville data, a number of factors must be considered to determine an appropriate modeling strategy: 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. Each factor is described below, and consideration of these factors in total resulted in a preference for the Dichotomous Hill model, with a set of additional model forms suitable for evaluation of sensitivity to model selection.

- Nature of the data set: For the Marysville workers data set, the outcome data are dichotomous (presence or absence of an effect), and thus, appropriate models are those suitable for dichotomous endpoints. The Marysville workers underwent radiographic evaluation in 2002−2005 to ascertain the presence or absence of radiographic abnormalities (i.e., prevalence data). Radiographic outcomes are coded as present or absent, leading to a dichotomous response structure. Appropriate models for this type of data include models such as logistic, probit, log-logistic, log-probit, Dichotomous Hill, and Michaelis-Menten (see Table 5-5). Goodness of model fit for these models may be evaluated using the Hosmer-Lemeshow goodness-of-fit statistic (Hosmer and Lemeshow, 2000); a low *p*-value (<0.05) indicates poor fit, while a higher *p*-value indicates adequate fit. Note that the computation of this statistic involves dividing the data set into bins, based on the predicted probability of the (dichotomous) outcome. The standard procedure is to use 10 bins (i.e., deciles), and this approach was used for all analyses shown here.

- Effect of exposure: Because the data set include estimates of individual exposure and the goal is to derive an RfC, appropriate models need to include an independent exposure variable. All the models listed above can estimate the effect of changes in exposure on risk of the outcome, although the parameter that reflects the magnitude of that effect changes across models. In models where exposure is included without logarithmic transformation, the *b* parameter corresponding to exposure is interpreted as a "slope" and represents the change in outcome per unit change in exposure. In models where exposure is natural log transformed, the interpretation is somewhat different; both the *a* and *b* parameters determine the shape of the exposure-response relationship (e.g., $a + b \times \ln(x) = \ln(\exp(a) \times x^b)$. Thus, *b* is a power parameter and behaves more like a shape parameter in this context, while $\exp(a)$ behaves like a traditional slope. This is an important distinction in interpreting models including natural log transformation of the exposure (i.e., log-logistic, log-probit, Michaelis-Menten, Dichotomous Hill).

Table 5-5. Models[a] considered to develop a point of departure (POD)

Name	Equation	Fitting parameters	
		N	Description
Logistic	$p(x) = \frac{1}{1 + \exp[-a - b \times x]}$	2	a = Intercept b = Slope
Probit	$p(x) = \Phi(a + b \times x)$	2	a = Intercept b = Slope
Log-logistic	$p(x) = bkg + \frac{1 - bkg}{1 + \exp[-a - b \times \ln(x)]}$	3	a = Slope b = Shape bkg = Background
Log-probit	$p(x) = bkg + (1 - bkg)\Phi(a + b \times \ln(\mathrm{x}))$	3	a = Slope b = Shape bkg = Background
Dichotomous Hill	$p(x) = bkg + \frac{Plateau - bkg}{1 + \exp[-a - b \times \ln(x)]}$	4	a = Slope b = Shape bkg = Background Plateau
Michaelis-Menten (or Dichotomous Hill model, with b fixed at 1)	$p(x) = bkg + \frac{Plateau - bkg}{1 + \exp[-a - \ln(x)]}$	3	a = Slope bkg = Background Plateau
Bivariate Dichotomous Hill with time (T)	$p(x,T) = bkg + \frac{Plateau - bkg}{1 + \exp[-a - b \times \ln(x) - c \times T]}$	4	a = Slope of exposure b = Shape c = Slope of time bkg = Background

[a]Equations used to derive the BMC for each model from *Benchmark Dose Technical Guidance* (U.S. EPA, 2012) are shown below:
Logistic: BMC = −ln [(1 − BMR)/(1 + BMR × exp(−a))]/b
Probit: BMC = [Φ^{-1} (BMR × (1 − Φ(a)) + Φ (a)) − a]/b
Log-logistic: BMC = exp[((−ln ((1/BMR) − 1)) − a)/b]
Log-probit: BMC = exp[(Φ^{-1} (BMR) 0− a)/b]
Michaelis-Menten: BMC = exp[(−ln ((*Plateau*—*bkg*)/((1—*bkg*) × BMR) − 1) − a]
Dichotomous Hill: BMC = exp[(−ln ((*Plateau*—*bkg*)/((1—*bkg*) × BMR) − 1) − a)/b]
Dichotomous Hill with time(T) covariate: BMC = exp [(−ln ((*Plateau*—*bkg*)/((1 − *bkg*) × BMR) − 1) − a − c × T)/b]

- Plateau in models: Some model forms have an explicit parameter representing a plateau (e.g., Dichotomous Hill and Michaelis-Menten), which is an asymptotic quantity interpretable as the maximum prevalence of the outcome that would ever be observed at very high levels of the predictor variables in the model (e.g., high levels of LAA exposure). In contrast, certain model forms (e.g., log-logistic and log-probit) do not estimate a separate plateau parameter, but instead have maximum asymptotic values of 100%. EPA wanted to understand whether the considered models implied an asymptotic maximum incidence for the endpoint (i.e., a "plateau") and to evaluate the sensitivity to alternative specified values for that plateau. Thus, EPA selected a model with an explicit plateau term for the option of fitting that plateau term to the

data and for the ability to do sensitivity analysis with alternative fixed plateau values to evaluate the sensitivity of results.

- Plateau—further considerations: For models with an explicit plateau parameter, EPA considered whether to let the plateau term be fit to the data or to select a fixed value prior to fitting the model. As described below, EPA chose to fix the value of the plateau prior to fitting these models to better consider a broader set of data on pleural thickening. However, EPA also conducted sensitivity analysis on the impact of this assumption for model results. Importantly, this plateau parameter of an asymptotic maximum prevalence cannot be directly observed in, and is not well estimated from the Marysville data because none of the workers experienced high enough exposure and follow-up. In the group of workers defined for primary exposure-response analysis (i.e., those hired in or after 1972 with radiographs performed in 2002−2005), the TSFE averaged 28.4 years and ranged from 23.14 to 32.63 years. Exposure-response models that include TSFE or otherwise incorporate the timing between exposure periods and observation, such as models using the residence time-weighted (RTW) exposure metric, could allow for the estimation of a plateau, but the limited data on the effect of elapsed time in the workers hired in or after 1972 does not support a reliable estimate of the asymptotic maximum prevalence. In addition, standard radiographs may not have perfect sensitivity or specificity to identify the outcomes of interest (thus "observed" prevalence may differ from "actual" prevalence). Models that do not include time from exposure to the x-ray observation would be estimating a plateau that might similarly be extrapolating on dose and might not appropriately estimate the impact of a longer follow-up period. For the RfC, the question is what happens when individuals are exposed over a lifetime (assumed to be 70 years). This may be difficult to answer if a given model results in a plateau significantly lower than what might result from sufficient duration or follow-up time. One option is to fix the plateau parameter at a value informed by the existing literature on observed prevalence in populations that had higher exposures and longer TSFE values. In a cross-sectional study of Libby workers and residents seen at a clinic in Libby, MT, Winters et al. (2012) observed a prevalence of 76% for pleural thickening, although the maximum TSFE was not known. Previous studies in populations exposed to asbestos (potentially amphibole and/or nonamphibole) have reported prevalences of pleural thickening of 82.4% among U.S. insulators with ≥40 years since first exposure (Lilis et al., 1991) and prevalence of pleural plaques of 85.7% among Swedish shipyard workers with 50−54 years since first exposure (Järvholm, 1992). Thus, a reasonable option would be to use the Dichotomous Hill or Michaelis-Menten model and fix the plateau term at a value (i.e., 85%) consistent with maximum observed prevalence rates in the asbestos literature. EPA performed a sensitivity analysis (see Section 5.3.4) to evaluate the effect of assumptions regarding the plateau on the POD.

- Effect of covariates: As with the discussion for effect of exposure, a desirable model attribute is the ability to estimate the effect of additional covariates. EPA evaluated a variety of possible covariates and determined that in the primary analytic data set of individuals evaluated in 2002−2005 and hired in 1972 or later, none showed evidence of potential confounding of the LAA exposure-LPT relationship. Each of the models listed above (logistic, probit, log-logistic, log-probit, Dichotomous Hill, and Michaelis-Menten) allow for the inclusion of covariates. Specifically for modeling

LAA exposure and risk of LPT, one of the most important covariates to consider is TSFE. As described above, the prevalence of pleural plaques (LPT was introduced as a diagnostic term in the ILO guidance in 2000) has been shown to increase as TSFE increases, even in the absence of continued asbestos exposure. Although the literature indicates TSFE is the most important time-related factor, other factors may be important to consider, including age at examination, hire year, job tenure (time elapsed from job start to job stop), and exposure duration (taking into account gaps in exposure). There are also nontime-related factors which may influence the association between LAA exposure and risk of LPT. These include gender, smoking status, and BMI. Smoking is a particularly important variable to consider when evaluating respiratory health outcomes. Each of these factors was investigated in the primary data set. To be a potential confounder, the factor must be associated with both LAA exposure and LPT, and must not be an intermediate in the causal pathway between exposure and outcome. The association with natural log-transformed LAA exposure in the subcohort was assessed using a linear regression model, and the association with LPT was assessed using a logistic regression model (see Table 5-6). While many of the time-related factors (with the exception of age at x-ray examination) as well as male gender and former smoker status were associated with each of the three exposure metrics, none were associated with risk of LPT. Thus, none of the factors met the criteria of being associated with both LAA exposure and LPT, and none were considered as potential confounders. Further consideration of potential confounding and effect modification is addressed in the uncertainty analyses described in Section 5.3.3.

- Background rate: There may be a nonzero background rate of LPT in the population, and it may be desirable to estimate this rate explicitly rather than using a model that implicitly assumes a background rate of zero. Certain model forms (e.g., log-logistic, log-probit, Dichotomous Hill, Michaelis-Menten) include an explicit parameter representing the background rate of the response while others (e.g., logistic, probit) do not include this parameter. Establishing a background rate for LPT prevalence in the population is challenging, as estimates from previous studies in a variety of populations vary widely (Weill et al., 2011; Rogan et al., 2000; Zitting, 1995; Cordier et al., 1987; Rogan et al., 1987; Castellan et al., 1985; Anderson et al., 1979); however, these previous studies do indicate that the background rate is unlikely to be zero. Because there is not a clear indication of what the background rate is in an unexposed population, models that allow estimation of a background rate rather than assuming it to be zero, were considered to have greater weight.

Table 5-6. Evaluation of association between covariates and exposure, and between covariates and LPT.[a] Cells display beta coefficient (standard error), *p*-value for predictor.

	Association with cumulative exposure	Association with mean exposure	Association with RTW exposure	Association with LPT
Time-related				
Hire yr	−0.3162 (0.0473), <0.0001	−0.1772 (0.0374), <0.0001	−0.3653 (0.0441), <0.0001	−0.1645 (0.1247), 0.1870
TSFE	0.2703 (0.0499), <0.0001	0.1564 (0.0383), <0.0001	0.3273 (0.0469), <0.0001	0.1702 (0.1237), 0.1690
Job tenure	0.1189 (0.0123), <0.0001	0.0397 (0.0115), 0.0008	0.1091 (0.0130), <0.0001	0.0038 (0.0346), 0.9124
Exposure duration	0.1186 (0.0122), <0.0001	0.0386 (0.0115), 0.0011	0.1102 (0.0129), <0.0001	0.0111 (0.0350), 0.7520
Age at x-ray	0.0185 (0.0199), 0.3551	0.0155 (0.0146), 0.2915	0.0265 (0.0199), 0.1840	0.0084 (0.0402), 0.8349
Other covariates				
Male gender	1.3638 (0.4337), 0.0021	0.9517 (0.3199), 0.0036	1.3264 (0.4348), 0.0028	0.4265 (1.0850), 0.6943
Ever smoker	0.4435 (0.2843), 0.1214	0.2804 (0.2094), 0.1830	0.4044 (0.2848), 0.1582	0.8997 (0.6870), 0.1903
Current	−0.0007 (0.3529), 0.9984	0.0566 (0.2624), 0.8297	−0.0337 (0.3537), 0.9243	0.5485 (0.8528), 0.5201
Former	0.7502 (0.317), 0.0196	0.4350 (0.2358), 0.0676	0.7069 (0.3178), 0.0280	1.0986 (0.7259), 0.1302
BMI[b]	−0.0049 (0.0227), 0.8309	0.0050 (0.0165), 0.7621	−0.0016 (0.0228), 0.9456	0.0309 (0.0426), 0.4690

[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 LPT status and the predictor is the covariate of interest.
[b]Data on BMI were missing for 21 individuals. Thus, the AIC for this model cannot be compared with the AIC for other models in the table.

Based on the considerations outlined above, EPA developed the following list of desirable model features (see Table 5-7):

a) Models suitable for a dichotomous outcome

b) Ability to estimate the effect of exposure via inclusion of slope (models using untransformed exposure), or slope and shape parameters (models using natural log-transformed exposure)

c) Ability to estimate effect of covariates

d) Ability to estimate or specify the plateau

e) Ability to estimate the background rate of LPT in the study population

Table 5-7. Model features considered in exposure-response modeling to develop a point of departure (POD)

	Model properties				
	Models suitable for a dichotomous outcome	**Allows estimation of slope and shape parameters (where present)**	**Allows estimation of effect of covariates**	**Allows estimation or specification of plateau**	**Allows estimation of background rate of LPT**
Probit/logistic	Yes	Yes for slope No for shape	Yes	No	No
Log-probit/log-logistic	Yes	Yes for slope No for shape	Yes	No	Yes
Michaelis-Menten	Yes	Yes for slope No for shape	Yes	Yes	Yes
Dichotomous Hill	Yes	Yes for slope Yes for shape	Yes	Yes	Yes

The epidemiological models described above (logistic, probit, log-logistic, log-probit, Dichotomous Hill, and Michaelis-Menten) are suited for dichotomous outcomes, and all allow for the inclusion of covariates. However, the Michaelis-Menten model does not allow for estimation of a separate shape parameter (*b* parameter is implicitly fixed at 1). The ability to estimate both *a* and *b* (rather than imposing a presumed shape) provides greater flexibility in exposure-response modeling, and thus the Dichotomous Hill model is preferred over the Michaelis-Menten model. The logistic and probit models do not include separate parameters for either the background rate or a plateau. The three remaining models—log-logistic, log-probit, Michaelis-Menten, and Dichotomous Hill—do allow for estimation of the effect of exposure and the background rate, but only the Dichotomous Hill model includes a separate plateau parameter. Therefore, the Dichotomous Hill model is considered to be the most flexible and potentially the most suitable based on biological and epidemiologic properties in the absence of information on actual model fit, which is also an important consideration in model selection. The Michaelis-Menten, log-probit, and log-logistic models are also reasonable alternatives (note that latter two models implicitly fix the plateau at 100%, above the maximum observed prevalence in reported studies). These models are also evaluated for sensitivity to modeling properties and assumptions. As described above, the plateau is an asymptotic parameter, and it may not be possible to reliably estimate given the limitations of the data. The Marysville workers who underwent health evaluations in 2002−2005 and whose job start date was on or after 1/1/1972

had relatively low levels of exposure and a narrow range of TSFE, and it is likely that estimation of the maximum prevalence of LPT by radiograph is not well supported in these data. One option to address this difficulty is to fix the plateau parameter at a value consistent with the asbestos literature reviewed above. This assessment will use a plateau value of 85%, based on the literature regarding maximum observed prevalence in populations reported to have had long follow-up periods and significant exposure to asbestos, although the sensitivity of the model to this assumption is examined in Section 5.3.4.

5.2.2.6.2. ***Considerations of exposure metric, statistical model fit and selection of exposure-response model.*** While the above description in Section 5.2.2.6.1 explains EPA's preference to use the Dichotomous Hill model for exposure-response modeling in this data set (along with a reasonable set of models to evaluate sensitivity to model form), the text below explains EPA's evaluation of options for the specific exposure metrics to use, and the results of the analysis of statistical fit among the considered models. As noted in Section 5.2.2.4, in the absence of an MOA for pleural health effects, an understanding of the general biology and the epidemiologic literature may help to inform the consideration of exposure metrics for exposure-response modeling. For pleural effects, the timing of exposure, the intensity of exposure, and the duration of exposure may all be important variables to predict the risk of LPT and were considered in the regression modeling.

In the Marysville data, exposure information was collected for each individual based on specific work location, season, and year. There are several ways in which these estimates of exposure by person by year can be aggregated into a single measure. Exposure estimates can be summed over each individual's work history to yield a cumulative exposure estimate for each individual. The cumulative exposure may also be divided by duration of (occupational) exposure to yield an average intensity of exposure (mean exposure). A third option for an exposure metric is to weigh more heavily exposures occurring in the more distant past, using a RTW[21] exposure metric for which each year is weighted by the number of years it occurs prior to the year in which prevalence is evaluated. These three expressions of exposure can be used to derive a POD with appropriate adjustment of the units to arrive at the RfC.

Table 5-8 shows the univariate model results for each of the model forms evaluated, using each of the three different parameterizations of exposure. All models had adequate goodness of fit (GOF), as indicated by the Hosmer-Lemeshow *p*-values (all had *p*-values ≥ 0.7, substantially higher than the standard cutoff value of 0.10, below which a model is considered to fit the data poorly), and were carried forward for further consideration. Because each of the models shown in Table 5-8 was evaluated on the same data set (same number of observations,

[21]The RTW exposure value associated with a constant concentration (c), with 70-years duration and the evaluation of response at age 70 is the sum of $1 \times C + 2 \times C + \ldots 70 \times C$, which is equal to about $C \times 71 \times (70/2)$ or $C \times 2485$.

and same response variable), it is appropriate to compare relative fit among them using the Akaike Information Criterion (AIC). The AIC for the models ranged from a low value of 73.8 (probit and Michaelis-Menten models using mean exposure) to a high of 79.3 (logistic model using RTW exposure). Note that the Dichotomous Hill model with estimated plateau yielded unrealistic parameter estimates when using either cumulative or RTW exposure (e.g., slope estimates >100) and were considered less reliable. Within each model form, mean exposure consistently provided a superior fit (as evidenced by lower AIC) compared to either cumulative or RTW exposure.

Each of the different candidate models shown in Table 5-8 is similar in general form, and comparison of model fit informed by the biological and epidemiologic features of the models does not strongly imply a preference for one model form over the others. For the mean exposure model, the AIC values for the logistic, probit, log-logistic, log-probit, Dichotomous Hill model with plateau fixed at 85%, and Michaelis-Menten model with plateau fixed at 85% ranged from 73.8 to 75.4, a difference of only 1.6 AIC units for the mean exposure model which indicates essentially equivalent fits. Figure 5-3 shows a plot of the fit for the Dichotomous Hill model with plateau fixed at 85% and the Michaelis-Menten model with plateau fixed at 85%.

Table 5-8. Univariate exposure-response modeling for any LPT in the Marysville workers who underwent health evaluations in 2002−2005 and whose job start date was on or after 1/1/1972 (*n* = 119), using a benchmark response (BMR) of 10% extra risk of any localized pleural thickening (LPT)

Model form	Exposure metric[a]	Hosmer-Lemeshow GOF *p*-value	AIC	Intercept (SE)	Background rate (SE)	*b*(SE), *p*-value	Benchmark value	Lower limit of benchmark value
Logistic	Mean	0.8035	74.0	−2.7529 (0.3976)	--	6.1969 (1.9469), 0.0015	0.16925	0.11299
	CE	0.8053	79.2	−2.5622 (0.3760)	--	0.2291 (0.0890), 0.0100	4.08863	2.62151
	RTW	0.7012	79.3	−2.5039 (0.3624)	--	0.0082 (0.0032), 0.0103	109.910	69.0617
Probit	Mean	0.8070	73.8	−1.5902 (0.1980)	--	3.6117 (1.0972), 0.0010	0.15369	0.10470
	CE	0.8147	78.7	−1.4978 (0.1908)	--	0.1320 (0.0510), 0.0096	3.82454	2.50223
	RTW	0.6996	78.8	−1.4632 (0.1838)	--	0.0047 (0.0019), 0.0105	102.910	67.3292
Log-logistic	Mean	0.7895	75.3	1.032 (1.0973)	0.0375 (0.0394)	1.3272 (0.6979), 0.0596	0.087768	0.024088
	CE	0.8727	77.0	−2.8335 (0.9114)	0.0376 (0.03)	1.1839 (0.5311), 0.0277	1.71154	0.46974
	RTW	0.7576	77.0	−5.7331 (2.0944)	0.0342 (0.0331)	1.0073 (0.4394), 0.0236	33.4520	7.50156
Log-probit	Mean	0.7745	75.4	0.5262 (0.6337)	0.0407 (0.0359)	0.7311 (0.3578), 0.0432	0.084358	0.024599
	CE	0.8752	76.9	−1.6462 (0.5098)	0.0417 (0.0298)	0.6685 (0.3101), 0.0331	1.72526	0.56792
	RTW	0.7548	76.8	−3.2071 (1.0398)	0.037 (0.0321)	0.5546 (0.2264), 0.0158	32.2062	9.39139

Table 5-8. Univariate exposure-response modeling for any LPT in the Marysville workers who underwent health evaluations in 2002−2005 and whose job start date was on or after 1/1/1972 (*n* = 119), using a benchmark response (BMR) of 10% extra risk of any localized pleural thickening (LPT) (continued)

Model form	Exposure metric[a]	Hosmer-Lemeshow GOF *p*-value	AIC	Intercept (SE)	Background rate (SE)	B (SE), *p*-value	Benchmark value	Lower limit of benchmark value
Dichotomous Hill, plateau = 85%	Mean	0.7854	75.4	1.4136 (1.2953)	0.0384 (0.0391)	1.4043 (0.7769), 0.0732	0.087535	0.024024
	CE	0.8803	76.8	−2.7993 (1.0922)	0.0404 (0.03)	1.3749 (0.7212), 0.059	1.78013	0.51909
	RTW	0.7527	76.8	−5.9883 (2.5304)	0.0366 (0.0338)	1.1266 (0.5493), 0.0425	34.2516	8.32733
Dichotomous Hill[b]	Mean	0.7895	77.3	1.032 (1.0973)	0.0375 (0.0394)	1.3272 (0.6979), 0.0596 Plateau = 1 (--)	0.087768	0.024088
	CE	1.0000	76.3	−129.53 (0.2141)	0.0654 (0.0239)	109.21 (--) Plateau = 0.4999 (0.1443)	3.23559	0.50437
	RTW	0.9999	76.4	−477.74 (0.9458)	0.0655 (0.0239)	108.91 (--) Plateau = 0.5047 (0.1489)	79.4159	0.000002882
Michaelis-Menten, plateau = 85%	Mean	0.7702	73.8	0.7728 (0.5074)	0.0201 (0.0292)	--	0.061813	0.029272
	CE	0.8315	75.1	−2.3490 (0.4933)	0.0310 (0.0258)	--	1.40562	0.67922
	RTW	0.7528	74.8	−5.4305 (0.5333)	0.0320 (0.0271)	--	30.6380	14.2184
Michaelis-Menten	Mean	0.7800	75.6	0.5494 (0.4847)	0.0214 (0.0287)	-- Plateau = 1.00 (--)	0.064145	0.028018
	CE	0.8298	77.1	−2.3217 (1.3330)	0.0309 (0.0262)	-- Plateau = 0.8342 (0.7120)	1.39843	0.57489
	RTW	0.7458	76.8	−5.2131 (1.2187)	0.0306 (0.0277)	-- Plateau = 0.7418 (0.5143)	28.9826	11.2141

Table 5-8. Exposure-response modeling for any LPT in the Marysville workers who underwent health evaluations in 2002−2005 and whose job start date was on or after 1/1/1972 (*n* = 119), using a benchmark response (BMR) of 10% extra risk of any localized pleural thickening (LPT) (continued)

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[a]CE indicates cumulative exposure (fibers/cc-yr), Mean indicates mean exposure (fibers/cc), RTW indicates residence time weighted exposure (fibers/cc-yr^2), calculated using the midpoint of each work season.

[b]Shaded cell indicates the model did not yield a reasonable estimate for one or more parameters.

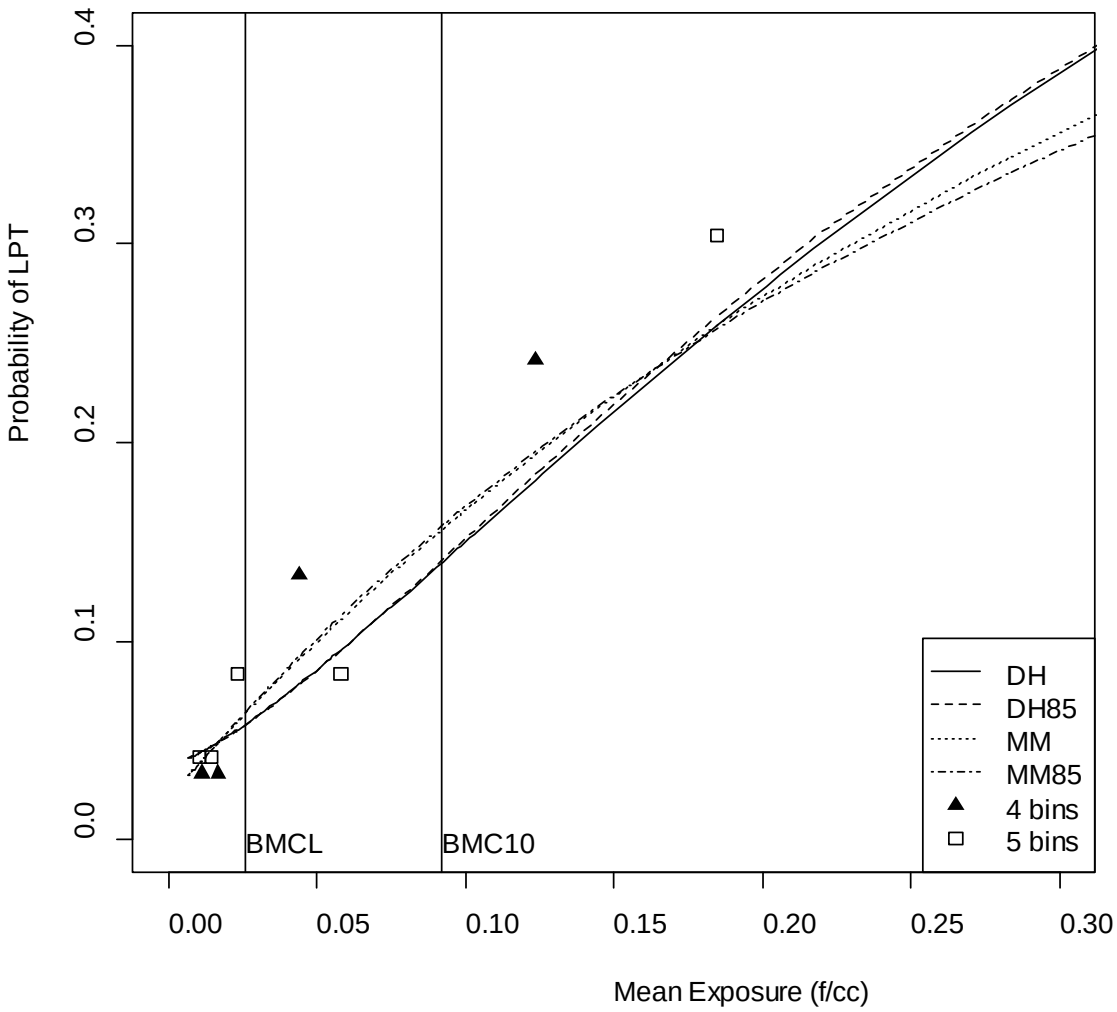


Figure 5-3. Plot of exposure-response models for probability of localized pleural thickening (LPT) as a function of mean concentration of occupational exposure in the subcohort. Based on the results in Table 5-8, the four lines show the predicted exposure-response shapes of the following models: Dichotomous-Hill model with estimated plateau (DH), Dichotomous-Hill model with plateau fixed at 85% (DH85), Michaelis-Menten model with estimated plateau (MM), and Michaelis-Menten model with plateau fixed at 85% (MM85). The Dichotomus-Hill with plateau fixed at 85% is the selected model and Michaelis-Menten with plateau fixed at 85% is the best fitted model according to AIC. The full range of observed exposure data extended to 0.77 fiber/cc; however, as interest in the fit is in the range of the BMC_{10}, the range of exposure values shown here is restricted to 0.3 fiber/cc. The two sets of unconnected symbols show the categorical probability estimates based on quartiles and quintiles of exposure plotted in the median concentration for each category. Data are aggregated in four bins based on quartiles (1,1,4,7 cases in each bin) and five bins based on quintiles (1,1,2,2,7 cases in each bin). Vertical lines at the BMC_{10} and BMCL are drawn at the corresponding estimates from Dichotomous-Hill model with plateau fixed at 85%. BMCs and BMCLs for other models are in Table 5-8.

As described above, the Dichotomous Hill model with plateau fixed at 85% possesses desirable biological/epidemiological properties and is the most flexible of the evaluated models. This model had an AIC at the lower range of the models evaluated (75.4 when using mean exposure or 76.8 when using cumulative or RTW exposure); the AIC for the model using mean exposure was within two AIC units of the best-fitting models, a difference that is generally considered indistinguishable with respect to relative model fit (Burnham and Anderson, 2002). Because it was considered the most flexible model, the Dichotomous Hill model with plateau fixed at 85% was selected as the primary model for RfC derivation. This model was carried forward through the extensive sensitivity analyses (see Section 5.3) because it was considered to be the model most likely to be able to detect sensitivity to covariates and alternative model parameterization.

The RfC is "an estimate (with uncertainty spanning perhaps an order of magnitude) of an exposure (including sensitive subgroups) that is likely to be without an appreciable risk of adverse health effects over a lifetime." (U.S. EPA, 1994b), where a lifetime is commonly assumed to be 70 years. Thus, consideration of the effect of time (specifically time elapsed from exposure to outcome evaluation) is an important aspect of deriving an RfC. The literature on pleural abnormalities and asbestos generally supports a conclusion that the amount of time elapsed between exposure and evaluation has a major impact on observed response. The model form and/or the selection of an exposure metric should incorporate considerations of time factors. As described above, in the primary data set (which had a very limited range of TSFE values) neither TSFE nor any of the other covariates evaluated were significantly associated with LPT. However, the epidemiologic literature is clear that the timing of exposure is an important factor in evaluating risk over a lifetime, and it was considered critical to address the time-course of exposure and LPT in deriving the RfC. Thus, one option would be to incorporate TSFE through the choice of exposure metric. Neither mean nor cumulative exposure takes into account the TSFE or the timing of subsequent exposures. The RTW exposure metric does incorporate information for each year's exposure of the time between that exposure and evaluation of the prevalence—exposure in a given time interval is weighted according to time elapsed, with exposure occurring earlier given greater weight. This approach might be preferable to a model including TSFE as a covariate along with mean or cumulative exposure because the RTW metric weights each year of exposure according to the time elapsed until health evaluation. However, while time prior to evaluation is "considered" when using the RTW exposure metric, the subcohort with better exposure data is still limited in that the range of TSFE in this group of workers is relatively narrow (from 23.14 to 32.63 years), which may explain the lack of predictive value of TSFE in this group. Thus, utilizing this approach to estimate a concentration yielding the same risk for a 70-year exposure is informed by a relatively small range of TSFE values.

Therefore, EPA considered explicitly including TSFE as a covariate in exposure-response modeling, along with either mean or cumulative exposure. As noted above, less variability is present in TSFE (and other time-related factors) for the subgroup of workers hired in 1972 or later, compared to the larger study population of Marysville workers who underwent health evaluations in 2002−2005 (regardless of hire date, n = 252). In this group, the median TSFE was 33.5 years (SD = 7.12 years) and the range was 23.1 to 47.3 years, considerably longer than the subset of these workers whose job start date was on or after 1/1/1972. As noted in Section 5.2.2.2, EPA selected the smaller subgroup for primary exposure analysis because the exposure data after 1972 is of higher quality, even though the range in TSFE is more limited. However, it is possible to use a larger subset of the Marysville workers with a wider range of time-related factors (but more uncertain exposure information) to model the effect of TSFE, then include this effect as a fixed parameter when modeling the exposure-response relationship among the primary analytic group of workers who underwent health evaluations in 2002−2005 and were hired ≥1972. This hybrid model may be used to calculate a BMCL for a scenario of lifetime exposure (70-years duration and 70-years TSFE). This procedure could use either mean exposure or cumulative exposure. The use of RTW may not be appropriate because RTW includes consideration of the timing of exposures and thus a model using RTW in the exposure metric and TSFE as a covariate might have two variables both reflecting the timing of exposure.

Modeling procedure

1) Fit the model (Dichotomous Hill with plateau fixed at 85%) in all the workers evaluated in 2002−2005 (regardless of hire date) with TSFE and LAA exposure (either represented as cumulative exposure [CE] or as mean exposure [C]) as predictor variables.

$$p(x,T) = bkg + \frac{Plateau - bkg}{1+\exp[-a - b\times\ln(x) - c\times T]} \quad (5\text{-}1)$$

2) Use the regression coefficient for TSFE calculated in (1), represented by "*c*", as a fixed parameter in the model for workers who underwent health evaluations in 2002−2005, using data only on those hired in 1972 or later; fit the model to the data on this subcohort using the individual data on both TSFE and LAA exposure as independent variables—note that as in the larger cohort of all workers evaluated in 2002−2005, LAA exposure may be modeled as either mean exposure or cumulative exposure.

3) Use some fixed value of TSFE to estimate the benchmark value and the lower limit conditional upon that TSFE.

$$Benchmark\ value = \exp\left(\frac{-\ln\left(\frac{Plateau - bkg}{(1-bkg)\times BMR} - 1\right) - a - c\times T}{b}\right) \quad (5\text{-}2)$$

The bivariate modeling results for this hybrid model option are shown in Table 5-9. Both mean and cumulative exposure metrics were evaluated on the basis of two measures of model fit. The AIC allows the comparison of the fit among two or more models of the same dependent variable, and AIC results within approximately two units can be considered to be of equivalent fit. However, two studies in the epidemiologic literature also compared mean concentration and cumulative exposure in relation to the risk of pleural plaques and found that when also including TSFE as an explanatory variable (as in the results shown in Table 5-9), mean exposure provided a significantly better model fit (Paris et al., 2008). In addition, another study (Järvholm, 1992) proposed model including TSFE and intensity of exposure and stated that this model is biologically interpretable; statistical modeling of pleural thickening (18% diffuse) showed that duration of exposure does not matter when TSFE is included in the model (Lilis et al., 1991).

Table 5-9. Estimated point of departure (POD) combining information from the Marysville workers who underwent health evaluations in 2002−2005 and hired in 1972 or later (Primary), and from all workers who underwent health evaluations in 2002−2005 (regardless of hire date), using a benchmark response (BMR) of 10% extra risk of LPT in the Dichotomous Hill model with plateau fixed at 85%. Models include LAA exposure as well as TSFE.

	Mean exposure		Cumulative exposure	
	Primary	**Individuals with radiographs in 2002−2005 (to get beta for TSFE)**	**Primary**	**Individuals with radiographs in 2002−2005 (to get beta for TSFE)**
Hosmer-Lemeshow GOF *p*-value	0.73626	0.34206	0.76267	0.037763
Model AIC[a]	75.4	242.7	76.8	242.6
Alpha (intercept)	−1.9798 (SE = 1.2270)	−3.4130 (SE = 1.1368)	−5.4574 (SE = 1.0644)	−4.6279 (SE = 1.2668)
Bkg (background)	0.03682 (SE = 0.04037)	0 (--)	0.0388 (SE = 0.0321)	0.0133 (SE = 0.0314)
Beta for TSFE	0.1075 (fixed)	0.1075 (SE = 0.0281), *p* = 0.0002	0.0957 (fixed)	0.0957 (SE = 0.0326), *p* = 0.0036
Beta for ln(exposure)	1.2750 (SE = 0.7159), *p* = 0.0775	0.4819 (SE = 0.1390), *p* = 0.0006	1.2400 (SE = 0.6809), *p* = 0.0711	0.4917 (SE = 0.1588), *p* = 0.0022
BMC/BMCL at 28 yr	0.0923/0.026 fiber/cc (Ratio = 3.5)[b]		1.8622/0.5770 fiber/cc-yr (Ratio = 3.2)	

[a]Results in this table are from two different data sets with different number of individuals and thus, the AICs for the models cannot be compared between the two data sets.
[b]For the model of Marysville workers who underwent health evaluations in 2002−2005 (without regard to date of hire), both the BMC and BMCL at 28 years TSFE were approximately 3-fold lower than the values in the primary analysis

For the Marysville data, the model with cumulative exposure did not fit well on the other measure of model fit. In the larger group of workers evaluated in 2002−2005 (regardless of hire date), fit of cumulative exposure had a low *p*-value (i.e., <0.10) for the Hosmer-Lemeshow goodness-of-fit statistic. Mean exposure did provide an adequate fit and was, therefore, carried forward in the analysis as the primary basis of the derivation of the lifetime RfC in Section 5.2.3. Although the model using cumulative exposure did not show an adequate fit based on the Hosmer-Lemeshow goodness-of-fit test, the model fit as measured by the AIC was nearly equivalent to the AIC for the mean exposure model, and the beta estimated for the effect of TSFE was similar to that estimated in the model using mean exposure. Therefore, the derivation of a chronic RfC based on the CE model is also shown in Section 5.2.3 for comparison.

EPA concluded in Section 5.2.2.2 that the subcohort with the better exposure data yields the more reliable estimate of the relationship of LPT to exposure concentration for the derivation of the RfC. The primary analysis (Table 5-9) applying the hybrid model to the subcohort had fewer cases and lower exposure concentrations (which are more relevant to environmental exposure levels) than the larger cohort and hence, the statistical power for the primary analysis is diminished and the *p*-value for the beta for exposure parameter in the subcohort is 0.078. The EPA's Benchmark Dose Technical Guidance [U.S. EPA (2012), see Figure 2A, p. 16] addresses the general issue of when there is a lack of statistical significance due to low power and states that studies of low power remain feasible for BMD modeling. The Benchmark Dose Technical Guidance [U.S. EPA (2012), p. 15−16] further notes that when other data support a conclusion that there is a relationship with dose, it can be acceptable to use results from a database for which the relationship is not statistically significant. There exists a clear exposure-response relationship between LAA and the risk of pleural abnormalities in the original study report [$p < 0.001$; Rohs et al. (2008)], and there exists a clear exposure-response relationship in the workers who underwent health evaluations in 2002−2005 ($p<0.0006$; see Table 5-9). Therefore, while the effect estimate for exposure is less precise in the subcohort than in the larger group of workers, this estimate is considered to be a more reliable estimate of the true effect of LAA on the risk of developing LPT for the purpose of deriving the RfC.

In the model using mean exposure intensity in the larger data set of individuals evaluated in 2002−2005, the beta coefficient for TSFE was 0.1075. This coefficient value was transported to the equivalent model in the subset of workers hired in 1972 or later; at a TSFE of 28 years (the median in this group of workers), the BMC and BMCL were 0.092 fiber/cc and 0.026 fiber/cc, respectively. The two-step hybrid modeling results in a higher BMCL: both the BMC and BMCL from the modelling of the larger cohort were about 3-fold lower at TSFE=28 years than the preferred values from the hybrid model.

Ideally, the objective of the RfC derivation is to compute the BMCL for 70 years (i.e., a lifetime) of exposure. However, the maximum observed TSFE in the primary cohort was 32.6 years, which while clearly a chronic exposure, cannot be expected to approximate a lifetime exposure in this particular circumstance when TSFE is the most important predictive factor for the prevalence of LPT. The BMCL values calculated at longer TSFEs were very low (e.g., a BMCL of 2.7×10^{-6} at TSFE of 70 years) and the ratio of BMC to BMCL grows exponentially such that these values at 70 years are considered to be unreliable (e.g., the BMC:BMCL ratio is 1,000 at TSFE of 70 years). This is likely because longer TSFE values are extrapolated well outside of the range of the data, and attempting to extrapolate beyond ~30 years leads to greater statistical uncertainty. Consequently, the BMC and BMCL values corresponding to 28 years were selected as the primary modeling result, with the BMCL of 0.026 fiber/cc serving as the POD for RfC derivation with some additional accommodation of the uncertainty in using less than lifetime exposure data to estimate lifetime risks.

At the BMCL (2.6×10^{-2} fiber/cc), the final model leads to an estimated probability of LPT of 0.06 at 28-years TSFE, and 0.61 at 70-years TSFE (see Figure 5-4). This 10-fold increase in the probability of the critical effect going from the median TSFE in the cohort, to the full lifetime, is used to derive a data-informed subchronic to chronic uncertainty factor (UF) for RfC derivation in the following section.

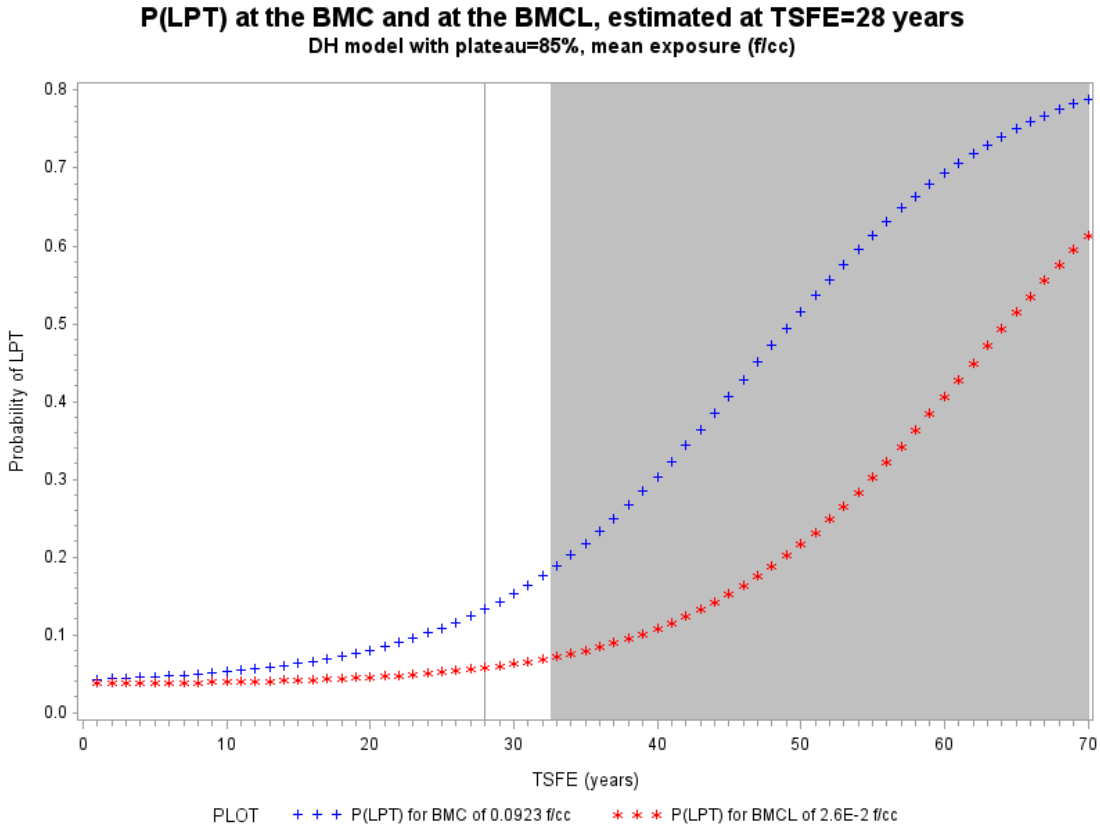


Figure 5-4. Predicted risk of localized pleural thickening (LPT) at the benchmark concentration (BMC) and the lower limit of the BMC (BMCL), using the hybrid Dichotomous Hill model with plateau fixed at 85%. The parameters for this were taken from Table 5-8. Note that the vertical reference line indicates TSFE = 28 years, used to calculate the BMC and BMCL. The shaded region indicates TSFE beyond that observed in the cohort of workers evaluated in 2002−2005.

5.2.3. Derivation of a Reference Concentration (RfC) for the Critical Effect of Localized Pleural Thickening (LPT) in the Marysville Workers Who Underwent Health Evaluations in 2002−2005 and Were Hired in 1972 or Later—Including Application of Uncertainty Factors (UFs)

Among the available studies that could provide exposure-response data for the relationship between LAA exposure and risk of LPT, consideration of study attributes led to the selection of a study of the Marysville, OH workers evaluated in 2002−2005 as the primary data

set for RfC derivation [(Rohs et al., 2008) see Section 5.2.1]. An updated job-exposure matrix was available for this follow-up of the original study group, with a refined understanding of exposure to LAA throughout plant operation (see Section 5.2.3.1 and Appendix F). However, due to remaining uncertainties in exposures prior to 1972, EPA elected to focus on exposure-response modeling for the subgroup of plant employees hired in 1972 or later (see Section 5.2.3.2). The critical effect selected for derivation of the RfC is LPT, a persistent change to normal tissue structure associated with decreased pulmonary function.

Using a 10% BMR for LPT, a BMC of 0.092, and a $BMCL_{10}$ of 0.026 fiber/cc were calculated for the mean exposure model (see Table 5-9). Following EPA practices and guidance (U.S. EPA, 2002, 1994b), application of the following default and data-informed UFs was evaluated resulting in a composite UF of 300.

- An interspecies uncertainty factor, UF_A, of 1 is applied for extrapolation from animals to humans because the POD used as the basis for the RfC was based on human data.

- An intraspecies uncertainty factor, UF_H, of 10 was applied to account for human variability and potentially susceptible individuals. Only adults sufficiently healthy for full-time employment were included in the principal study and the study population was primarily male. Other population groups, such as the elderly, women, children, and those with preexisting health conditions, were not evaluated in the principal study but may have a different response to LAA exposure.

- An uncertainty factor for extrapolating from a lowest-observed-adverse-effect-level (LOAEL) to a no-observed-adverse-effect-level (NOAEL), UF_L, of 1 was applied because this factor was addressed as one of the considerations in selecting a BMR for BMC modeling.

- A database uncertainty factor, UF_D, of 3 was applied to account for database deficiencies in the available literature for the health effects of LAA.

  Although a large database exists for asbestos in general, only four study populations exist for LAA specifically: the Minneapolis, MN community study, the Marysville, OH worker cohort, the Libby worker cohort, and the ATSDR community screening (which includes some Libby worker cohort participants). Studies conducted in three of these populations, the Libby worker cohort (Larson et al., 2012a), Minneapolis community study (Alexander et al., 2012), and Marysville workers (Rohs et al., 2008), have all demonstrated substantial numbers of LPT cases occurring at the lowest exposure levels examined in each study (Christensen et al., 2013), lending confidence to the use of LPT as a critical effect and (Rohs et al., 2008) as the principal study for RfC derivation.

  However, studies in the Libby population have also demonstrated an association between exposure to LAA and autoimmune effects (Marchand et al., 2012; Noonan et al., 2006; Pfau et al., 2005). Because these studies did not provide exposure-response information, it is unknown whether a lower POD or RfC would be derived for these effects. For other (non-Libby) forms of amphibole asbestos, there is evidence for

autoimmune effects from a study of individuals in a community exposed to tremolite. In the Metsovo population, there were changes in immune parameters in tremolite-exposed individuals without pleural plaques, and additional immune markers (including autoantibodies) were increased in individuals with pleural plaques (Zerva et al., 1989). Also it has been hypothesized that shorter asbestos fibers reach the pleura via passage through lymphatic channels (Peacock et al., 2000), although experimental evidence is lacking for this or alternative potential mechanisms of fiber migration. This uncertainty in the sequence of health effects (pleural or autoimmune) is the basis for selecting a UF_D of 3.

- In addition, this assessment applied a data-informed UF. A data-informed subchronic-to-chronic uncertainty factor, UF_S, of 10 was applied because, for this particular health endpoint, even ~30 years of observation (Rohs et al., 2008) is insufficient to describe lifetime risks. Although chronic exposure has been generally defined as more than approximately 10% of lifetime, the EPA's RfC guidance (U.S. EPA, 1994b) states that for human data "[t]he best data to use for calculating an RfC would be a population study of humans that includes sensitive individuals exposed for lifetime or chronic duration, and that evaluates the critical endpoint or an appropriate early marker for the disease…. However, the amount of exposure in a human study that constitutes subchronic is not defined, and could depend on the nature of the effect and the likelihood of increased severity or greater percent response with duration." Similarly, the 2014 *Guidance for Applying Quantitative Data to Develop Data-Derived Extrapolation Factors for Interspecies and Intraspecies Extrapolation* (U.S. EPA, 2014) advises that "[e]xtrapolation is most scientifically robust when data are first evaluated before using defaults." Consistent with those documents, EPA first evaluated the data on follow-up time (in this case TSFE) both with respect to the data on LAA and what is known from the literature about other amphiboles and asbestos generally before considering extrapolation.

  For LAA, the study by Rohs et al. (2008) is a follow-up on the Lockey et al. (1984) investigation, and while the earlier study showed the prevalence of all pleural abnormalities together as 2.0% in 1980 (see Table 4-8), the study by Rohs et al. (2008) showed that in 2002−2005, the prevalence of LPT increased to 26.2% (in workers without other asbestos exposure; see Table 5-3 and Figure 5-2), a 13.1-fold increase in 22-23 years with very low additional exposure during the additional years of follow-up.

  There are no epidemiologic data on the relationship between TSFE and the prevalence of pleural plaques for other amphiboles. There are data on other epidemiologic cohorts exposed to general asbestos. While the type of fiber exposure is not defined in any of the other studies of pleural plaques and TSFE, it could be reasonably inferred from listed occupations to be either mostly chrysotile or mixed chrysotile and amphibole exposures.

  One study of shipyard workers likely exposed to mostly chrysotile that also used x-ray to diagnose pleural plaques (Järvholm, 1992) presented data by 5-year intervals of TSFE from 0 to 54 years. Although people with higher TSFE were likely exposed to higher concentrations (due to relative lack of historical industrial hygiene), the prevalence of having pleural plaques was consistently greater with longer TSFE and the prevalence increased with increasing time. The prevalence increased from 1.7%

at 12 years of TSFE to 24% at 27 years of TSFE and then to 86% at 52 years of TSFE—a rise of 50-fold in 40 years. A 3.6-fold increase was observed for the last 25 years. The prevalence at 27 years of TSFE is similar to prevalence as in the Marysville, OH cohort which had a 26.2% prevalence at about 33 years of TSFE. One study of multiple occupations with undetermined asbestos exposure, likely mostly chrysotile or mixed chrysotile and amphibole exposures, that used HRCT to diagnose pleural plaques (Paris et al., 2009) presented data by quartiles of TSFE. Note that, since HRCT is known (ATS, 2004) to identify 1.5−2 times more plaques than x-ray detects, the relationship with TSFE may be different than with x-ray data. In this HRCT study, the prevalence increased 3.2 fold in 42 years, from 11.7% at 18 years of TSFE to 37.6% at 60 years of TSFE. However, unlike Järvholm (1992), the intervals of TSFE in this study were of widely divergent length. For example, the growth between two narrowly defined intervals of similar length was 1.7-fold in only 5.5 years from TSFE of 39.5 years to TSFE of 45 years. Note that in both of these studies, the growth rate was consistent, but uneven over periods of observations.

It is clear from supporting studies on exposure to other types of asbestos (some of which use HRCT rather than x-ray data and therefore are identifying a different outcome) that the qualitative pattern holds true that prevalence of pleural plaques continue to increase with TSFE as high as 50−60 years, but the range of rates varies across these studies from a 3.2-fold increase after 42 years to a 50-fold increase after 40 years TSFE. Data specific to LAA (where x-rays were used to diagnose pleural plaques or LPT) shows a 13.1-fold increase in the 22-23 years observed between the original analysis of the LAA-exposed cohort by Lockey et al. (1984) and the follow-up study by Rohs et al. (2008).

The risk of pleural plaques, and thus LPT, continues to increase throughout life (even with less-than-lifetime exposures). Because the RfC is intended to apply to noncancer effects due to lifetime exposure, the limitation in the observed TSFE in the principal study and in the supporting epidemiologic data strongly suggests extrapolation from known exposures to lifetime exposures.

As the first attempt at extrapolation, EPA considered basing the point of departure on the modeled BMCL for lifetime exposure and follow-up (TSFE = 70 years) and the target benchmark response rate of 10% extra risk. However, there is considerable uncertainty in that extrapolation as indicated by a ratio of 1,000 when comparing lifetime BMC to lifetime BMCL ($BMC_{70y} = 0.0027$: $BMCL_{70y} = 2.7 \times 10^{-6}$). Next, EPA examined the ratio of the central estimates from the model. EPA calculated the ratio of the model-predicted BMC at TSFE of 28 to the modeled BMC at TSFE of 70 years; that ratio is approximately 34.

As noted at the end of Section 5.2.2.6.2, EPA also used the model to examine the estimated increase in the central estimate of the response rate for increases in TSFE from the 28 years used to derive the point of departure to a TSFE of 70 years. That ratio depends on the concentration whose risk is being evaluated, so EPA calculated that ratio at the point of departure concentration (0.026 fiber/cc) that is the primary modeling result. For that concentration, the central estimate of the risk at TSFE = 70 years is ~10-fold greater than the central estimate of the risk at TSFE = 28 years (from 6% to 61%) as shown in Figure 5-4.

There is some uncertainty as to whether the prevalence would increase in the same manner for additional years of TSFE outside the range of observed data as it does within the range of the observed data on LAA. There are limited non-Libby asbestos data and extrapolations that point to an uncertainty value of about 3. However, having considered the epidemiologic data and the potential extrapolation information, EPA concluded that a data-informed UF_S of 10 is appropriate in this situation where most of the epidemiologic data, including the LAA data, predicts a 10-fold increase or more in the prevalence of pleural plaques (or LPT). Some extrapolations project a factor that might be as high as 34-fold, but only if the rate of increase remained the same at larger values of TSFE. For these reasons, a data-informed UF_S=10 was applied.

Composite UF = $UF_A \times UF_H \times UF_L \times UF_D \times UF_S = 1 \times 10 \times 1 \times 3 \times 10 = 300$

The derivation of the RfC from the morbidity studies of the Marysville, OH worker cohort [i.e., Rohs et al. (2008)] was calculated from a POD, $BMCL_{10}$ for LPT of 0.026 fiber/cc, and dividing by a composite UF of 300. As derived below, the chronic RfC is **9×10^{-5} fiber/cc** for LAA:

$$\begin{aligned} \text{Chronic RfC for LPT} &= BMCL_{10} \div UF \\ &= 0.026 \text{ fiber/cc} \div 300 \\ &= 8.67 \times 10^{-5} \text{ fiber/cc, rounded to } 9 \times 10^{-5} \text{ fiber/cc} \end{aligned} \quad (5\text{-}3)$$

Note that for the primary RfC for LAA and all the alternative RfCs for LAA, the fiber concentrations are presented here as continuous lifetime exposure in fibers/cc where exposure measurements are based on analysis of air filters by PCM. Current analytical instruments used for PCM analysis have resulted in a standardization of minimum fiber width considered visible by PCM between 0.2 and 0.25 µm. Historical PCM analysis (1960s and early 1970s) generally had less resolution, and fibers with minimum widths of 0.4 or 0.44 µm were considered visible by PCM (Amandus et al., 1987b; Rendall and Skikne, 1980). Methods are available to translate exposure concentrations measured in other units into PCM units for comparison.

While this assessment is informed by studies of other types of asbestos, it is not a complete toxicity review of other amphiboles or of chrysotile asbestos.

5.2.3.1. *Derivation of a Reference Concentration (RfC) for the Alternative Endpoint of Any Pleural Thickening (APT) in the Marysville Workers Who Underwent Health Evaluations in 2002−2005 and Were Hired in 1972 or Later*

As shown in the uncertainty analyses in Section 5.3.5 (see Table 5-17), use of an alternative critical effect of APT results in an almost identical $BMCL_{10}$ as derived for the primary analysis using LPT as the critical effect. In the subcohort, the number of cases of APT is identical to the number of cases of LPT, and in the larger group of workers evaluated in

2002−2005 used to estimate the effect of TSFE, the number of cases of APT is very similar to the number of LPT cases (n = 69 cases of APT and n = 66 cases of LPT). In this larger group, the regression coefficient for the effect of TSFE was very close when using either of these two endpoints—values of 0.1108 for APT and 0.1075 for LPT. Thus, using the same uncertainty factors as described above, the chronic RfC is 9×10^{-5} fiber/cc for LAA, using an alternative endpoint of APT:

$$\begin{aligned} \text{Chronic RfC for APT} &= \text{BMCL}_{10} \div \text{UF} \\ &= 0.027 \text{ fiber/cc} \div 300 \\ &= 9.0 \times 10^{-5} \text{ fiber/cc, rounded to } 9 \times 10^{-5} \text{ fiber/cc} \end{aligned} \quad (5\text{-}4)$$

This value is identical to the primary RfC derived using a critical effect of LPT, when rounded to one significant digit. These results provide additional support to further substantiate the primary RfC.

5.2.3.2. *Derivation of a Reference Concentration (RfC) for the Alternative Endpoint of Any Radiographic Change (ARC) in the Marysville Workers Who Underwent Health Evaluations in 2002−2005 and Were Hired in 1972 or Later*

As shown in the uncertainty analyses in Section 5.3.5 (see Table 5-17), use of an alternative critical effect of any radiographic change (ARC) results in an almost identical BMCL_{10} as derived for the primary analysis using LPT as the critical effect. In the subcohort, the number of cases of ARC is identical to the number of cases of LPT, and in the larger group of workers evaluated in 2002−2005 used to estimate the effect of TSFE, the number of cases of APT is very similar to the number of LPT cases (n = 71 cases of ARC, and n = 66 cases of LPT). In this larger group, the regression coefficient for the effect of TSFE was very close when using either of these two endpoints—values of 0.1115 for ARC and 0.1075 for LPT. Thus, using the same uncertainty factors as described above, the chronic RfC is 9×10^{-5} fiber/cc for LAA, using an alternative endpoint of ARC:

$$\begin{aligned} \text{Chronic RfC for ARC} &= \text{BMCL}_{10} \div \text{UF} \\ &= 0.027 \text{ fiber/cc} \div 300 \\ &= 9.0 \times 10^{-5} \text{ fiber/cc, rounded to } 9 \times 10^{-5} \text{ fiber/cc} \end{aligned} \quad (5\text{-}5)$$

This value is identical to the primary RfC derived using a critical effect of LPT, when rounded to one significant digit. These results provide additional support to further substantiate the primary RfC.

5.2.4. Derivation of a Reference Concentration (RfC) for Localized Pleural Thickening (LPT) in the Marysville Workers Who Underwent Health Evaluations in 2002−2005 and Were Hired in 1972 or Later Based on the Cumulative Exposure Model

As shown in the analyses in Section 5.2.2 (see Table 5-9), the model with TSFE and CE yields a similar overall fit to the model based on TSFE and mean exposure as judged by AIC values within two units (242.6 vs. 242.7). However, the CE model yielded an unacceptably low value for the Hosmer-Lemeshow goodness-of-fit test (p =0.04 <0.1) when also including TSFE in the model, and therefore, the mean exposure model was selected for the derivation of the RfC. This same pattern was corroborated in the analysis of the combined cohort in Appendix E where the same bivariate Dichotomous Hill model with plateau fixed at 85% passed the Hosmer-Lemeshow goodness-of-fit test for the model with TSFE and mean exposure but yielded an unacceptably low value for the model with TSFE and CE (p = 0.006 <0.1; see Table E-4).

However, as CE has been a traditional exposure metric of asbestos exposure, there may be interest in an estimate of the RfC for such a model based on TSFE and CE. The use of an alternative model based on the TSFE and CE data yields a $BMCL_{10}$ of 0.577 fiber/cc-yr using LPT as the critical effect among individuals evaluated in 2002−2005 and hired in 1972 or later at a TSFE of 28 years (the median in this group of workers). In order to adjust the POD to units of concentration (fibers/cc), this POD was divided by the mean duration of occupational exposure (18.23 years) to yield an adjusted $BMCL_{10}$ of 0.0317 fiber/cc. Using the same uncertainty factors as described above, the value of an RfC for LAA based on a model fit to TSFE and CE would be 1×10^{-4} fiber/cc:

$$\begin{aligned} \text{Chronic RfC for LPT} &= BMCL_{10} \div UF \\ &= 0.0317 \text{ fiber/cc} \div 300 \\ &= 1.06 \times 10^{-4} \text{ fiber/cc, rounded to } 1 \times 10^{-4} \text{ fiber/cc} \end{aligned} \quad (5\text{-}6)$$

This value is approximately 11% higher than the primary RfC derived using a critical effect of LPT and a model fit to TSFE and C. As noted previously, this result using CE is included for comparative purposes with the primary RfC, but was not selected as the primary RfC as the model based on CE did not indicate an adequate fit to the Marysville subcohort of workers evaluated in 2002−2005 and hired in 1972 or later when also including TSFE in the model.

5.2.5. Derivation of a Reference Concentration (RfC) for the Alternative Endpoint of Any Pleural Thickening (APT) in the Marysville Cohort with Combined X-Ray Results from 1980 and 2002−2005 Regardless of Date of Hire

EPA also conducted modeling of the full Marysville cohort to substantiate the derivation of the RfC in the primary analytic subset of workers evaluated in 2002−2005 and hired in 1972 or later and considered in the previous sections. The "combined cohort" was assembled using all

individuals who participated in the health examination in 1980 (Lockey et al., 1984) and 2002−2005 (Rohs et al., 2008), and who were not exposed to asbestos from a source outside of the Marysville facility (see Table 5-3 and Appendix E for details). Due to differences in the 1980 x-ray evaluations compared with the 2002−2005 x-ray evaluations, an alternative critical effect of APT was used in the combined cohort modeling.

The modeling of the combined cohort is described in detail in Appendix E. A suite of model forms (univariate and bivariate) and exposure metrics (mean exposure, cumulative exposure, RTW exposure) were evaluated using the combined cohort of 434 individuals. Two models (Cumulative Normal Dichotomous Hill and Cumulative Normal Michaelis-Menten models), which incorporated TSFE into the plateau term rather than as an independent predictor alongside the exposure metric, were also evaluated as a supplement to the standard suite of models.

The results for the BMC and BMCL for the three endpoints (LPT—defined as LPT diagnosed in 2002−2005 and PT in 1980, APT, and ARC) are presented in Tables E-3, E-4, and E-5. Any pleural thickening is selected as the preferred endpoint for the alternative derivation of the reference concentration (RfC) for the combined cohort because the endpoint of APT is more inclusive (it includes those with LPT and those with DPT in the absence of LPT) and eliminates the uncertainty regarding the type of pleural thickening observed in the 1980 study (Lockey et al., 1984) using the 1971 ILO guidance. The two models selected for derivation of an RfC were (1) the same bivariate Dichotomous Hill model with fixed plateau used in the primary analysis based on TSFE and mean concentration and (2) the cumulative normal Dichotomous Hill model with fixed background rate of APT based on TSFE and CE. Additionally, in keeping with the primary analysis of the subcohort hired in 1972 or later, an analogous hybrid analysis of the subcohort based on the combined cohort was also conducted based on the two selected models. All of these results are presented at a value of TSFE = 70 years for those models that were able to reasonably extrapolate the TSFE value outside the observed range (47 years maximum) and for the median value of TSFE in the combine cohort (25 years) for models where the extrapolation to 70 years was not reasonable.

Following EPA practices and guidance (U.S. EPA, 2002, 1994b) 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 (UF_S) of 10 to account for the lack of information on people at risk for a complete lifetime (UF_S = 10). 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 5-10. The RfCs are rounded to one significant digit.

Table 5-10. (Copy of Table E-11) Reference concentrations (RfCs) for the alternative endpoint of any pleural thickening (APT) in the Marysville cohort with combined x-ray results from 1980 and 2002−2005 regardless of date of hire

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

Abbreviations: TSFE (time since first exposure), C (mean exposure), CE (cumulative exposure), CN DH (cumulative normal Dichotomous Hill), BV DH FP (bivariate Dichotomous Hill with fixed plateau).
[a]Hybrid model informed by the combined cohort; background rate of APT was fixed at 3% to facilitate model convergence.

For comparison, the above values all fall within approximately threefold when compared to the primary RfC for LPT of 9×10^{-5} fiber/cc derived in Section 5.2.3 from the Marysville workers who underwent health evaluations in 2002−2005 and were hired in 1972 or later. These results provide additional support to further substantiate the primary RfC.

5.2.6. Summary of Reference Concentration Values (RfCs) for the Different Health Endpoints and Different Sets of Workers in the Marysville Cohort

The primary derivation of the reference concentration is based on the critical effect of LPT in the Marysville workers who underwent health evaluations in 2002−2005 and were hired in 1972 or later. Multiple alternative values were derived using other health endpoints, other regression models, and other sets of workers from the Marysville cohort. The results of the different derivations are shown in Table 5-11. The range of values is from 3×10^{-5} fiber/cc to 2×10^{-4} fiber/cc.

Table 5-11. Multiple derivations of a reference concentration from the Marysville, OH cohort. Primary RfC value in bold.

Location	Study population	Health endpoint	Occupational LAA exposure	Residential LAA exposure	Occupational TSFE	Residential TSFE	Model	Exposure metrics	RfC	Section
Cohorts										
Libby, MT	Workers	LPT	Measured	Unknown	Measured	Unknown	---	---	---	5.2.1
Minneapolis, MN	Residents	LPT	---	Modeled	---	Unclear	---	---	---	5.2.1
Marysville, OH	Workers	LPT, APT, ARC	Measured ≥1972	---	Measured	---	---	---	---	5.2.1
RfC estimates										
Marysville, OH	**Hired ≥1972**	**LPT**	**Measured**	**None**	**Measured**	**---**	**Hybrid Rohs DH_{85}; TSFE = 28 yr**	**TSFE and C**	**9×10^{-5}**	**5.2.3**
Marysville, OH	Hired ≥1972	APT	Measured	None	Measured	---	Hybrid Rohs DH_{85}; TSFE = 28 yr	TSFE and C	9×10^{-5}	5.2.3.1
Marysville, OH	Hired ≥1972	ARC	Measured	None	Measured	---	Hybrid Rohs DH_{85}; TSFE = 28 yr	TSFE and C	9×10^{-5}	5.2.3.2
Marysville, OH	Hired ≥1972	LPT	Measured	None	Measured	---	Hybrid Rohs DH_{85}; TSFE = 28 yr	TSFE and CE	1×10^{-4}	5.2.4
Marysville, OH	All hires	APT	Measured ≥1972	None	Measured	---	Combined cohort CN DH; TSFE = 25 yr	TSFE and CE	1×10^{-4}	5.2.5 App. E
Marysville, OH	All hires	APT	Measured ≥1972	None	Measured	---	Combined cohort CN DH; TSFE = 25 yr	TSFE and C	2×10^{-4}	5.2.5 App. E
Marysville, OH	All hires	APT	Measured ≥1972	None	Measured	---	Hybrid combined cohort DH_{85}; TSFE = 25 yr	TSFE and CE	1×10^{-4}	5.2.5 App. E

Table 5-11. Multiple derivations of a reference concentration from the Marysville, OH cohort. Primary RfC value in bold. (continued)

Marysville, OH	All hires	APT	Measured ≥1972	None	Measured	---	Combined cohort CN DH; TSFE = 70 yr	TSFE and CE	3×10^{-5}	5.2.5 App. E
Marysville, OH	All hires	APT	Measured ≥1972	None	Measured	---	Hybrid combined cohort DH_{85}; TSFE = 70 yr	TSFE and CE	3×10^{-5}	5.2.5 App. E

Abbreviations: Health endpoint (LPT = localized pleural thickening, APT = any pleural thickening, ARC = any radiographic change).
Models (hybrid Rohs = 2-step model fit to full Rohs cohort then Rohs subcohort, hybrid combined cohort = 2-step model fit to combined cohort then to the Rohs subcohort, DH_{85} = Dichotomous Hill with plateau fixed at 85%, CN DH = cumulative normal Dichotomous Hill).
Exposure metrics (TSFE = time since first exposure, C = mean concentration, CE = cumulative exposure).

5.3. UNCERTAINTIES IN THE INHALATION REFERENCE CONCENTRATION (RFC)

Some sources of uncertainty remain in the derivation of the RfC. This section identifies the major sources of uncertainty and, where possible, uses a sensitivity analysis to evaluate the potential impact of these uncertainties on the point of departure.

5.3.1. Uncertainty in the Exposure Reconstruction

As in all epidemiologic studies, uncertainties are present in the exposure assessment. In this case, some uncertainty lies in the employment history, and some individuals had extensive overtime work. Employment history was self-reported during interviews with each individual for the original study (Lockey et al., 1984), and any errors in this process could affect the LAA exposure estimates. While the uncertainties related to a lack of quantitative measurements are not relevant to the analysis of workers hired in 1972 or later, it is important to recognize that exposure assessment post-1972 also has some limitations. The main source of uncertainty is incomplete exposure measurements for some of the occupations/tasks before industrial hygiene improvements that started about 1973 or 1974 and continued throughout the 1970s (see Appendix F, Figure F-1).

Some uncertainty exists when the Libby ore was first used in the facility. Company records indicated that the date was between 1957 and 1960, and the University of Cincinnati used the best available information from focus group interviews to assign 1959 as the year of the first usage of Libby vermiculite ore (see Appendix F). In 1957 and 1958, only vermiculite ore from South Carolina was thought to be used. From 1959 to 1971, vermiculite ores from both Libby, MT and South Carolina were used. From 1972 to 1980, vermiculite ores from Libby, MT, South Carolina, South Africa, and Virginia were used, with Libby vermiculite ore being the major source. Libby vermiculite ore was not used in the facility after 1980. However, industrial hygiene measurements (based on PCM) collected after 1980 showed low levels of fibers in the facility. PCM analysis does not determine the mineral/chemical make-up of the fiber and, thus, cannot distinguish among different kinds of asbestos.

Uncertainty also exists in the data regarding the asbestos content in other vermiculite ore sources before and after the Libby ore was used. As reported in Appendix C, EPA analysis of bulk vermiculite ores from Virginia and South Africa showed the presence of only a few or no amphibole asbestos fibers. The South Carolina vermiculite ore contained relatively more fibers than the Virginia and South African vermiculite ores but still far fewer fibers than the Libby vermiculite ore. Using the industrial hygiene data, the University of Cincinnati estimated that the fiber content of the South Carolina ore was about 8.7% of that of the Libby ore (see Appendix F). This result is consistent with data comparing South Carolina and Libby vermiculite ores from samples tested in 1982 (U.S. EPA, 2000a). Based on the industrial hygiene data, the concentration of fibers detected in the workplace was near background after

1980. The exposure distribution in Marysville workers is summarized in Table 5-12, which shows the mean, cumulative, and RTW exposure metrics for the full cohort of workers, the subset of those evaluated in 2002−2005, and the primary analytic group of workers evaluated in 2002−2005 and hired in 1972 or later. To evaluate the potential impact of assumptions regarding exposure after 1980 when the use of Libby vermiculite ores was considered to have ceased, EPA conducted a sensitivity analysis using the hybrid Dichotomous Hill model with plateau fixed at 85%, but truncating exposures at 12/31/1980 (see Table 5-13). Note that except where stated otherwise, this model (hybrid Dichotomous Hill model with plateau fixed at 85%) was used for all sensitivity analyses. Using the truncated exposures, the POD increased from 2.6×10^{-2} fiber/cc, to 3.9×10^{-2} fiber/cc. However, note that for the model with truncated exposures, the modeling in the larger group of workers evaluated in 2002−2005 showed a poor fit (Hosmer-Lemeshow GOF p-value <0.10). These results are included for comparative purposes but should be interpreted with caution.

Table 5-12. Exposure distribution among workers at the O.M. Scott plant in Marysville, OH

	All individuals evaluated in 1980 and/or in 2002–2005[a]		Individuals evaluated in 2002–2005		Individuals evaluated in 2002–2005, hired in 1972 or later	
Exposure metrics, based on arithmetic mean	**Mean (SD)**	**Median (25^{th}–75^{th} percentiles)**	**Mean (SD)**	**Median (25^{th}–75^{th} percentiles)**	**Mean (SD)**	**Median (25^{th}–75^{th} percentiles)**
Cumulative exposure, all yr (fibers/cc-yr)						
Arithmetic mean	7.9232 (17.9598) Range: 0.003–96.91	1.1252 (0.3414–3.7684)	8.75 (19.12) Range: 0.005–96.91	1.26 (0.51–5.20)	1.439 (2.5479) Range: 0.005–17.33	0.5048 (0.2188–1.5519)
Geometric mean	2.9258 (7.0248) Range: 0.001–37.73	0.2132 (0.1004–1.2635)	3.24 (7.48) Range: 0.002–37.73	0.29 (0.14–1.78)	0.4756 (0.8734) Range: 0.002–6.05	0.1785 (0.087–0.4632)
Mean exposure, all yr (fibers/cc)						
Arithmetic mean	0.3733 (0.7942) Range: 0.007–4.34	0.0566 (0.0267–0.2364)	0.31 (0.65) Range: 0.007–4.10	0.05 (0.02–0.20)	0.0716 (0.1239) Range: 0.007–0.77	0.0234 (0.0133–0.074)
Geometric mean	0.1366 (0.3101) Range: 0.003–1.70	0.0111 (0.0068–0.0719)	0.11 (0.25) Range: 0.003–1.59	0.01 (0.006–0.07)	0.0236 (0.0422) Range: 0.003–0.26	0.0085 (0.0062–0.0222)
Residence time-weighted exposure, all yr (fibers/cc-yr), calculated using midpoint of season dates						
Arithmetic mean	193.3093 (519.3874) Range: 0.0007–3,500.66	19.4767 (4.2550–78.0944)	294.38 (687.95) Range: 0.12–3,500.66	34.31 (11.07–154.36)	33.7415 (69.2231) Range: 0.12–474.01	10.2075 (3.9055–29.1246)
Geometric mean	72.2260 (204.1052) Range: 0.0003–1,373.22	4.1835 (0.9229–25.2179)	110.14 (270.86) Range: 0.05–1,373.22	6.24 (3.06–49.81)	11.1415 (24.2783) Range: 0.05–168.17	3.3526 (1.6814–8.5014)
Cumulative exposure, through 1980 (fibers/cc-yr)						
Arithmetic mean	7.6544 (17.8658) Range: 0.003–95.09	0.9708 (0.2120–3.3925)	8.27 (18.95) Range: 0.005–95.09	0.97 (0.22–4.65)	0.9638 (2.2774) Range: 0.005–15.37	0.212 (0.0564–0.5849)
Geometric mean	2.8324 (7.0007) Range: 0.001–37.20	0.1277 (0.0502–1.0805)	3.08 (7.43) Range: 0.002–37.20	0.13 (0.05–1.55)	0.3119 (0.8027) Range: 0.002–5.48	0.0478 (0.0244–0.1279)
Mean exposure, through 1980 (fibers/cc)						
Arithmetic mean	0.4863 (0.9568) Range: 0.008–4.34	0.0766 (0.0375–0.2950)	0.51 (0.98) Range: 0.008–4.33	0.07 (0.04–0.40)	0.1422 (0.2911) Range: 0.008–1.84	0.0352 (0.0193–0.1027)

Table 5-12. Exposure distribution among workers at the O.M. Scott plant in Marysville, OH (continued)

	All individuals evaluated in 1980 and/or in 2002−2005[a]		Individuals evaluated in 2002−2005		Individuals evaluated in 2002−2005, hired in 1972 or later	
Geometric mean	0.1767 (0.3732) Range: 0.003−1.70	0.0110 (0.0074−0.0968)	0.19 (0.38) Range: 0.003−1.68	0.01 (0.007−0.11)	0.0452 (0.1013) Range: 0.003−0.66	0.0102 (0.0063−0.0261)
Residence time-weighted exposure, through 1980 (fibers/cc-yr), calculated using midpoint of season dates						
Arithmetic mean	189.5463 (517.2418) Range: 0.0007−3,475.17	16.0931 (2.7315−69.9986)	287.78 (685.61) Range: 0.12−3,475.17	30.08 (6.07−137.64)	27.2008 (65.8222) Range: 0.12−448.51	5.9930 (1.4107−16.0968)
Geometric mean	70.9061 (203.4978) Range: 0.0003−1,365.69	2.4223 (0.6805−23.5698)	107.84 (270.24) Range: 0.05−1,365.69	4.05 (1.34−43.96)	8.8655 (23.3699) Range: 0.05−160.64	1.3228 (0.6124−3.6592)

[a]See Appendix E for details of how the individual health outcome data for all workers who participated in the Lockey et al. (1984) study and the follow-up study by Rohs et al. (2008) were combined.

Table 5-13. Effect of truncating exposures after 1980 and of using arithmetic or geometric mean to summarize multiple fiber measurements

	Exposures based on arithmetic mean—Primary Analysis		**Exposures based on arithmetic mean, truncated at 1980**	
	Primary	**Individuals with radiographs in 2002−2005 (to get beta for TSFE)**	**Primary**	**Individuals with radiographs in 2002−2005 (to get beta for TSFE)**
Hosmer-Lemeshow GOF *p*-value	0.73626	0.34206	0.63257	0.00790
Model AIC	75.5	242.7	78.0	244.6
Alpha (intercept)	−1.9798 (SE = 1.2270)	−3.4130 (SE = 1.1368)	−3.4612 (SE = 0.9790)	−4.14881 (SE = 1.4937)
Bkg (background)	0.03682 (SE = 0.04037)	0 (--)	0.0594 (SE = 0.0360)	0.0079 (SE = 0.0491)
Beta for TSFE	0.1075 (fixed)	0.1075 (SE = 0.0281), $p = 0.0002$	0.1167 (fixed)	0.1167 (SE = 0.0379), $p = 0.0023$
Beta for ln (mean exposure)	1.2750 (SE = 0.7159), $p = 0.0775$	0.4819 (SE = 0.1390), $p = 0.0006$	1.4054 (SE = 1.3328), $p = 0.2938$	0.4223 (SE = 0.1517), $p = 0.0058$
BMC and BMCL at 28 yr (fibers/cc)	0.0923 and 2.6×10^{-2}		0.2761 and 3.9×10^{-2}	
	Exposures based on geometric mean		**Exposures based on geometric mean, truncated at 1980**	
	Primary	**Individuals with radiographs in 2002−2005 (to get beta for TSFE)**	**Primary**	**Individuals with radiographs in 2002−2005 (to get beta for TSFE)**
Hosmer-Lemeshow GOF *p*-value	0.23188	0.07022	0.68399	0.02812
Model AIC	75.7	244.1	78.1	245.6
Alpha (intercept)	−1.0630 (SE = 1.9499)	−3.6638 (SE = 1.1191)	−2.4799 (SE = 1.9039)	−4.1735 (SE = 1.0727)
Bkg (background)	0.0367 (SE = 0.0461)	0 (--)	0.0578 (SE = 0.0401)	0 (--)
Beta for TSFE	0.1234 (fixed)	0.1234 (SE = 0.0276), $p < 0.0001$	0.1266 (fixed)	0.1266 (SE = 0.0276), $p < 0.0001$
Beta for ln (mean exposure)	1.2527 (SE = 0.7173), $p = 0.0833$	0.4012 (SE = 0.1213), $p = 0.0011$	1.2118 (SE = 1.0841), $p = 0.2659$	0.3256 (SE = 0.1015), $p = 0.0015$
BMC and BMCL at 28 yr (fibers/cc)	0.0298 and 9.1×10^{-3}		0.0796 and 9.9×10^{-3}	

Another potential source of uncertainty in the exposure reconstruction is the method used to average multiple fiber measurements for a given location (within the Marysville facility) and time period. The arithmetic mean of multiple measurements was used here, but an alternative approach would be to use the geometric mean, which has the effect of "dampening" outliers or extreme values. EPA conducted a sensitivity analysis for exposures estimated using the geometric mean of multiple fiber measurements and found that the PODs were lower than those estimated for the primary analysis (9.1×10^{-3} fiber/cc considering all years of exposure, and 9.9×10^{-3} fiber/cc if exposures were truncated after 1980) (see Table 5-13). The lower PODs are a result of the approximately threefold lower exposures estimated for each individual worker when using the geometric mean; in the Marysville workers evaluated in 2002−2005 and hired in 1972 or later, the median of each individual's mean exposure intensity estimated using the arithmetic versus the geometric mean of multiple fiber measurements in the plant were 0.0234 fiber/cc and 0.0085 fiber/cc, respectively. Note that for both models utilizing geometric mean exposures, the modeling in the larger group of workers evaluated in 2002−2005 showed poor fit (Hosmer-Lemeshow GOF p-value <0.10). These results are included for comparative purposes but should be interpreted with caution.

Potential coexposure to other chemicals was present in the Marysville facility (see Section 4.1.2.2.2). These other chemicals were used after expansion of vermiculite ore in another area of the facility. Industrial hygiene data showed very low levels of fibers in the areas where the additional chemicals were added to the expanded vermiculite. In addition, none of these chemicals are volatile. The most likely route of exposure to these chemicals is through dermal contact. It is unlikely that any coexposure to these particular chemicals would alter the exposure-response relationship of LAA in the respiratory system (see Section 4.1.2.2.2).

The University of Cincinnati research team assumed no exposure to LAA occurred outside of the workplace for the Marysville workers. The interviews with the Marysville workers revealed that about 10% of the workers reported bringing raw vermiculite home. These interviews also revealed that changing clothes before leaving the workplace was standard practice at the end of the shift, and approximately 64% of the workers showered before leaving the workplace. For these workers, it is likely that additional exposure outside the workplace was minimal. However, for the remainder of the workers, it is reasonable to assume that additional exposure could have occurred at home. Additional data collected by the University of Cincinnati research team document that no increased prevalence of pleural or parenchymal change consistent with asbestos exposure was observed in household contacts of the workers from the Marysville facility (Hilbert et al., 2013).

5.3.2. Uncertainty in the Radiographic Assessment of Localized Pleural Thickening (LPT)

The use of conventional radiographs to diagnose pleural thickening has several limitations. More severe and larger lesions are more reliably detected on radiographs. There are

also potential interferences. Fat pads may be mistaken for pleural plaques or LPT because they generally occur against the ribcage in a similar location (Gilmartin, 1979); this is one source of potential disagreement among x-ray readers. Often signs of trauma (e.g., fractured ribs) and radiographic signs of past tuberculosis infection can be seen and are noted by the reader. In these cases, LPT would not be diagnosed. There is a certain amount of subjectivity when viewing the x-rays in determining which features are representative of pleural thickening and whether signs of alternative etiology can be noted; thus, multiple certified readers are generally consulted, and a consensus of opinions determines the diagnosis. Regardless, the potential for outcome misclassification still exists. However, uncertainty in the presence or absence of localized pleural thickening in each individual is decreased by the use of three highly qualified chest radiologists evaluating the radiographic films and the use of the majority vote of the readers for the diagnosis.

BMI was investigated as a potential explanatory variable because fat pads can sometimes be misdiagnosed as pleural thickening. The effect of such outcome misclassification would be to attenuate the observed association between exposure and outcome. In the Marysville data, BMI was not measured in the 1980 examination but was available for most participants of the 2000s examination (available for most of those in the data sets used to derive the RfC). To address whether fat deposits may affect outcome classification, EPA considered the effect of adding BMI as a covariate in the model. However, BMI did not display an association with odds of localized pleural thickening in this population ($p = 0.6933$).

5.3.3. Uncertainty Due to Potential Confounding

Along with the effect of BMI, other covariates were also evaluated for potential confounding of the association between LAA exposure and LPT in the Marysville workers (see Section 5.2.2.6.1). Covariates included both demographic characteristics (gender, smoking status, BMI) as well as potentially exposure-related factors (hire year, job tenure, exposure duration, and age at x-ray).

Smoking is a particularly important variable to consider when evaluating respiratory health outcomes. Although data are mixed, a few studies suggest smoking may affect the risk of developing asbestos-related pleural thickening or timing of such pleural thickening development. However, no studies were identified that assessed the relationship between LPT specifically and any measure of smoking status. Plaques as defined in earlier ILO classification systems have not been associated with smoking in asbestos-exposed workers (Mastrangelo et al., 2009; Paris et al., 2009; Koskinen et al., 1998).

Some evidence indicates that small interstitial opacities (asbestosis) and asbestos-related DPT may be associated with smoking. Studies among populations exposed to other general types of asbestos have reported mixed effects on the impact of smoking on risk of radiographic abnormalities; two studies reported a significant association between risk of all pleural

thickening, including both pleural plaques and DPT (McMillan et al., 1980), or any pleural abnormality (Welch et al., 2007) and smoking after controlling for some measure of asbestos exposure. A larger number of studies reported borderline associations when examining risk of pleural changes (Adgate et al., 2011; Paris et al., 2008; Dement et al., 2003; Zitting et al., 1996; Yano et al., 1993; Lilis et al., 1991; Baker et al., 1985) or no association with smoking (Soulat et al., 1999; Neri et al., 1996; Ehrlich et al., 1992; Delclos et al., 1990; Rosenstock et al., 1988). Possible reasons for the different findings include varying quality of smoking information (some used categories of ever/never or former/current/never, while others used pack-years) and differences in the specific outcome studied.

Rohs et al. (2008) did not find a difference in smoking prevalence among those with and without any radiographic changes but also did not report results controlling for LAA exposure, or for LPT specifically.

None of the potential confounding factors examined were significantly associated with LPT after controlling for LAA exposure in the primary data set of workers evaluated in 2002−2005 and hired in 1972 or later. However, the effect of each covariate was reexamined in the primary (hybrid) model which utilized information from the larger set of workers evaluated in 2002−2005, regardless of hire date (see Table 5-14). Each covariate was included (one at a time) in the primary model, and the statistical significance and effect on the model parameters evaluated. None were statistically significantly related to risk of LPT, with *p*-values for the corresponding beta coefficients ranging from 0.1533 (gender) to 0.9858 (hire year). Note that because these main effects were not statistically significantly associated with LPT, they would not be expected to modify the association between LAA exposure (controlling for TSFE) and LPT. It is unlikely that there would be opposing effects for exposure and the covariates examined that would "cancel each other out" and mask true effect measure modification. Thus, effect modification was not considered to be an issue in these analyses. It is not surprising that the time-related factors were not statistically significant (and had little effect on the estimated beta coefficient for exposure) because these factors were highly correlated with TSFE (which was already included in the primary model). The effect of exposure was higher when including gender and smoking status (current, ex- or never smoker) and lower when including ever-smoker status and BMI. Although the effect of gender was not significant, there were relatively few women in the Marysville workers population (n = 16 in the workers evaluated in 2002−2005, and n = 13 in the subgroup hired in 1972 or later). In the primary analytic group, the prevalence of LPT was not very different by gender, but the comparison is limited by sample size—there was 1 woman among the total of 13 with LPT (prevalence of 7.7%), while the other 12 cases (including the individual with LPT and DPT) were among the 106 men (prevalence of 11.3%). However, women also tended to have lower LAA exposure in this study population—for example, median cumulative exposure was 0.17 (interquartile range: 0.05, 0.26) fiber/cc-yr among women, compared with 0.56 (interquartile range: 0.23, 1.78) fibers/cc-yr among

men—which could explain the lower prevalence. Larson et al. (2012a) found that among Libby workers (93.2% of whom were male), the prevalence of LPT was 37% among men and 9% among the 23 women included in the study, but exposure levels by gender were not provided in the published report. In the Minneapolis community study, the prevalence of all pleural abnormalities was 16.5% among men, compared to 4.6% among women [adjusted odds ratio and 95% confidence interval of 3.8 (1.6, 8.9); (Alexander et al., 2012)], but again, exposure levels by gender were not reported. Thus, the potential for different effects by gender merits further investigation.

In the Marysville workers, the variables representing smoking history (either current versus ex- versus never smoker, or ever smoker versus never smoker) were not statistically significant. However, the limited sample size (only three cases were never smokers) and limited nature of the smoking information precluded further analysis of smoking; thus, further research is needed on the effect of smoking in relation to LPT risk among asbestos-exposed populations.

Table 5-14. Effect of including covariates into the final model

	Primary analysis	**Including gender**	**Including ever smoker status**	**Including smoking status (compared to never smoker)**	**Including BMI**
Hosmer-Lemeshow GOF *p*-value	0.73625	0.72137	0.43468	0.88918	0.95082
Model AIC	75.5	75.0	76.1	78.5	60.7†
Alpha (intercept)	−1.9798 (SE = 1.2270)	4.8281 (SE = 5.1146)	−2.8954 (SE = 1.2344)	1.2111 (SE = 4.0064)	−3.0224 (SE = 2.1693)
Bkg (background)	0.03682 (SE = 0.04037)	0.0603 (SE = 0.0258)	0.0212 (SE = 0.0246)	0.0677 (SE = 0.0262)	0 (--)
Beta for TSFE	0.1075 (fixed)	0.1075 (fixed)	0.1075 (fixed)	0.1075 (fixed)	0.1075 (fixed)
Beta for ln (mean exposure)	1.2750 (SE = 0.7159), *p* = 0.0775	2.8080 (SE = 1.5440), *p* = 0.0715	1.1182 (SE = 0.4558), *p* = 0.0156	3.6756 (SE = 2.6246), *p* = 0.1640	0.9723 (SE = 0.3583), *p* = 0.0079
Beta for covariate	--	−5.0804 (SE = 3.5349), *p* = 0.1533	1.1701 (SE = 0.9993), *p* = 0.2440	Ex-smoker: −2.2659 (SE = 2.9748), *p* = 0.4477 Current smoker: 2.2180 (SE = 2.7013), *p* = 0.4132	0.0238 (SE = 0.0600), *p* = 0.6933
		Including hire yr	**Including job tenure (yr)**	**Including exposure duration (yr)**	**Including age at x-ray (yr)**
Hosmer-Lemeshow GOF *p*-value		0.73619	0.46477	0.70317	0.41903
Model AIC		77.5	77.2	77.4	77.3
Alpha (intercept)		−2.0004 (SE = 0.0006)	−1.2689 (SE = 1.9188)	−1.5075 (SE = 1.9288)	0.4511 (SE = 8.4602)
Bkg (background)		0.0368 (SE = 0.0404)	0.0350 (SE = 0.0426)	0.0368 (SE = 0.0421)	0.0437 (SE = 0.0558)
Beta for TSFE		0.1075 (fixed)	0.1075 (fixed)	0.1075 (fixed)	0.1075 (fixed)
Beta for ln (mean exposure)		1.2757 (SE = 0.7175), *p* = 0.0779	1.2498 (SE = 0.6919), *p* = 0.0734	1.2747 (SE = 0.7179), *p* = 0.0784	1.4362 (SE = 1.2550), *p* = 0.2548
Beta for covariate		0.00001 (SE = 0.0006), *p* = 0.9858	−0.0358 (SE = 0.0665), *p* = 0.5914	−0.0234 (SE = 0.0681), *p* = 0.7321	−0.0422 (SE = 0.1391), *p* = 0.7621

5.3.4. Uncertainty Due to Time Since First Exposure (TSFE)

Some uncertainty is associated with the length of follow-up of the Marysville cohort. There was relatively little variation in TSFE among the workers evaluated in 2002−2005 and hired in 1972 or later. It is anticipated that the prevalence of localized pleural thickening in the study population will likely continue to increase with passage of time. However, EPA took that into account both in modeling and in its application of uncertainty factors. EPA utilized information from the broader group of workers evaluated in 2002−2005 (i.e., regardless of hire date) and with a wider range of TSFE, to estimate the effect of time. However, because even this larger group lacked information on full lifetime exposure (maximum TSFE of 47 years), the modeling approach may not accurately reflect the exposure-response relationship that would be seen with a longer follow-up time. As one approach to gauge the sensitivity of the model, the plateau parameter—representing theoretical maximum prevalence of LPT when both exposure and TSFE are very large—was investigated further (see Table 5-15). As described above, the plateau parameter for the primary modeling was fixed at a literature-derived value of 85% (Järvholm, 1992; Lilis et al., 1991). The sensitivity of the POD to this assumption was investigated by looking at two alternative fixed values, 70 and 100% (i.e., the log-logistic model), as well as estimating the plateau parameter from the data. The value of 70% was selected for sensitivity analysis because in a cross-sectional study of Libby workers and residents seen at a clinic in Libby, Winters et al. (2012) observed a prevalence of 72% for pleural thickening, although the maximum TSFE was not known. Note that for the model with estimated rather than fixed plateau, the modeling in the larger group of workers evaluated in 2002−2005 showed poor fit (Hosmer-Lemeshow GOF p-value <0.10); these results are included for comparative purposes but should be interpreted with caution.

Table 5-15. Effect of different assumptions for the plateau parameter

	Primary	Individuals with radiographs in 2002−2005 (to get beta for TSFE)	Primary	Individuals with radiographs in 2002−2005 (to get beta for TSFE)
	Plateau fixed at 85%—Primary analysis		Plateau fixed at 100% (log-logistic model)	
Hosmer-Lemeshow GOF *p*-value	0.73626	0.34206	0.74177	0.13912
Model AIC	75.5	242.7	75.3	243.3
Plateau	0.85 (fixed)	0.85 (fixed)	1.0 (fixed)	1.0 (fixed)
Alpha (intercept)	−1.9798 (SE = 1.2270)	−3.4130 (SE = 1.1368)	−2.0260 (SE = 1.0437)	−3.5167 (SE = 1.0092)
Bkg (background)	0.03682 (SE = 0.04037)	0 (--)	0.0359 (SE = 0.0403)	0 (--)
Beta for TSFE	0.1075 (fixed)	0.1075 (SE = 0.0281), *p* = 0.0002	0.0969 (fixed)	0.0969 (SE = 0.0245), *p* = 0.0001
Beta for ln (mean exposure)	1.2750 (SE = 0.7159), *p* = 0.0775	0.4819 (SE = 0.1390), *p* = 0.0006	1.2109 (SE = 0.6454), *p* = 0.0631	0.4007 (SE = 0.1093), *p* = 0.0003
BMC/BMCL at 28 yr (fibers/cc)	$0.0923/2.6 \times 10^{-2}$		$0.0924/2.6 \times 10^{-2}$	
	Plateau fixed at 70%		Plateau estimated from the Marysville data rather than fixed	
Hosmer-Lemeshow GOF *p*-value	0.72544	0.26136	0.73285	0.07394
Model AIC	75.7	242.4	77.5	244.3
Plateau	0.70 (fixed)	0.70 (fixed)	1 (--)	0.6263 (SE = 0.2611)
Alpha (intercept)	−2.0159 (SE = 1.5078)	−3.2410 (SE = 1.5622)	−3.5258 (SE = 1.0451)	−3.2538 (SE = 1.8317)
Bkg (background)	0.0378 (SE = 0.0407)	0.0027 (SE = 0.0386)	0.0385 (SE = 0.0401)	0.0130 (SE = 0.0483)
Beta for TSFE	0.1247 (fixed)	0.1247 (SE = 0.0417), *p* = 0.0060	0.1458 (fixed)	0.1458 (SE = 0.1087), *p* = 0.1812
Beta for ln (mean exposure)	1.3610 (SE = 0.8225), *p* = 0.1006	0.6385 (SE = 0.2474), *p* = 0.0104	1.2073 (SE = 0.6537), *p* = 0.0673	0.8311 (SE = 0.9541), *p* = 0.3845
BMC/BMCL at 28 yr (fibers/cc)	$0.0920/2.7 \times 10^{-2}$		$0.1022/3.0 \times 10^{-2}$	

The effects on the POD resulting from different assumptions regarding the plateau were small. When assuming different fixed values (70, 85, and 100%) the POD only ranged from 2.6×10^{-2} to 2.7×10^{-2} fiber/cc. Estimating the plateau from the data led to a slightly higher POD of 3.0×10^{-2} fiber/cc. These results lend confidence that assumptions regarding maximum prevalence of LPT in the population do not have a substantial impact on the estimated POD.

As described in Section 5.2.2.6.1, one option to incorporate TSFE would be to utilize the RTW exposure metric, which incorporates aspects of both exposure duration and TSFE. This option was not selected for RfC derivation due to the narrow range of TSFE among the primary analytic group of Marysville workers who underwent health evaluations in 2002−2005 and whose job start date was on or after 1/1/1972. However, this approach was used as a sensitivity analysis, estimating the concentration that, if experienced over 70 years, would yield the BMR. The model with RTW as the metric derives as its POD a "benchmark residence time-weighted" quantity in units of fibers/cc-yr^2 and its associated confidence interval. In order to convert the benchmark quantity in units of fibers/cc-yr^2 and its associated lower limit into a 70-year exposure concentration (in units of fibers/cc), the constant 70-year concentration yielding that RTW should be determined where 70 years is both the duration and the time elapsed between the first year of exposure and the health evaluation. That concentration is equal to the benchmark RTW (or its lower limit) divided by the residence time-weighted value for exposures across 70 years: 1+….+70 = [(70 × 71 years)/2], as sum of first N natural numbers is equal to $[N \times (N + 1)]/2$. The results of using RTW exposure with the preferred model (Dichotomous Hill with plateau fixed at 85%) are shown in Table 5-16. For comparison, results also using the RTW exposure metric but using alternate model forms are also shown; the model fits and results are very similar for the Dichotomous Hill, log-logistic, and log-probit models, with the PODs all ~0.003 fiber/cc for a scenario of 70-years exposure duration and 70-years TSFE. The Michaelis-Menten model provided a lower AIC (2 units lower than the Dichotomous Hill model), and the POD was slightly higher (0.0057 versus 0.0034 fiber/cc).

Table 5-16. Exposure-response modeling for any localized pleural thickening (LPT) in the Marysville workers who underwent health evaluations in 2002−2005 and whose job start date was on or after 1/1/1972 (*n* = 119), using a benchmark response (BMR) of 10% extra risk of any LPT, and RTW exposure

	Dichotomous Hill, plateau = 85%	Michaelis-Menten	Log-logistic	Log-probit
Hosmer-Lemeshow GOF *p*-value	0.7527	0.7528	0.7576	0.7548
AIC	76.8	74.8	77.0	76.8
Intercept (SE)	−5.9883 (2.5304)	−5.4305 (0.5333)	−5.7331 (2.0944)	−3.2071 (1.0398)
Background rate (SE)	0.0366 (0.0338)	0.0320 (0.0271)	0.0342 (0.0331)	0.0370 (0.0321)
B (SE), *p*-value	1.1266 (0.5493), 0.0425	--	1.0073 (0.4394), 0.0236	0.5546 (0.2264), 0.0158
Benchmark RTW (fibers/cc-yr^2)	34.2516	30.6380	33.4520	32.2062
Benchmark RTW lower limit (fibers/cc-yr^2)	8.32733	14.2184	7.50156	9.39139
BMC for TSFE = 28 yr (fibers/cc)[a]	0.08436	0.075463	0.082394	0.079326
BMCL for TSFE = 28 yr (fibers/cc)[a]	0.020511	0.035021	0.018477	0.023132

[a]BMCs and BMCLs are expressed in fibers/cc, and are estimated as benchmark value or its lower limit divided by [(70 × 71)/2] yr^2 or divided by [(28 × 29)/2] yr^2.

Advantages of this approach using the RTW exposure metric in the subcohort are that it relies solely on the individuals with higher quality exposure information and consistent radiograph evaluation, and uses an exposure metric that weights more heavily exposure occurring in the more distant past. However, the modeling still relies solely on the subgroup of workers with little variation in TSFE, and whose TSFE values are for less than a full lifetime. This lack of variability in TSFE limits the ability to explore how risk of LPT varies across the life span. However, it does provide an important comparison for the primary RfC; the BMCLs estimated using this approach range from 0.018 to 0.035 fiber/cc, similar to the BMCL estimated in the primary analysis (0.026 fiber/cc).

Another source of information regarding TSFE comes from the study by Larson et al. (2010a) which examined serial radiographs conducted on a group of Libby vermiculite workers

with pleural or parenchymal changes. The mean follow-up time was 21.6 years, with a maximum of 44.9 years. They found that among those workers with localized pleural thickening, all cases were identified within 30 years, and that the median time from hire to the first detection of localized pleural thickening was 8.6 years. Although the retrospective evaluation of radiographs is a different and more sensitive procedure, these findings indicate that the range of follow-up time in the Marysville subcohort is likely sufficient to support the exposure-response modeling developed in this current assessment. Note that the likelihood that prevalence of localized pleural thickening is expected to increase over the life span is a principal rationale cited for the selection of a subchronic-to-chronic UF of 10 in this current assessment.

5.3.5. Uncertainty in the Endpoint Definition

The critical effect selected for RfC derivation is localized pleural thickening. As a sensitivity analysis, an alternative critical effect of any radiographic change was also investigated and found to yield an essentially identical POD (i.e., a BMCL of 2.7×10^{-2}, compared with 2.6×10^{-2} in the primary analysis), as that using the same modeling approach in the primary analysis. Almost no information existed on radiographic changes other than LPT in the primary analytic group of workers (evaluated in 2002−2005, hired in 1972 or later) because only one case of DPT was reported and that individual also had LPT. No individuals had interstitial changes. However, some individuals had DPT and/or interstitial changes (with and without LPT) in the larger group of workers evaluated in 2002−2005, which allowed investigation of the effect of TSFE considering alternative endpoint definitions.

The primary analysis contrasted individuals with LPT (with or without other radiographic endpoints) to those without any radiographic changes. In the group of workers evaluated in 2002−2005, this had the effect of excluding five individuals with DPT and/or interstitial changes, but without LPT. In the subgroup of workers hired in 1972 or later, this distinction had no effect because the single case of DPT also had LPT (and thus was included as a case), and no individuals showed interstitial changes. As a sensitivity analysis, the modeling procedure was repeated, using three alternative endpoint definitions (see Table 5-17). The first contrasts all those with LPT (with or without other endpoints) to those without LPT. Thus, the comparison group could include those with DPT and/or interstitial changes but without LPT. The second model used an endpoint of "any radiographic change." The third sensitivity model contrasted those with LPT only to those with no radiographic abnormalities. Note that for two of the alternative models (those contrasting LPT with no LPT, and any radiographic change with no radiographic change) the modeling in the larger group of workers evaluated in 2002−2005 showed poor fits (Hosmer-Lemeshow GOF p-values <0.10); these results are included for comparative purposes, but should be interpreted with caution.

Table 5-17. Effect of using different case/noncase definitions

	LPT vs. no radiographic abnormalities—primary analysis		**LPT vs. no LPT**		**Any radiographic abnormality vs. no radiographic abnormalities**		**LPT alone vs. no radiographic abnormalities**		**Any pleural thickening vs. no radiographic abnormalities**	
	All individuals with radiographs in 2002−2005 (*n* = 247)	PRIMARY (hired ≥1972, *n* = 119)	All individuals with radiographs in 2002−2005 (*n* = 252)	PRIMARY (hired ≥1972, *n* = 119)	All individuals with radiographs in 2002−2005 (*n* = 252)	PRIMARY (hired ≥1972, *n* = 119)	All individuals with radiographs in 2002−2005 (*n* = 237)	PRIMARY (hired ≥1972, *n* = 118)	All individuals with radiographs in 2002−2005 (*n* = 237)	PRIMARY (hired ≥1972, *n* = 118)
Hosmer-Lemeshow GOF *p*-value	0.34206	0.73626	0.05378	0.73640	0.09052	0.73552	0.18854	0.73497	0.10716	0.73565
AIC	242.7	75.5	249.9	75.5	250.0	75.5	230.9	74.1	247.0	75.5
Alpha (intercept)	−3.4130 (SE = 1.1368)	−1.9798 (SE = 1.2270)	−3.4421 (SE = 1.1192)	−1.8537 (SE = 1.2275)	−3.4126 (SE = 1.1376)	−2.1027 (SE = 1.2268)	−3.7837 (SE = 1.1633)	−2.2944 (SE = 1.1804)	−3.4334 (SE = 1.1347)	−2.0812 (SE = 1.2268)
Bkg (background)	0 (--)	0.03682 (SE = 0.04037)	0 (--)	0.03669 (SE = 0.04038)	0 (--)	0.03697 (SE = 0.04037)	0 (--)	0.0341 (SE = 0.0409)	0 (--)	0.03694 (SE = 0.04037)
Beta for TSFE	0.1075 (SE = 0.0281), *p* = 0.0002	0.1075 (fixed)	0.1034 (SE = 0.0275), *p* = 0.0002	0. 1034 (fixed)	0.1115 (SE = 0.0282), *p* = 0.0001	0. 1115 (fixed)	0.1056 (SE = 0.0282), *p* = 0.0002	0.1056 (fixed)	0.1108 (SE = 0.0282), *p* = 0.0001	0.1108 (fixed)
Beta for ln(mean exposure)	0.4819 (SE = 0.1390), *p* = 0.0006	1.2750 (SE = 0.7159), *p* = 0.0775	0.4342 (SE = 0.1324), *p* = 0.0012	1.2764 (SE = 0.7161), *p* = 0.0772	0.5125 (SE = 0.1415), *p* = 0.0004	1. 2739 (SE = 0.7160), *p* = 0.0778	0.3507 (SE = 0.1404), *p* = 0.0132	1.1247 (SE = 0.6467), *p* = 0.0846	0.5042 (SE = 0.1409), *p* = 0.0004	1.2741 (SE = 0.7160), *p* = 0.0777
BMC/BMCL at 28 yr (fibers/cc)	--	0.0923/ 2.6×10^{-2} (Ratio = 3.5)	--	0.0918/ 2.6×10^{-2} (Ratio = 3.5)	--	0.0929/ 2.7×10^{-2} (Ratio = 3.5)	--	0.0931/ 2.5×10^{-2} (Ratio = 3.8)	--	0.0928/ 2.7×10^{-2} (Ratio = 3.4)

The effect of TSFE in these sensitivity analyses using different endpoint definitions was very similar to that in the primary model and led to nearly identical PODs (2.5 to 2.7 × 10^{-2} fiber/cc). These results lend confidence to the primary analysis.

Additionally, EPA conducted a sensitivity analysis using a multinomial model to incorporate information from all outcome groups. The multinomial logistic model is similar to the logistic model and compares each outcome group to the referent group (i.e., no radiographic change) and estimates separate model parameters (intercepts and beta coefficients) for each comparison. With only two outcome groups, the logistic and multinomial models are equivalent. As described earlier, there were noticeable differences when contrasting individuals who had LPT alone, with those who had LPT along with DPT and/or interstitial changes. Thus, two different multinomial models were considered. In the first, the outcome groups were (1) no radiographic change (referent), (2) any LPT (with or without other radiographic changes), and (3) DPT and/or interstitial changes (without LPT) (see Table 5-18). In the second model, the outcome groups were defined as (1) no radiographic change (referent), (2) LPT alone, (3) LPT along with other radiographic changes, and (4) DPT and/or interstitial changes (without LPT). Each of these was contrasted to a logistic model, which is equivalent except that those with DPT and/or interstitial changes without LPT are excluded (i.e., as was done for the primary analysis).

Table 5-18. Exposure-response modeling for any localized pleural thickening (LPT) in the Marysville workers who underwent health evaluations in 2002−2005 (*n* = 252), comparing the multinomial model and logistic model with different outcome group definitions[a]

	Logistic	Multinomial Model 1	Multinomial Model 2
Pearson GOF *p*-value	0.5170	0.9653	0.9999
AIC[b]	249.6	299.3	348.5
$Alpha_1$ (intercept)	−5.1351 (SE = 0.8638)	−5.1980 (SE = 0.8695)	−5.3174 (SE = 0.8946)
$Alpha_2$ (intercept)	--	−8.4598 (SE = 2.9194)	−7.4075 (SE = 2.4490)
$Alpha_3$ (intercept)	--	--	−8.3324 (SE = 2.9481)
$Beta_1$ for mean exposure	0.5878 (SE = 0.2596), *p* = 0.0236	0.5914 (SE = 0.2595), *p* = 0.0225	0.3208 (SE = 0.2957), *p* = 0.2779
$Beta_2$ for mean exposure	--	0.9443 (SE = 0.4625), *p* = 0.0412	1.5242 (SE = 0.4097), *p* = 0.0002
$Beta_3$ for mean exposure	--	--	1.0483 (SE = 0.4988), *p* = 0.0356
$Beta_1$ for TSFE	0.1103 (SE = 0.0237), *p* <0.0001	0.1120 (SE = 0.0239), *p* <0.0001	0.1144 (SE = 0.0245), *p* <0.0001
$Beta_2$ for TSFE—DPT/interstitial changes vs. no change	--	0.1221 (SE = 0.0753), *p* = 0.1050	0.0958 (SE = 0.0651), *p* = 0.1413
$Beta_3$ for TSFE	--	--	0.1173 (SE = 0.0768), *p* = 0.1266

[a]The multinomial model is a generalized form of the logistic regression for >2 outcome categories (not ordered). The model is of the form

$$p_i(x,t) = 11 + \exp[-a_i - b_i \times x - c_i \times t]$$

Where p_i is the probability of being in the i^{th} outcome group, and separate intercepts (a) and beta coefficients (b, c) are estimated for effect of predictors on probability of being in each group. Multinomial Model 1 contrasts no radiographic change (referent, Group 0) to those with any LPT (Group 1) and to those with DPT and/or interstitial changes but without LPT (Group 2). Multinomial Model 2 contrasts no radiographic change (referent, Group 0) to those with LPT alone (Group 1), to those with LPT along with DPT and/or interstitial changes (Group 2), and to those with DPT and/or interstitial changes but without LPT (Group 3).

[b]AIC not comparable between multinomial model and logistic model because the number of individuals is different (multinomial, *n* = 252 compared to logistic, *n* = 247).

The effect of TSFE was very similar across all the models and outcome groups, with the corresponding beta coefficent ranging from 0.0958 to 0.1221 (compared to 0.1075 in the primary analysis). The effect of mean exposure was much more variable, and the corresponding beta coefficients were notably higher for those with DPT and/or interstitial changes (either alone or along with LPT) compared to those for LPT alone. These results are in accordance with the descriptive statistics shown in Table 5-4, which highlighted that while exposure patterns were different among outcome groups, there was relatively less variation in TSFE. These results lend confidence to the effect of TSFE used in the primary analysis.

5.3.6. Summary of Sensitivity Analyses

EPA conducted numerous sensitivity analyses for comparison with the primary analysis used to derive the RfC.[22] These included analyses to explore the effect of exposure assessment decisions (e.g., use of the cumulative exposure metric, truncation of exposures post-1980, and use of arithmetic versus the geometric mean for exposure reconstruction); potential confounding factors (time-related and nontime-related); the effect of TSFE (e.g., assumptions regarding the plateau and use of the RTW exposure metric); and the definition of cases and noncases (e.g., varying case/noncase groups, use of the multinomial model). The results of other sensitivity analyses are summarized in Table 5-19. In each case, the estimated BMCL was within an order of magnitude of the POD. The biggest impacts came from using cumulative exposure (rather than mean exposure), truncating exposures after 1980, and using the geometric mean versus the arithmetic mean for exposure reconstruction (differences of −68 to +50% from the POD). Assumptions regarding the plateau parameter (or estimating the plateau rather than fixing its value) had a very small effect on the BMCL (differences of 0 to +5% from the POD). Similarly, small differences in case and noncase definition led to small changes in the BMCL (differences of −3.9 to +3.9%). Finally, the use of RTW exposure alone (rather than mean exposure and TSFE) as the predictor in the subset of workers evaluated in 2002−2005 and hired in 1972 or later, led to a difference of −19.2% in the BMCL.

[22]The primary analysis used a hybrid Dichotomous Hill model with plateau fixed at 85%, with mean exposure as the exposure metric. The effect of TSFE was estimated in the set of Marysville workers evaluated in 2002−2005, and carried over to the modeling performed in the subset of these workers who were hired in 1972 or later. The BMCL was estimated for a TSFE of 28 years, which served as the POD for RfC derivation. A composite UF of 300 was applied to account for various sources of uncertainty, leading to an RfC of 9×10^{-5} fiber/cc.

Table 5-19. Summary of sensitivity analyses. Exposure-response modeling performed using mean exposure in the hybrid Dichotomous Hill model with plateau fixed at 85%, Marysville workers who underwent health evaluations in 2002−2005 and whose job start date was on or after 1/1/1972 (*n* = 119). Effect of TSFE estimated in workers evaluated in 2002−2005 regardless of hire date.

Sensitivity analysis	BMC/BMCL at 28 yr (fibers/cc)	Percentage difference in BMCL from primary analysis[a] [(sensitivity analysis-primary)/primary] × 100
Primary modeling	$0.0923/2.6 \times 10^{-2}$	--
Use of cumulative exposure rather than mean exposure	$0.0266/8.2 \times 10^{-3*}$	−68.46
Exposures based on arithmetic mean, truncated at 1980	$0.2761/3.9 \times 10^{-2}$	+50.00
Exposures based on geometric mean	$0.0298/9.1 \times 10^{-3}$	−65.00
Exposures based on geometric mean, truncated at 1980	$0.0796/9.9 \times 10^{-3}$	−61.92
Plateau fixed at 70%	$0.0920/2.7 \times 10^{-2}$	+3.85
Plateau fixed at 100%	$0.0924/2.6 \times 10^{-2}$	0.00
Plateau estimated	$0.1022/3.0 \times 10^{-2}$	+15.38
Contrast any LPT vs. no LPT	$0.0918/2.6 \times 10^{-2}$	0.00
Contrast any radiographic change vs. no radiographic change	$0.0929/2.7 \times 10^{-2}$	+3.85
Contrast LPT only vs. no radiographic change	$0.0931/2.5 \times 10^{-2}$	−3.85
Alternative modeling using RTW exposure in the subgroup of workers evaluated in 2002−2005, hired in 1972 or later	$0.0844/2.1 \times 10^{-2}$	−19.23

[a]The BMC and BMCL are 1.8622 and 0.5770 fibers/cc-yr, respectively. These values were divided by 70 yr to obtain the BMC and BMCL in terms of fiber/cc.

Multiple statistical model forms applied to different sets and subsets of the principal study population all yield results within less than an order of magnitude around the BMCL. Each of these sensitivity analyses further substantiates the BMCL used to derive the RfC.

5.4. CANCER EXPOSURE-RESPONSE ASSESSMENT

5.4.1. Overview of Methodological Approach

The inhalation unit risk (IUR) is defined as an upper-bound excess lifetime cancer risk estimated to result from continuous exposure to an agent at a concentration of 1 µg/L in water, or 1 µg/m^3 in air. However, current health standards for asbestos are based on health effects

observed in occupational cohorts and are given in fibers/cc of air as counted by PCM (OSHA, 1994; U.S. EPA, 1988a). Thus, when examining the available health effects data on cancer for LAA, the best available studies at this time report exposure concentration in terms of fibers/cc counted by PCM (see Section 4.1.4). The cancer effects identified in populations with exposure to LAA (see Section 4.1.4) are cancer mortality from mesothelioma and lung cancer (see Section 5.4.2.2 for other cancers identified in populations exposed to asbestos in general). Therefore, the IUR represents the upper-bound excess lifetime risk of mortality from either mesothelioma or lung cancer in the general U.S. population from chronic inhalation exposure to LAA at a concentration of 1 fiber/cc of air.

IURs are based on human data when appropriate epidemiologic studies are available. The general approach to developing an IUR from human epidemiologic data is to first quantitatively evaluate the exposure-response relationship (slope) for that agent in the studied population. For the current assessment, the first step was to identify the most appropriate data set available to quantitatively estimate the effects of LAA exposure on cancer mortality. Once the relevant data describing a well-defined group of individuals along with their exposures and health outcomes were selected (see Section 5.4.2), an appropriate statistical model form (i.e., Poisson or Cox) was selected that adequately fit the specific nature of the data, and then each person's individual-level exposures were modeled using a variety of possible exposure metrics informed by the epidemiologic literature. Exposure-response modeling was conducted for each cancer mortality endpoint individually (see Section 5.4.3). In some cases, the statistical model forms and the specific metrics of exposure used for each cancer endpoint may have been different. For example, the 1988 EPA general asbestos assessment found different model forms/metrics for mesothelioma and lung cancer. Appropriate covariates, which may be important predictors of cancer mortality, were included in the statistical models. These models were then evaluated to assess how the different exposure metric representing estimated occupational exposures fit the observed epidemiologic data. The empirical model fits were compared against those models suggested by the epidemiologic literature before selecting one model for mesothelioma mortality and one for lung cancer mortality.

The selected cancer exposure-response relationships (slopes) for mesothelioma (KM) and lung cancer (KL), which were estimated from the epidemiologic data on the Libby workers cohort, were then applied to the general U.S. population in a life-table analysis using age-specific mortality statistics to determine the exposure level that would be expected to result in a specified level of response over a lifetime of continuous exposure. EPA typically selects a response level of 1% extra risk because this response level is generally near the low end of the observable range for such data. Extra risk is defined as equaling $(R_x - R_o) \div (1 - R_o)$, where R_x here is the lifetime cancer mortality risk in the exposed population and R_o is the lifetime cancer mortality risk in an unexposed population (i.e., the background risk). In the case of lung cancer, the expected lifetime risk of lung cancer mortality in the unexposed general U.S. population is approximately

5%; thus, this human health assessment seeks to estimate the level of exposure to LAA that would be expected to result in a 1% extra lifetime risk of lung cancer mortality equivalent to a lifetime risk of lung cancer mortality of 5.95%: [(0.0595 − 0.05) ÷ (1 − 0.05) = 0.01]. This corresponds to a relative risk (R_x/R_o) of about 1.2, which is near the low end of the observable range for most epidemiologic studies of cancer. For mesothelioma mortality, an absolute risk was considered, rather than extra risk, for two reasons: (1) mesothelioma is very rare in the general population and (2) mesothelioma is almost exclusively caused by exposure to asbestos and other mineral fibers, including LAA. Because the background rate of mesothelioma is negligible, absolute risk models of exposure-response were considered more appropriate than relative risk models, thereby justifying the definition of the target response rate in absolute terms rather than in relative terms.

A life-table analysis (see Appendix G for details) was used to compute the 95% lower bound on the level of LAA at which a lifetime exposure corresponds to a 1% extra risk of lung cancer mortality (1% absolute risk for mesothelioma) in the general U.S. population using age-specific mortality statistics and the exposure-response relationships for each cancer endpoint as estimated in the Libby worker cohort. This lower bound on the level of exposure serves as the POD for extrapolation to lower exposures and for deriving the unit risk. Details of this analysis are presented in Section 5.4.5. Cancer-specific unit risk estimates were obtained by dividing the extra risk (1%) by the POD. The cancer-specific unit risk estimates for mortality from either mesothelioma or lung cancer were then statistically combined to derive the final IUR (see Section 5.4.5.3). Uncertainties in this cancer assessment are described in detail in Section 5.4.6.

5.4.2. Choice of Study/Data—with Rationale and Justification

This human health assessment is specific to LAA. The current assessment does not seek to evaluate quantitative exposure-response data on cancer risks from studies of asbestos that did not originate in Libby, MT. However, this assessment does draw upon the exposure-response models developed for other kinds of amphibole asbestos, as described in the epidemiologic literature, to address uncertainty in model selection.

The available sources of cancer data include the cohort of workers employed at the vermiculite mining and milling operation in and around Libby, MT. This cohort has been the subject of several epidemiologic analyses of cancer risks, described in detail in Section 4.1.4 (Larson et al., 2010b; Moolgavkar et al., 2010; Sullivan, 2007; Amandus and Wheeler, 1987; McDonald et al., 1986a). There have also been published reports on cases of mesothelioma in the Libby, MT area (Whitehouse et al., 2008) and mortality data published by the ATSDR (2000). However, published mortality data on Libby, MT residents (Whitehouse et al., 2008; ATSDR, 2000) could not be used in exposure-response modeling due to lack of quantitative exposure data.

The most appropriate available data set with quantitative exposure data for deriving quantitative cancer mortality risk estimates based on LAA exposure in humans is the cohort of workers employed at the vermiculite mining and milling operation in and around Libby, MT (hereafter referred to as the Libby worker cohort). These data are considered the most appropriate to inform this human health assessment for several reasons: (1) these workers were directly exposed to LAA, (2) detailed work histories and job-specific exposure estimates are available to reconstruct estimates of each individual's occupational exposure experience, (3) the cohort is sufficiently large and has been followed for a sufficiently long period of time for cancer to develop (i.e., cancer incidence) and cause mortality, and (4) the broad range of exposure experiences in this cohort provided an information-rich data set, which allowed evaluation of several different metrics, or mathematical expressions, of exposure. Uncertainties in these data are discussed in Section 5.4.6.

The only other available epidemiology study cohort exposed to LAA was the cohort of workers from a Marysville, Ohio vermiculite processing plant [see Section 4.1.1.2; (Rohs et al., 2008; Lockey et al., 1984)]. The study of pleural changes in this population was the basis of the noncancer exposure-response analyses (see Section 5.3). Regarding mortality among the Marysville workers, Dunning et al. (2012) reported two mesothelioma deaths and 16 lung cancer deaths. The Libby worker cohort was a more suitable candidate for cancer exposure-response modeling than the Marysville worker cohort due to the larger number of cases (see Table 5-3 compared to Tables 5-20 and 5-22).

5.4.2.1. *Description of the Libby Worker Cohort*

Cancer mortality in the Libby worker cohort has been extensively studied (see Section 4.1.4). McDonald et al. (2004), McDonald et al. (2002), and McDonald et al. (1986a) published three studies on a subset of the cohort. Scientists from NIOSH conducted two epidemiologic investigations, resulting in several published reports on different subsets of the cohort (Sullivan, 2007; Amandus et al., 1988; Amandus and Wheeler, 1987). Berman and Crump (2008) published analysis of data lagged 10 years (provided by Sullivan). Moolgavkar et al. (2010) reanalyzed the Sullivan (2007) data with mortality follow-up through 2001. Larson et al. (2010b) analyzed an ATSDR reconstruction of the Libby worker cohort from company records with exposure estimates obtained from NIOSH for each job title with mortality follow-up through 2006.

According to Sullivan (2007), nearly all of these study subjects were workers on-site at the Libby, MT vermiculite mine, mill, or processing plant. Although the mine and other facilities were several miles from downtown Libby, MT, some of the study subjects worked at vermiculite ore expansion plants, at the Export Plant, or at offices in the town (see Section 4.1.1.2). Workers may have also been assigned jobs as truck drivers or jobs working in the screening plant, railroad loading dock, expansion plants, or an office. Individuals'

demographic and work history data were abstracted from company personnel and pay records. A database created by NIOSH in the 1980s contained demographic data and work history starting from September 1935 and vital status at the end of 1981 for 1,881 workers. NIOSH compared these data with company records on microfilm, and work history data were reabstracted to ensure data quality. One person was removed from the cohort because company records stated that he was hired but never worked (Sullivan, 2007). Nine workers with Social Security numbers listed in company records were excluded because demographic and work history data were not available, leaving 1,871 workers in the cohort available for epidemiologic analysis. Table 5-20 shows the demographic, mortality, and exposure characteristics of this cohort (with follow-up to 2006).

Table 5-20. Demographic, mortality, and exposure characteristics of the Libby worker cohort

Characteristic	All workers
Number of workers	1,871
Number of deaths from all causes	1,009
Number of deaths from mesothelioma	18
Number of deaths from lung cancer	111
Number of deaths from laryngeal cancer	2
Number of deaths from ovarian cancer	0
Number of deaths from intestinal or colorectal cancer	15
Number of deaths from chronic obstructive pulmonary disease	71
Mean yr of birth	1929
Mean yr of hire	1959
Mean age at hire (yr)	30.2
Mean person-yr of follow-up (no lag)	35.9
Total person-yr of follow-up (no lag)	67,101
Mean employment duration (yr)	2.6
Mean cumulative exposure (fibers/cc-yr)	96.0
Median cumulative exposure (fibers/cc-yr)	9.8
Range of cumulative exposures (no lag) (fibers/cc-yr)[a]	0−1,722

[a]According to the work histories and JEM, there were 26 workers who had zero exposure. These individuals (7 men and 19 women) all worked at the office downtown.

NIOSH updated the cohort vital status through 2006 using the National Death Index [NDI (Bilgrad, 1999)] and these data were used for this analysis. Workers known to be alive on or after January 1, 1979 (the date NDI began tracking deaths nationwide), but not found in the NDI search, were assumed to have been alive on December 31, 2006 (Sullivan, 2007). Nearly 54% of workers in the cohort (n = 1,009) had died by December 31, 2006. NIOSH researchers obtained death certificates from across the United States (while exposure occurred in and around Libby, deaths could have occurred elsewhere) for deaths prior to 1979, and the causes of death were coded to the ICD revision that was in effect at the time of death by a single National Center for Health Statistics-trained nosologist. After 1979, ICD codes were obtained from the NDI-Plus. For workers known to be deceased, the underlying cause of death was determined from death certificates and coded to the ICD codes using the rubrics of the ICD revision in effect at the time of death [ICD-5 (WHO, 1938), ICD-6 (WHO, 1948), ICD-7 (WHO, 1957), ICD-8 (WHO, 1967), ICD-9 (WHO, 1977), or ICD-10 (WHO, 1992)].

Basic demographic information on the occupational cohort members was largely complete. However, when data were missing, they were statistically imputed (i.e., estimated) by NIOSH based on several reasonable assumptions regarding gender, race, and date of birth. For example, seven workers with unknown gender were assumed to be male because 96% of the workforce was male, and NIOSH's review of names did not challenge that assumption (Sullivan, 2007). Workers of unknown race (n = 935) were assumed to be white because workers at this facility were known to be primarily white, and U.S. Census Bureau data from 2004 indicate that 95% of the local population identify themselves as white (Sullivan, 2007). Date of birth was estimated for four workers with unknown birth dates by subtracting the cohort's mean age at hire from the worker's hire date. The impact of this imputation procedure on the analytic results can reasonably be expected to be minimal.

5.4.2.2. *Description of Cancer Endpoints*

The cancer exposure-response assessment focuses on two cancer endpoints, mesothelioma and lung cancer, although there is evidence that other cancer endpoints may also be associated with exposure to asbestos in general. The IARC has concluded that sufficient evidence in humans is present that other types of asbestos (chrysotile, crocidolite, amosite, tremolite, actinolite, and anthophyllite) are causally associated with mesothelioma and lung cancer, as well as cancer of the larynx and the ovary (Straif et al., 2009). Among the entire Libby worker cohort, only two deaths were found to be due to laryngeal cancer, and no deaths from ovarian cancer occurred among the 84 female workers. Therefore, EPA did not evaluate these other outcomes as part of this current assessment. The limited number of female workers in this cohort is discussed later as a source of uncertainty in the derived estimates (see Section 5.4.6).

The endpoint for both mesothelioma and lung cancer was mortality, not incidence. Incidence data are not available for the Libby worker cohort. Nevertheless, mortality rates approximate incidence rates for cancers such as lung cancer and mesothelioma because the survival time between cancer incidence and cancer mortality is short. According to the National Cancer Institute's Surveillance Epidemiology and End Results (SEER) data on cancer incidence, mortality, and survival (Howlader et al., 2013), the median length of survival with mesothelioma is less than 1 year, with 2-year survival for males about 20%, and 5-year survival for males about 6%. For lung cancer, the median length of survival is less than 1 year, with 2-year survival for males about 25% and 5-year survival for males about 17%. Therefore, while the absolute rates of cancer mortality at follow-up may underestimate the rates of cancer incidence, it is considered to be unlikely that such discrepancies would be of significant magnitude. The use of mortality statistics instead of incidence statistics as a source of uncertainty in the derived estimates is further discussed in Section 5.4.6.

It is well established in the literature that mortality rates calculated from death certificates are lower than true mortality rates due to lung cancer and, to a larger degree, mesothelioma. These discrepancies are due mainly to misdiagnoses and imperfect sensitivity of the coding system. Lung cancer sensitivity[23] ranged from 86% in an asbestos-exposed cohort (Selikoff and Seidman, 1992), to 95% in the general population (Percy et al., 1981); mesothelioma sensitivity ranges from 40% for ICD-9 (Selikoff and Seidman, 1992) to about 80% for ICD-10 (Camidge et al., 2006; Pinheiro et al., 2004). This underestimation of the true mortality rate results in a lower estimated risk compared with that which would be estimated based on the true rate. EPA modeled the risk of mesothelioma mortality using an absolute risk model, while the risk of lung cancer mortality is modeled using a relative risk model. The underestimation of risk is much more pronounced for the absolute risk model (mesothelioma) than for the relative risk model (lung cancer). For the relative risk model, misdiagnosis rates would need to be different with respect to exposure levels, and this is unlikely among the Libby workers that were included in the lung cancer analysis because nosologists are blinded to exposure levels when coding lung cancer as a cause of death. Therefore, EPA considered use of a procedure to adjust risks for mesothelioma underascertainment (see Section 5.4.5.1.1) ―but not for lung cancer.

Mesothelioma did not have a distinct ICD code prior to introduction of the 10th revision (ICD-10), which although released in 1992, was not implemented in United States until 1999. Death certificates from 1940 to 1978 were reviewed by the NIOSH principal investigator (Sullivan, 2007) to identify any mention of mesothelioma on the death certificate, as is the standard procedure for assessing mesothelioma mortality and has been used in other analyses of Libby worker cohort mesothelioma mortality (Larson et al., 2010b; McDonald et al., 2004). For deaths in the Libby worker cohort occurring from 1979 to 1998, death certificates were obtained

[23]Sensitivity is measured by the percentage of actual lung cancer deaths that are detected.

if the NDI identified the cause of death as one of the possible mesothelioma codes identified by Marsh et al. (2001), as respiratory cancer, nonmalignant respiratory disease, digestive cancer, or unspecified cancer. For deaths in the Libby worker cohort that occurred after 1998, the ICD-10 code for mesothelioma was used. In total, 18 mesothelioma deaths were identified by NIOSH using the methods of Sullivan (2007), which serve as the basis for this current assessment; 19 mesothelioma deaths were identified by Larson et al. (2010b) for the same cohort from all death certificates rather than from death certificates with one of the specifically targeted set of causes of death identified above in Sullivan (2007).

Whitehouse et al. (2008) identified four mesothelioma cases among workers that, as the authors suggested, were not included in the Sullivan (2007) study with mortality follow-up through 2001; no other information was provided. Three mesothelioma cases from these four were most likely accounted for during the update of the NIOSH cohort from 2001 to 2006, which serves as the basis for this current assessment. Whitehouse et al. (2008) also provided detailed information on 11 residential cases, but this information could not be used in exposure-response analyses for this current assessment because there is no quantitative exposure information for these cases and no information defining or enumerating the population from which these cases arose.

Lung cancer mortality was based on the underlying cause of death identified by the ICD code on death certificates according to the ICD version in use at the time of death. Based on these different ICD codes, lung cancer mortality included malignant neoplasms of the trachea, bronchus, and lung, and was identified by the following codes: ICD-5 code "047" (excluding "47c, Cancer of unspecified respiratory organs"), ICD-6 codes "162" or "163," ICD-7 codes "162.0" or "163" (excluding "162.2, Cancer of the pleura"), ICD-8 and ICD-9 code "162," and ICD-10 codes "C33" or "C34." In all, there were 111 deaths with an underlying cause attributed to lung cancer. All deaths after 1960 were coded as bronchus or lung because the ICD versions in use at that time distinguished malignant neoplasms of the trachea as distinct from neoplasms of the bronchus and lung. Other investigators of this cohort have used slightly different definitions of lung cancer or used different follow-up periods, as described in Section 4.1.1.1 (Studies of Libby, MT Vermiculite Mining and Milling Operations Workers).

5.4.2.3. *Description of Libby Worker Cohort Work Histories*

NIOSH staff abstracted demographic data and work history data from company personnel and payroll records. An individual's work history was determined from job change slips, which recorded any new job assignment, date of change, and change in hourly pay rate (which differed by the job assignment). Work history records span the time period from September 1935 to May 1982. Dates of termination were unknown for 58 of 640 workers (9%) who left employment before September 1953. EPA adopted the assumption used by NIOSH (Sullivan, 2007) that these people worked for 384 days, based on the mean duration of employment among all workers

with known termination dates before September 1953. The majority of workers in this cohort as a whole and those hired on or after January 1, 1960 worked at multiple jobs; many of the workers switched jobs repeatedly, and the changes in exposures associated with changes in job is accounted for through the use of the job- and time-specific JEM described in the following section.

5.4.2.4. *Description of Libby Amphibole Asbestos Exposures*

The operations at the mine and in and around Libby, the conditions of exposure, and the job-specific estimates of exposure intensity have been thoroughly described in Section 4.1 (Sullivan, 2007; Amandus et al., 1987b; McDonald et al., 1986a). Briefly, miners extracted vermiculite ore from an open-pit mine that operated on Zonolite Mountain outside the town of Libby, MT. The ore was processed locally in a dry mill (1935−1974) and/or two wet mills (1950−1974 and 1974–1990). The resulting concentrate was transported by railroad to processing plants around the United States where the vermiculite was expanded for use in loose-fill attic insulation, gardening, and other products (see Section 2.1). EPA adopted the JEM developed and used by Sullivan (2007), which was in turn based on that used in the earlier NIOSH study for jobs through 1982 (Amandus et al., 1987b; Amandus and Wheeler, 1987). As discussed in more detail in Section 4.1, Amandus et al. (1987b) defined 25 location operations in the Libby facilities for which they estimated exposure intensity based on available information (see Table 5-21). A job category may have involved more than one location operation, and the 8-hour time-weighted average (TWA) exposure (8-hour TWA) for each job category in the JEM was calculated from the exposure intensity and time spent at each location operation (Amandus et al., 1987b).

Table 5-21. Exposure intensity (fibers/cc) for each location operation from the beginning of operations through 1982 [(Amandus et al., 1987b); Table VII]

Location operation	Yr									
	<1950	1950–59	1960–63	1964–67	1968–70	1971	1972–74	1975–76	1977–79	1980–82
Downtown office building	0	0	0	0	0	0	0	0	0	0
Bus ride	1.2	1.2	1.2	1.2	1.2	1.2	1.2	0	0	0
Mine office	1.0	1.0	1.0	1.0	1.0	1.0	1.0	0.5	0.5	0.5
Mine misc.	1.6	1.6	1.6	1.6	1.6	1.6	1.6	0.8	0.8	0.8
Mine—nondrilling	2.6	2.6	2.6	2.6	2.6	2.6	2.6	0.6	0.6	0.6
Transfer point	2.2	2.2	2.2	2.2	2.2	2.2	2.2	0.6	0.6	0.6
Quality control lab	13.1	13.1	13.1	2.6	2.6	2.6	2.6	0.6	0.6	0.6
Service area by mill	1.9	1.9	1.9	3.8	1.9	1.9	1.9	0.2	0.2	0.2
Dry mill	168.4	168.4	168.4	33.2	33.2	33.2	16.6	--	--	--
Dry mill sweeping	182.1	182.1	182.1	35.9	35.9	35.9	19	--	--	--
Old and new wet mill—millwright	--	7.0	7.0	7.0	7.0	7.0	7.0	0.6	0.6	0.6
Old wet mill—nonmillwright	--	3.7	3.7	3.7	3.7	3.7	3.7	--	--	--
New wet mill—nonmillwright	--	--	--	--	--	--	3.2	2.0	0.8	0.8
Skip area	88.3	88.3	88.3	17.4	17.4	17.4	4.8	0.6	0.6	0.6
Concentrate hauling	5.5	5.5	5.5	5.5	5.5	5.5	5.5	0.4	0.4	0.4
River station binside	21.2	21.2	21.2	21.2	21.2	21.2	21.2	0.7	0.7	0.7
River conveyor tunnel	112.5	112.5	112.5	112.5	112.5	112.5	112.5	0.3	0.3	0.3
River office binside	10.6	10.6	10.6	10.6	10.6	10.6	10.6	0.2	0.2	0.2
Verxite plant	22.6	22.6	2.8	2.8	2.8	--	--	--	--	--

Table 5-21. Exposure intensity (fibers/cc) for each location operation from the beginning of operations through 1982 [Amandus et al. (1987b); Table VII] (continued)

Location operation		Yr									
		<1950	1950–59	1960–63	1964–67	1968–70	1971	1972–74	1975–76	1977–79	1980–82
Tails belt		7.3	7.3	7.3	7.3	7.3	7.3	7.3	0.7	0.7	0.7
Screen plant		--	--	--	--	--	--	--	0.5	0.5	0.5
Drilling	High	23	23	23	23	9.2	9.2	9.2	0.6	0.6	0.6
	Low	6.7	6.7	6.7	6.7	6.7	9.2	9.2	0.6	0.6	0.6
Ore loading	High	82.5	27.7	10.7	10.7	3.2	3.2	3.2	0.2	0.2	0.2
	Low	24	15	9	9	3.2	3.2	3.2	0.2	0.2	0.2
River dock	High	116.9	42.5	17	17	17	5.1	5.1	0.5	0.5	0.5
	Low	38	19	6.4	6.4	5.1	5.1	5.1	0.5	0.5	0.5
Bagging plant	High	12.9	12.9	12.9	12.9	12.9	12.9	4.3	1.2	1.2	1.2
	Low	4.6	4.6	4.6	4.6	4.6	4.6	4.3	1.2	1.2	1.2

For the later data in Table 5-21 from 1967 through 1982, over 4,000 air samples analyzed for fibers by PCM analysis were available to inform the exposure intensity estimates for the 25 location operations. Therefore, the JEM for 1967−1982 is based on direct analytic measurements in air for each location operation (Amandus et al., 1987b). With the exception of two location operations in the dry mill, no air samples were available for other location operations at the mine and processing facilities before 1967. In order to estimate exposures that occurred before that time, the NIOSH researchers interviewed plant employees and based estimates of exposure intensities on known changes in operations over the years and professional judgments regarding the relative intensity of exposure. Exposure intensity for 23 of the 25 pre-1967 location operations was extrapolated from post-1967 measurements based on reasoned assumptions for each location operation (Amandus et al., 1987b).

In contrast to the exposure information available for 1967 through 1982, the amount and quality of measurement data in the facility in earlier years were much more limited (Amandus et al., 1987b). A total of 40 dust samples were taken, exclusively in the dry mill, over the years 1950−1964. Using these measurements, higher exposures were inferred to occur before 1964 than in later years.

Air samples collected by the State of Montana were available for the dry mill from 1956−1969, but at that time these were analyzed for total dust, not asbestos fibers. Total dust samples (collected by a midget impinger) were examined by light microscopy, but no distinction was made among mineral dusts, debris, and asbestos fibers. All objects were counted and reported in the units of million particles per cubic foot (mppcf). Amandus et al. (1987b) developed a range of conversion ratios between total dust and asbestos fiber counts based on the comparison of contemporaneous air sampling in the dry mill (see Section 4.1.1.2) and selected a conversion ratio of 4.0 fibers/cc per mppcf to estimate exposure intensity for two location operations in the dry mill for the years prior to 1967. Uncertainties in the selection of this conversion ratio are described in detail in Section 5.4.6.1.2.1.

The exposure intensity (fibers/cc) for each of the location operations (see Table 5-21) was used to calculate an estimate of daily occupational exposure for each job category in the JEM. In developing a job exposure estimate for a given 8-hour workday, the estimated exposure intensity at each location/operation was multiplied by the fraction of the day that someone in that job spent at that location/operation, at that point in time. If a job involved working in more than one location or operation, these estimates were summed over an 8-hour workday. The resulting JEM available for this current assessment and previous epidemiologic studies of the Libby worker cohort is based on the air concentration of fibers as enumerated by PCM, which measures fibers longer than 5 μm with an aspect ratio >3:1 [i.e., the fiber size regulated under the Occupational Safety & Health Administration [OSHA] standard (OSHA, 2006)]. Additionally, only fibers that are wide enough to be viewed on PCM can be detected with this method. Amandus et al. (1987b) considered fibers >0.44 μm in diameter to be visible by PCM in the

historical filter analysis. More recent techniques have refined the PCM method, and fibers greater than 0.25 μm in diameter are now considered PCM fibers (IPCS, 1986). Uncertainties related to difference in defining PCM fibers are discussed in Section 5.4.6.1.2.1.

Amandus et al. (1987b) recognized the uncertainty in the pre-1968 exposures estimates for the cohort. Although there is some uncertainty in the dust-to-fiber conversion, this conversion (4.0 fibers/cc per mppcf) was based on dust and fiber data contemporaneously collected in the dry mill and only applied to the dry mill environment. Amandus et al. (1987b) considered a range of possible conversion factors (1.2−11.5 fibers/cc per mppcf). Greater uncertainty may lie with the reasoned assumptions used to extrapolate exposures to the early decades for all location operations considered. For example, there were four location operations for which Amandus et al. (1987b) estimated a range of possible exposure intensities—drilling, ore loading, the river dock, and the bagging plant, where intensity of exposure may vary as much as threefold between the low and high estimates (see Table 5-21). Finally, some workers were employed after 1982 and up until 1993, when demolition of the facilities was completed (Larson et al., 2010b). These exposures were not evaluated by Sullivan (2007) and were not included in the NIOSH JEM. Because exposure concentrations in 1982 (see Table 5-21) were generally at or below 1.2 fibers/cc, it is unlikely that the overall cumulative exposures of this limited set of workers were significantly underestimated by not including exposures during this time. Uncertainties in all aspects of the JEM and the associated exposure assessment are described in Section 5.4.6.1.2.

There was one important limitation of the NIOSH work history data in assigning exposure levels for each job. In the earlier study (Amandus and Wheeler, 1987), workers with "common laborer" job assignments and some workers with unknown job assignments hired between 1935 and 1959 all received the same, relatively low exposure levels estimated for the mill yard (Sullivan, 2007). In addition, reabstracting work histories for the more recent study (Sullivan, 2007) identified several job assignments not mentioned in the earlier publications. Sullivan (2007) estimated exposure for the additional job and calendar time period-specific combinations based on professional experience and review of exposure records from earlier studies of the Libby worker cohort (Amandus et al., 1987b; Amandus and Wheeler, 1987; McDonald et al., 1986a). EPA found that of the 991 workers hired before 1960, 811 workers (82%) had at least one job with an unknown exposure assignment, with 706 (71%) listing neither job department nor job assignment. In the more recent study by Sullivan (2007), these workers' exposures were all estimated using the same TWA exposure intensity estimated for all jobs during that time period (66.5 fibers/cc). The lack of information on specific exposure information for such a large portion of these early workers, during the time period when exposures were higher, resulted in significant exposure misclassification and effectively yielded exposure estimates that were differentiated only by the duration of each worker's employment. Because of the lack of more specific measured fiber exposure data during this early period, EPA

experienced difficulties in identifying an adequate exposure-response model fit for the complete cohort including all hires. These difficulties are described in detail in Section 5.4.3.4. As a result, the IUR analyses were based on the subset of workers hired after 1959 (i.e., on or after January 1, 1960), totaling 880 workers (i.e., full cohort [*n* = 1,871] minus those hired before 1960 [*n* = 991]). Of these 880 workers hired after 1959, 28 (3%) workers had at least one job with an unknown job assignment with nine having all job and department assignments between 1960−1963 listed as unknown. As described in Sullivan (2007), NIOSH estimated that these workers had a TWA exposure intensity of 66.5 fibers/cc. Uncertainties in the exposure assessment for this subcohort are described in Section 5.4.6.1.2.4. While the Sullivan (2007) study was limited to the white male workers, EPA's analysis includes all workers regardless of race or gender. Table 5-22 shows the demographic, mortality, and exposure characteristics of the subcohort hired after 1959.

Table 5-22. Demographic, mortality, and exposure characteristics of the subset of the Libby worker subcohort hired after 1959

Characteristic	Subcohort hired after 1959
Number of workers	880
Number of deaths from all causes	230
Number of deaths from mesothelioma	7
Number of deaths from lung cancer	32
Number of deaths from laryngeal cancer	2
Number of deaths from ovarian cancer	0
Number of deaths from colorectal cancer	5
Number of deaths from chronic obstructive pulmonary disease	18
Mean yr of birth	1942
Mean yr of hire	1971
Mean age at hire (yr)	28.6
Mean person-yr of follow-up (no lag)	32.2
Total person-yr of follow-up (no lag)	28,354
Mean employment duration (yr)	2.4
Mean cumulative exposure (fibers/cc-yr)	19.2
Median cumulative exposure (fibers/cc-yr)	3.4
Range of cumulative exposures (no lag) (fibers/cc-yr)[a]	0−462

[a]According to the work histories and JEM, there were 21 subcohort workers who had zero cumulative exposure. These 21 individuals all worked at the office downtown.

Figure 5-5 shows a three-dimensional representation of the JEM used by Sullivan (2007) and in this cancer exposure-response assessment (note that the figure does not include all jobs and is meant to be illustrative rather than comprehensive). The three axes show the intensity of fiber exposure as an 8-hour TWA (fibers/cc, vertical axis) for selected job categories over time (horizontal axes). For several jobs, the estimated 8-hour TWA was greater than 100 fibers/cc for the decades prior to 1963.

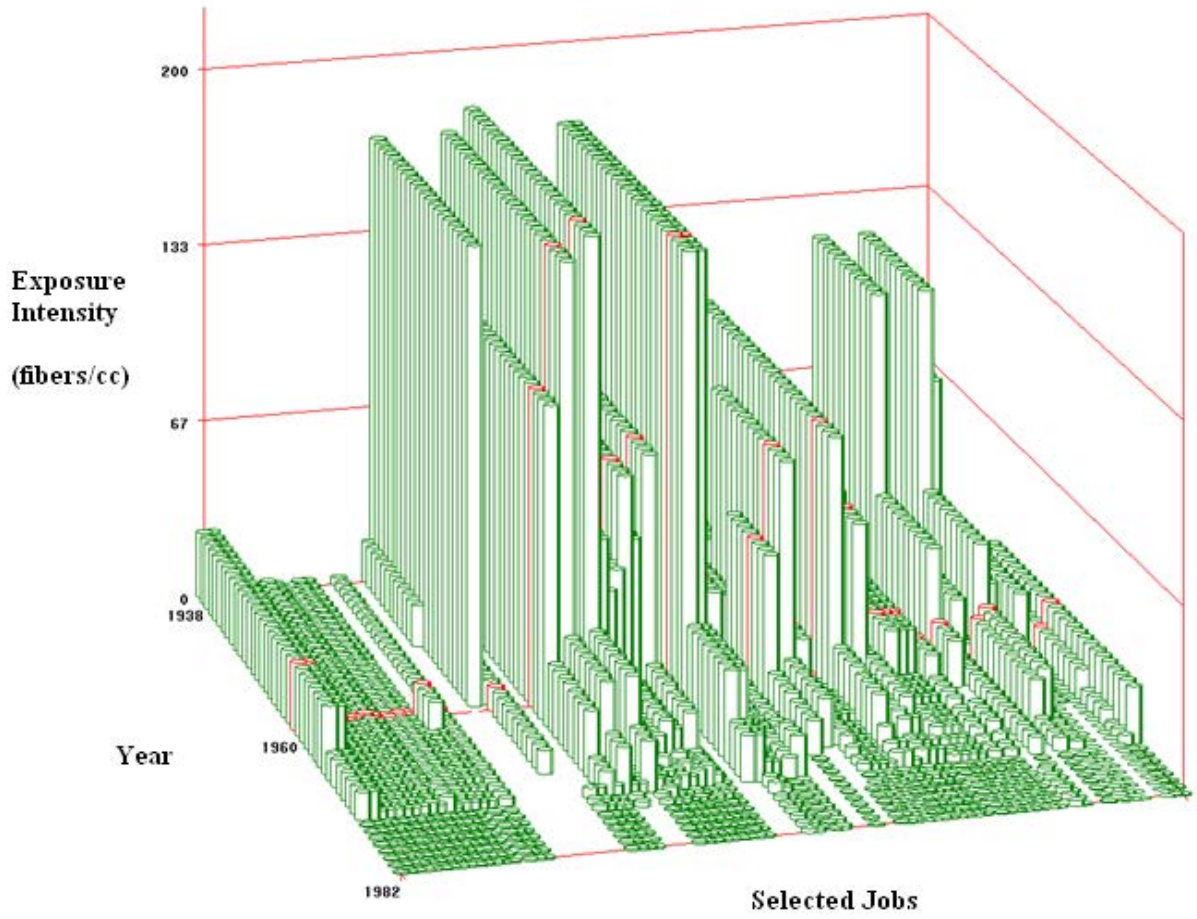


Figure 5-5. Plot of the National Institute for Occupational Safety and Health (NIOSH) job-exposure matrix for different job categories over time. The height of each bar represents the intensity of exposure as an 8-hour TWA (fibers/cc) for a job in a particular year. Each row for "Selected Jobs" represents a specific job category. The line at 1960 marks the beginning of jobs included in the subcohort of Libby workers used to derive the inhalation unit risk.

5.4.2.5. *Estimated Exposures Based on Job-Exposure Matrix (JEM) and Work Histories*

Exposure-response modeling of epidemiologic data is based on several considerations as summarized by Finkelstein (1985):

> After identification of an occupational hazard one of the goals of occupational epidemiology is to quantify the risks by determining the dose-response relations for the toxic agent. In many circumstances little is known about the dose received by target tissues; the data available usually pertain only to exposure to various concentrations of the toxic material in the workplace. The calculation of dose requires additional physiological and chemical information relating to absorption, distribution, biochemical reactions, retention, and clearance.
>
> In asbestos epidemiology the usual measure of exposure is the product of the concentration of asbestos dust in the air (fibers or particles per mL) and the duration of exposure to each concentration summed over the entire duration of exposure (years).

Cumulative exposure (CE) has been the traditional method of measuring exposure in epidemiologic analyses of many different occupational and environmental exposures and was the exposure metric applied to the risk of lung cancer mortality in the IRIS assessment for general asbestos (U.S. EPA, 1988a). That said, different health outcomes may be best described using different exposure metrics. The risk of mesothelioma mortality in the IRIS assessment for general asbestos (U.S. EPA, 1988a) used a different exposure metric based on a linear function of concentration added to a function of TSFE and duration of exposure. Additional exposure metrics were also assessed for both mesothelioma and lung cancer mortality risks.

Two alternative approaches to developing exposure metrics to describe the effects of concentrations of asbestos dust in the air on the risks of mortality have also been proposed. The first alternative was proposed by Jahr (1974), who studied silica-induced pneumoconiosis and suggested that exposures to occupational dusts could be weighted by the time since exposure. This yields an exposure metric that gives greater weight to earlier exposures. The second alternative was proposed by Berry et al. (1979) who subsequently suggested the application of exposure metrics that allowed for the clearance of dust or fibers by using a decay term on exposures.

For the evaluation of mortality risk from mesothelioma for general asbestos, U.S. EPA (1988a) used a different exposure metric than was used for lung cancer mortality, which factored in the TSFE. As observed in U.S. EPA (1988a), it is important to note that different characterizations of estimated occupational exposures may be reasonably expected to be associated with different endpoints.

Many studies have been limited in the availability of detailed exposure data—especially at the individual level. In the Libby worker cohort, detailed work histories were matched with job-specific exposure estimates, allowing for the reconstruction of each individual's estimated

occupational exposure over time. The individual-level data were developed based on a uniform estimate of exposure in a given job during a given point in time multiplied by individual-level data on duration. From this information-rich, individual-level data set from NIOSH, EPA constructed a suite of the different metrics of occupational exposure which had been proposed in the asbestos literature or used in the IRIS asbestos assessment (U.S. EPA, 1988a). This suite of metrics was defined a priori to encompass a reasonable set of proposed exposure metrics to allow sufficient flexibility in model fit to these data. The types of exposure metrics evaluated were intended to allow for more or less weight to be placed on earlier or later exposures. These simulated exposure metrics were derived mathematically to approximate underlying processes that are not well understood (see Section 5.4.6). Thus, the empirical fit of various exposure metrics to the observed epidemiologic data is evaluated statistically, and the exposure metrics have epidemiological interpretation but do not necessarily have direct biological interpretations.

The first exposure metric—CE—is a simple addition of each day's exposure across time (see eq 5-7). CE has been widely used in modeling risk of cancer in occupational epidemiology and has been used for modeling lung cancer (Larson et al., 2010b; Moolgavkar et al., 2010; Berman and Crump, 2008; Sullivan, 2007; McDonald et al., 2004) and mesothelioma (McDonald et al., 2004) in the Libby worker cohort. When using this exposure metric in the risk model, all exposures (other than for years removed from consideration based on a lag assumption) have equal weight regardless of when they occurred and lead to the same estimated cancer risk whether exposure happened early or later in life.

EPA calculated each individual's occupational CE to LAA over time from their date of hire until the date they ceased to be employed in the Libby operations or until the date NIOSH collected the work history data for those still employed in May 1982. Workers were assumed to remain at their CE on the last day of work until death or the end of the follow-up period on December 31, 2006. Each worker's CE at any time point (daily increment) since their date of hire was computed as the sum of their exposure intensity (fibers/cc) on each specific occupational day (x_t) from Day 1 through Day k. Mathematically, this was defined as

$$\text{CE at time } t_k = \sum_{j=1}^{k} x_{t_j} \qquad (5\text{-}7)$$

Where

x_{t_j} = the estimated job-specific exposure intensity for the day t_j, and

t_k = the day on which the exposure is estimated.

A second exposure metric—RTW exposure—gives additional weight to early exposures. By doing so, the RTW exposure metric allows the possibility that early exposures are more influential on cancer mortality predictions in the model. Unlike many chemicals that are rapidly

metabolized in the body and excreted, asbestos fibers are durable, and some remain in the body for years. Fibers that remain in the lung may continue to damage lung cells and tissue unless they are removed or cleared (see Section 3.2). Similarly, fibers that translocate to the pleura may damage cells as long as they remain in this tissue. Therefore, a fiber exposure may not only damage tissue during the initial exposure, but fibers may remain in these tissues, with tissue fiber concentration as well as cellular and tissue damage accumulating over time. While this represents a biological point of view, in an epidemiologic context in which the exposure is ambient fiber concentration and the event of interest is simply a cause of death (rather than survival time), it is uncertain what metrics of exposure might fit the observed data and could be considered most appropriate, so EPA considered several.

The RTW exposure metric in this current assessment is sometimes called the cumulative burden, or the area under the curve. A type of RTW metric was proposed for modeling of mesothelioma mortality by Newhouse and Berry (1976) based on a general understanding of the relationship between tumor incidence rate and time to cancer (Cook et al., 1969) as well as animal models of mesothelioma (Berry and Wagner, 1969).

A similar type of RTW metric was proposed in Peto (1978) and was subsequently applied by Peto et al. (1982), discussed by Finkelstein (1985), and applied in the derivation of the IUR in the 1988 IRIS assessment for asbestos (U.S. EPA, 1988a). McDonald et al. (2004) and Moolgavkar et al. (2010) used RTW-type metrics for modeling mesothelioma in the Libby worker cohort, and McDonald et al. (2004) applied an RTW metric for modeling lung cancer mortality in the Libby worker cohort.

In calculating RTW, each day's exposure is multiplied by the time since exposure occurred up to the time t_k when RTW is estimated (see eq 5-8). The intent of RTW CE is to allow for earlier exposures to contribute greater weight.

$$\text{RTW CE at time } t_k = \sum_{j=1}^{k} x_{t_j} \times (t_k - t_j) \qquad (5\text{-}8)$$

Where

x_{t_j} = the estimated job-specific exposure intensity for the day t_j, and

t_k = the day k on which the exposure is estimated.

The CE and RTW exposure metrics result in sustained or increasing metrics of exposure across time. However, some cellular and genetic damage can be repaired over time after exposure, decreasing the cancer risk from exposure over time. Additionally, asbestos fibers are cleared (removed) from the lung through natural processes and translocated to other tissues (see

Section 3.2.1.1). Therefore, when considering lung cancer, it is possible that removal of asbestos fibers from the lung could reduce lung cancer risk over time. Although less is known about removal of asbestos from the pleura, clearance mechanisms may be operative in that tissue as well (see Section 3.2.1.2). As noted earlier, Berry et al. (1979) proposed the use of exposure metrics which addressed the issue of clearance through a mathematical decay term that modified estimated occupational exposures. For mesothelioma, modeling a decay term on exposure has been proposed by Berry (1999). Based on this proposal, several studies applied a decay term to modeling mesothelioma mortality (Berry et al., 2009; Reid et al., 2009; Barone-Adesi et al., 2008; Gasparrini et al., 2008; Clements et al., 2007; Hodgson et al., 2005; Berry et al., 2004). Similarly, publications indicate that the relative risk of lung cancer due to asbestos exposure declines 15−20 years after the cessation of exposure to asbestos (Magnani et al., 2008; Hauptmann et al., 2002).

Mathematically allowing for the magnitude of earlier exposures to diminish with advancing time was considered to be a method of giving less weight in the analyses to earlier exposures compared to the previous two exposure metrics. Therefore, two additional exposure metrics were considered, in which a decay rate was applied to the CE and RTW exposure metrics (see eq 5-9 and 5-10).

For each exposure metric, the application of a half-life was calculated by depreciating each time interval's (t_{j-1}; t_j) exposure according to a model of exponential decay with various half-lives ($T_{1/2}$) of 5, 10, 15, and 20 years. Note that the particular kinetics of LAA fibers are not fully understood, and the relevance of these particular half-lives was determined from the statistical fit of these exposure metrics to the risk of cancer mortality, rather than the biological half-life of the fibers. For a very large half-life, decay is very slow, and these metrics would be very similar to the CE and RTW exposure metrics.

$$\text{CE with half-life at time } t_k = \sum_{j=1}^{k}\left\{ x_{t_j} \times \exp\left[\frac{\ln(0.5)\times(t_k - t_j)}{T_{1/2}}\right]\right\} \qquad (5\text{-}9)$$

Where

x_{t_j} = the estimated job-specific exposure intensity for the day t_j,

t_k = the day k on which the exposure is estimated, and

$T_{1/2}$ = half-life of 5, 10, 15 or 20 years.

$$\text{RTW with half-life at time } t_k = \sum_{j=1}^{k}\left\{ x_{t_j} \times (t_k - t_j) \times \exp\left[\frac{\ln(0.5)\times(t_k - t_j)}{T_{1/2}}\right]\right\} \qquad (5\text{-}10)$$

In addition to the considerations described above for selecting metrics to represent estimated ambient exposure to LAA for use in predicting the risk of mortality, there is the important issue of potentially modifying the exposure metrics to account for cancer latency. Without knowledge of the specific timing of etiologically relevant exposure that may initiate and promote cancers that ultimately result in mortality, any exposure metric may include exposures during some time period that do not have bearing on the risk of mortality. In the absence of such information on the specific cancer latency associated with a specific exposure, Rothman (1981) suggested that the most relevant exposure period could be identified by comparing the fit of exposure metrics across multiple lag periods to allow for the identification of the optimal latency period. This has since become a standard practice in occupational and environmental epidemiology. Accordingly, exposure estimates for all exposure metrics were adjusted to account for the time period between the onset of cancer and mortality. The lag period defines an interval before death, or end of follow-up, during which any exposure is excluded from the calculation of the exposure metric. Cohort members who died or were lost within the initial years of follow-up were assigned lagged exposure values of zero if they had not been followed for longer than the lag time. The various exposure metrics were lagged at 10, 15, and 20 years to account for different potential cancer latencies within the limitations of the available data. Metrics without a lag were fit for comparison purposes and to aid in identifying pattern with increasing lag time but were not considered to be biologically reasonable, given that the outcome under analysis is cancer mortality (specifically, mesothelioma and lung cancer), for which latency periods of 10 years or more have been suggested for asbestos (U.S. EPA, 1988a). Consequently, metrics that were not adjusted by lagging exposure in the final years before mortality (or the end of follow-up) were not considered further in the development of an IUR for LAA.

In addition to the exposure metrics used in the lung cancer mortality analysis, modeling of mesothelioma mortality (see Section 5.4.3.1) included additional exposure models. The Peto model (Peto et al., 1982; Peto, 1979) uses a cubic power function of TSFE and a linear function of exposure concentration. The model developed by Peto was later adapted in the IRIS (U.S. EPA, 1988a) asbestos assessment. The linear function of concentration was developed based on estimated average workplace concentrations over several asbestos cohorts exposed to chrysotile, amphiboles, and mixed fibers. The two amphibole-exposed cohorts were U.S workers exposed to amosite and Australian workers exposed to crocidolite; for both cohorts there was little exposure information at the time these reports were published. As Health Effects Institute-Asbestos Research (HEI, 1991) noted "No extensive measurements of historical exposure levels are available for the cohorts exposed predominantly to crocidolite or amosite." The only other mesothelioma models proposed in the literature for amphibole asbestos were developed by Berry (1991) for crocidolite. Berry et al. (2012) found that models that allow for clearance (mathematically, multiplicative $\exp[-\lambda \times T]$) better match the actual mortality

experience of the Wittenoom, Australia crocidolite cohort with more than 50 years follow-up, compared with Peto-type models. In particular, they found that models with a higher power of TSFE of 5.4 (compared to power = 3 for Peto) and a decay rate of 15%/year (half-life of approximately 5 years) fits the observed data best, followed by models with a power of TSFE of 3.9 and a decay rate of 6.8%/year (half-life of approximately 10 years). However, the exposure data calculated for the Berry analysis was based on just one study of airborne levels. Nevertheless, cumulative exposures calculated from these have been shown to be internally valid based on association with fiber lung burden (Berry et al., 2012).

Peto's model [also used in the 1988 IRIS assessment for asbestos (U.S. EPA, 1988a)] is

$$\text{Im} = C \times Q_k \times KM \qquad (5\text{-}11)$$

where

Im = the observed deaths from mesothelioma/person-years (i.e., the mesothelioma mortality rate),

C = the average concentration of asbestos in the air,

KM = an estimated slope describing the relationship between LAA exposure and mesothelioma mortality, and

Q_k = the function of the TSFE (t) and the duration of exposure (d):

$$\text{For } t \leq 10,\ Q_k = 0$$

$$\text{For } 10 < t \leq d + 10,\ Q_k = (t - 10)^k$$

$$\text{For } t > d + 10,\ Q_k = (t - 10)^k - (t - 10 - d)^k.$$

Alternatively, $\text{Im} = C \times Q_k \times KM \times \exp(-\lambda \times t)$ defines the Peto model with clearance. Possible values of λ and k suggested in the literature (Berry et al., 2012) are $\lambda = 0.068$ or 0.15 and $k = 3.9$ or 5.4. As the Peto model and the Peto model with clearance were both proposed in the amphibole asbestos literature, these models were carried forward in the analysis below.

5.4.3. Exposure-Response Modeling

As discussed above, consideration of biology and previous epidemiologic studies informed the range of models considered. There is not sufficient information to select models for the epidemiology data on the basis of the biological mechanism of action for lung cancer or mesothelioma (see Section 3). In this situation, EPA's 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 consider exposure-response models suggested in the

epidemiologic literature. For LAA, possible exposure metrics were explored for model fit to the chosen model forms. The exposure metric options were selected to provide a range of shapes that was sufficiently flexible to allow for a variety of ways that time and duration might relate to cancer risk in the data being modeled.

The following sections provide information about modeling of the full cohort first, the difficulties in identifying adequately fitting models to these data, and the decision to base the analysis on a subcohort of workers that allowed for identifying adequately fitting models.

5.4.3.1. *Modeling of Mesothelioma Exposure Response in the Libby Worker Cohort*

In a population, not, or only sparingly, exposed to asbestos, the background incidence of mesothelioma is extremely low, about 1 in a million (Hillerdal, 1983). The evaluated exposure-response models examine the relationship of the absolute risk of mesothelioma mortality attributable to LAA exposure, because it is not clear that a background risk of mesothelioma mortality exists among people who were truly unexposed to asbestos (as opposed to the relative risk model, which is used for lung cancer mortality; see Section 5.4.3.3). EPA does not have a specific technical guidance for model selection based on human cancer data, but as a general consideration, EPA's BMD Technical Guidance (U.S. EPA, 2012) states that "The initial selection of a group of models to fit to the data is governed by the nature of the measurement that represents the endpoint of interest and the experimental design used to generate the data." Here, the most prominent feature of the data is the rarity of mesothelioma deaths. Correspondingly, Poisson models are employed to estimate the absolute risk of mesothelioma, as the Poisson distribution is an appropriate model for use with data that are counts of a relatively rare outcome, such as observed mesothelioma deaths in the Libby worker cohort. Other parametric survival models, such as the Weibull model have been used for absolute risk calculation, but they are not generally used for data with rare outcomes. Consequently, there are no examples in the literature of the Weibull or other parametric survival model ever being used for modeling mesothelioma mortality. Previous analyses of mesothelioma mortality in the Libby worker cohort also used the Poisson model (Moolgavkar et al., 2010; McDonald et al., 2004). Mathematically, the Poisson distribution specifies the probability of k events occurring as

$$P(k) = \frac{\lambda^k e^{-\lambda}}{k!} \qquad (5\text{-}12)$$

where λ is parameterized with the exposure metric (defined in Section 5.4.2.5). Then, life-table analysis is used to estimate risks in the general U.S. population for the derivation of the unit risk of mesothelioma mortality (see Section 5.4.5.1). In the standard Poisson distribution, the assumption is that the mean is equal to the variance. However, actual count data often exhibit

overdispersion, a statistical consideration when the variance is larger than the mean; thus, EPA evaluated potential for overdispersion.

Estimation of the exposure-response relationship for mesothelioma mortality was performed using a Monte Carlo Markov Chain (MCMC) Bayesian approach with an uninformative or diffuse (almost flat) prior [WinBUGS Version 1.4; (Spiegelhalter et al., 2003)]. Use of diffuse priors is a standard procedure in Bayesian analysis, in situations like this one, when there is no prior knowledge about the toxicity of LAA under a particular model. Because this analysis focuses only on the Libby worker cohort and does not try to factor in data from other sources in estimating potency, use of a diffuse prior is considered appropriate for this analysis.

The benefit of using the WinBUGS software implementing Bayesian MCMC approach is computational ease and that it provides a posterior distribution of the mesothelioma coefficient (KM) rather than just a point estimate. A diffuse (high variance) Gaussian distribution, truncated to exclude negative parameter values, is used as a diffuse prior. With such a prior, results of MCMC analysis are expected to be similar to maximum likelihood estimation in a non-Bayesian analysis. Standard practices of MCMC (Spiegelhalter et al., 2003) analysis were followed for verifying convergence and sensitivity to the choice of initial values. The posterior distribution is based on three chains with a burn-in of 10,000 (i.e., the first 10,000 simulations are dropped so that remaining samples are drawn from a distribution close enough to the true stationary distribution to be usable for estimation and inference) and thinning rate of 10 (i.e., only each 10^{th} simulation is used—thus reducing autocorrelation), such that 3,000 total simulations constitute the posterior distribution of KM. The mean of the posterior distribution served as a central estimate, and the 90% credible interval[24] defined the 5^{th} percentile and the 95^{th} percentile of the distribution, which served as bounds for the 95^{th} lower and upper one-sided confidence intervals, respectively.

The fit of multiple metrics of exposure, the Peto model and the Peto model with clearance (see Section 5.4.2.5), as well as exposure intensity, duration of exposure, age at death or loss to follow-up, and TSFE were compared using the Deviance Information Criterion (DIC). The DIC (Spiegelhalter et al., 2002) is used in Bayesian analysis and is an analogue of the AIC, with smaller values indicating a better statistical fit to the data. Use of the DIC and AIC is standard practice in comparing the fit of nonnested models to the same data set with the same dependent outcome variable but different independent covariates. According to Burnham and Anderson (2002), "These methods allow the data-based selection of a 'best' fitting model and a ranking and weighting of the remaining models in a predefined set." Because of the small number of deaths from mesothelioma in absolute terms, only uni- and bivariate models (with age or TSFE as the second covariate) were considered. Gender and race were not used as covariates because

[24]A credible interval is the Bayesian analogue of a confidence interval.

all mesothelioma deaths were observed in men assumed to be white (Sullivan, 2007). Each exposure metric was lagged by 0, 10, 15, or 20 years, where appropriate. Lags of more than 20 years were not considered as the first mesothelioma death in the workers happened between 15 and 20 years after starting employment.

5.4.3.2. *Results of the Analysis of Mesothelioma Mortality in the Full Libby Worker Cohort*

While the final analytic exposure-response modeling for mesothelioma is based on the subcohort of workers hired after 1959 when exposure data were considered to be superior as it does not suffer from the lack of exposure information for many of the workers in earlier years (see Section 5.4.3.4). It is important to understand how different metrics of exposure in the epidemiologic literature are related to risk in the full cohort as these age- and time-related variables are well characterized in the full cohort. A parallel set of tables is provided for the subcohort of workers hired after 1959 in Section 5.4.3.5.

Tables 5-23 to 5-25 show rates of mesothelioma mortality in the full cohort by duration of exposure, age of first exposure, and TSFE. Mesothelioma rates look to be independent of the age of first exposure, but duration of exposure and TSFE both show relationships with mesothelioma mortality rate. EPA also evaluated the potential for overdispersion of the counts of mesothelioma deaths. In the Libby worker cohort, mean and variance of exposure are nearly identical at 9.62×10^{-3} and 9.53×10^{-3}, respectively, making overdispersion very unlikely.

Table 5-23. Mesothelioma mortality rate shown by duration of exposure (yr) in the full Libby worker cohort including all hires (*n* = 1,871)

	Duration				
	0–1 yr	**1–2 yr**	**2–3 yr**	**3–5 yr**	**5+ yr**
Deaths/PY	3/40,417	1/7,493	3/4,429	2/4,984	9/9,778
Rate × 10^{-4}	0.7	1.3	6.8	4.0	9.2

PY = Person-yr

Table 5-24. Mesothelioma mortality rate shown by age at first exposure in the full Libby worker cohort including all hires (*n* = 1,871)

	Age		
	15–25 yr old	**25–35 yr old**	**35+ yr old**
Deaths/PY	5/30,872	11/22,447	2/13,782
Rate × 10^{-4}	1.6	4.9	1.5

Table 5-25. Mesothelioma mortality rate shown by time since first exposure (TSFE) in the full Libby worker cohort including all hires (*n* = 1,871)

	Time since first exposure					
	<15 yr	**15−25 yr**	**25−35 yr**	**35−45 yr**	**45−55 yr**	**55−68.1 yr**
Deaths/PY	0/27,186	2/16,553	5/12,775	8/6,818	2/3,025	1/744
Rate × 10^{-4}	0	1.2	3.9	11.7	6.6	13.4

For the full Libby worker cohort (*n* = 1,871), in the continuous analysis examining one explanatory variable at a time (see Table 5-26), the duration of exposure provided a considerably better model fit than the other possible exposure metrics, indicating that this exposure metric was the best single predictor of mesothelioma mortality in the full Libby worker cohort. A model, which included duration of exposure and age at death or censoring, provided the overall best fit (DIC = 196). Counterintuitively, the inclusion of information on the concentration of exposure in addition to the duration of exposure (as expressed by CE, which is the product of duration and concentration) resulted in a degradation in model fit compared to the model with just the duration of exposure (see Table 5-26). From the models proposed in the amphibole asbestos literature, the Peto model (see eq 5-11) had a much higher DIC of 233.7 in the analysis of the full cohort. For the Peto model, KM was estimated to be 1.85×10^{-9} and its 95th upper bound was 2.59×10^{-9}. The Peto model with power terms on time-since-first-exposure $k = 3.9$ and 5.4 and clearance terms of 6.8 and 15% per year, respectively, did not improve fit over the standard Peto model.

Table 5-26. Comparison of model fit of various univariate exposure metrics for mesothelioma mortality in the full Libby worker cohort including all hires (n = 1,871).[a] Only models with DIC within 10 units of the DIC of the model with the lowest DIC are shown.[b]

Variable	DIC
Duration of exposure	202.9
Age at death or censoring	209.2
CE lagged 15 yr	209.5
CE lagged 10 yr	209.9
RTW lagged 10 yr with 5-yr half-life	210.4
CE lagged 10 yr with 20-yr half-life	210.6
RTW with 5-yr half-life	210.7
RTW with 10-yr half-life	211.0
CE	211.4
Time since first exposure	211.4

[a]Because one of the mesothelioma deaths occurred less than 20 yr from start of the exposure, lag 20 metrics assigned no exposure to this case, which resulted in the very poor fit of exposure metrics lagged 20 yr.
[b]Lower DIC values represent better fits.

It is likely that the poorer fit seen when using information on exposure concentration is the result of the fact that duration of exposure is measured with comparatively little error, while derivation of specific exposure concentrations may be subject to a sizable measurement error. Moreover, as described in Section 5.4.2.3, for 706 of 991 (71%) workers hired from 1935 to 1959, only the duration of exposure was known, and the same exposure concentration was estimated for them. Thus, the same average estimated exposure intensity for that time period had been used for these workers (Sullivan, 2007). Particularly large exposure measurement error, among more than two-thirds of the workers hired prior to 1960 who had the same estimated exposure intensity, resulted in the duration of exposure being the best predictor of mesothelioma mortality. Additionally, estimates of exposure intensity prior to 1968 have greater uncertainty associated with them than more recent exposure measurements, which are based on fiber counts in air samples analyzed by PCM. For the majority of job locations (23 of 25), no exposure measurements were available before 1968, and exposures were estimated based on employee interviews (in 1982) and what was known about major changes in operations between 1935 and 1967. For two exposure locations, the dust-to-fiber conversion ratio is based on measurements taken in the late 1960s, so extrapolations from the mid 1960s to the early 1960s is likely to be more certain than extrapolation further back in time. The metric using only duration of exposure fit best and the additional incorporation of exposure intensity information, as expressed as the CE, only worsened the fit. Therefore, it is unlikely that IUR estimates can be developed using

the full cohort data because the early exposure values (which were predominantly inferred from later data and based on missing exposure information) were not predictive of mesothelioma mortality.

5.4.3.3. *Modeling and Results of Lung Cancer Exposure Response in the Full Libby Worker Cohort*

As noted in the previous section, while the final analytic exposure-response modeling is based in the subcohort of workers hires after 1959, it is important to understand how different metrics of exposure that appear in the epidemiologic literature are related to risk in the full cohort. A parallel set of tables is provided for the subcohort of workers hired after 1959 in Section 5.4.3.6.

Tables 5-27 to 5-29 show the mortality rates of lung cancer mortality by duration of exposure, age of first exposure, and TSFE for the full Libby worker cohort (n = 1,871). Note that people in Montana may be different from those in the whole United States and therefore may be a more appropriate comparison but the reference population is smaller and less stable. The United States reference rates/risks are more stable. Looking at both SMRs allows the evaluation of the rates/risks in Libby workers with greater context. Lung cancer rates in the Libby worker cohort are substantially higher than mesothelioma rates (see Section 5.4.3.2). Basic stratified models of lung cancer rates and standardized mortality ratios (SMRs) in this population show increased rate with increases in duration of exposure greater than 5 years, age at first exposure and TSFE.

Table 5-27. Lung cancer mortality rate shown by duration of exposure (yr) in the full Libby worker cohort including all hires (n = 1,871)

	Duration				
	0−1 yr	**1−2 yr**	**2−3 yr**	**3−5 yr**	**5+ yr**
Deaths/PY	60/40,417	9/7,493	6/4,429	5/4,984	31/9,778
Rate × 10^{-4}	14.8	12.0	13.5	10.0	31.7
White male deaths/white male PY	57/37,761	9/7,030	6/4,168	5/4,767	31/9,610
White male rate × 10^{-4}	15.1	12.8	14.4	10.5	32.3
White male $SMR_{Montana}$	2.3	2.0	2.2	1.6	5.0
White male $SMR_{U.S.}$	2.0	1.7	1.9	1.4	4.2

SMR standardized to white male lung cancer mortality rates obtained from NCI (2012).

Table 5-28. Lung cancer mortality rate shown by age at first exposure in the full Libby worker cohort including all hires (*n* = 1,871)

	Age		
	15–25 yr old	**25–35 yr old**	**35+ yr old**
Deaths/PY	28/30,872	42/22,447	41/13,872
Rate × 10^{-4}	9.1	18.7	29.7

SMR not computed due to lack of comparable rates.

Table 5-29. Lung cancer mortality rate shown by time since first exposure (TSFE) in the full Libby worker cohort including all hires (*n* = 1,871)

	Time since first exposure (yr)					
	<15	**15–25**	**25–35**	**35–45**	**45–55**	**55–68.1**
Deaths/PY	12/27,186	19/16,553	35/12,775	21/6,818	21/3,025	3/744
Rate × 10^{-4}	4.4	11.5	27.4	30.8	69.4	40.3
White male deaths/white male PY	11/25,651	19/15,569	33/12,112	21/6,482	21/2,843	3/680
White male rate × 10^{-4}	4.3	12.2	27.2	32.4	73.9	44.1
White male $SMR_{Montana}$	0.7	1.9	4.2	5.0	11.5	6.9
White male $SMR_{U.S.}$	0.6	1.6	3.5	4.2	9.6	5.7

SMR standardized to white male lung cancer mortality rates obtained from NCI (2012).

EPA does not currently have specific technical guidance for model selection based on human cancer data. However, the process and criteria used in the assessment are explained below. Standard models from similar exposure-response analyses available in the epidemiologic literature may be candidate models for exposure-response analyses when they are appropriate to the epidemiologic data at hand.

As noted above for mesothelioma, models are selected and evaluated based on the nature of the data set, which for lung cancer, warrants the ability to use the time-dependent data. The mesothelioma mortality data were modeled using the Poisson model within a Bayesian framework to estimate the absolute risk, because mesothelioma is very rare in the general population not, or sparingly, exposed to asbestos (Hillerdal, 1983). 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 which does not have a well-defined background risk in the absence of asbestos exposure. 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.

Standard epidemiologic models for relative risk include Poisson, logistic, conditional logistic, and Cox models. Multistage clonal expansions models are also available. However, only the Cox models and clonal expansion models can accommodate the analysis of time-varying covariates as in the case of the Libby worker cohort. While different researchers have used two-stage clonal expansion models to model asbestos-related health endpoints from an occupational cohort of asbestos textile workers in South Carolina (Zeka et al., 2011; Richardson, 2009), divergent model results raise questions about the resilience of this method when applied to epidemiologic cohorts. Specifically, the two-stage clonal expansion analysis by Richardson (2009) fit the data well and was complementary and consistent with his accompanying Cox regression analysis, while the two-stage clonal expansion analysis by Zeka et al. (2011) on the same cohort population, but with a different length of mortality follow-up, did not completely converge, indicating poor model fit. One issue is that epidemiologic cohorts may be less regular in nature than toxicological studies in the sense that epidemiologic cohorts can be dynamic, with people joining at different times, possibly leaving and then rejoining. By comparison, in animal studies, it is more typical for all the subjects to undergo the identical exposure protocol. Additionally, the degree to which the results of two-stage clonal expansion models depends upon multiple additional assumptions is not yet well understood and EPA does not have reliable information available on which to make the required assumptions for the Libby worker cohort (e.g., the number of cells at risk, constraints on the spontaneous rates of first and second mutations, allowing for a fixed lag between malignant transformation of a cell and death from cancer, etc.). Therefore, in addition to the basic stratified models of lung cancer risk by duration of exposure, by age at first exposure, and by TSFE, 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 (i.e., time-dependent exposure information), the long history of usage in analyses of occupational cohorts, and the commonality of usage in other epidemiologic analyses of the Libby workers cohort.

No other standard epidemiological model formulations allow for the analysis of time-varying exposures in the manner achieved by the Cox proportional hazards model. The exposure-response relationship (proportional hazards ratio) determined in this model intrinsically takes into account the effects of other causes of mortality that are unrelated to exposure (i.e., independent censoring). Further, all comparisons are made within the cohort by comparing the mortality experience of people with different exposures within the same cohort population. Nonetheless, the issue of competing risks that are dependent on exposure (e.g., asbestosis or nonmalignant respiratory disease) is an acknowledged uncertainty for this and other types of analyses (see Section 5.4.6).

The Cox proportional hazards model (Cox, 1972) is one of the most commonly used statistical models for the epidemiologic analysis of survival and mortality in cohort studies with extensive follow-up, including studies of the Libby worker cohort (Larson et al., 2010b; Moolgavkar et al., 2010). In the Cox proportional hazards model, the conditional hazard function, given the covariate array *Z*, is assumed to have the form

$$\lambda(t \mid Z) = \lambda_0(t)\exp(\beta^T Z) \qquad (5\text{-}13)$$

where β is the vector of regression coefficients, $\lambda_0(t)$ denotes the baseline hazard function, and T denotes transposition of the vector. One of the strengths of this model is that knowledge of the baseline risk function is not necessary, and no particular shape is assumed for the baseline hazard; rather, it is estimated nonparametrically. The contributions of covariates to the hazard are multiplicative. When Z represents exposure and $\beta^T Z$ is small, the Cox proportional hazards model is consistent with linearity of the dose-response relationship for low doses.

The Cox proportional hazards model assumes that a function of covariates (i.e., exposures) result in risks that are a constant multiple of the baseline hazard in unexposed individuals over some timescale, typically calendar time or age. This proportionality is assumed to be constant across the range of observed exposures, given the set of modeled covariates, and can be evaluated across time. When the proportional hazards assumption holds, it is possible to estimate the hazard ratio of exposure (relative risk) without estimating the hazard function in the unexposed (or in the lowest exposures seen within the study group), because this baseline hazard function drops out of the calculations.

Other methods common to occupational epidemiology, such as the use of standardized mortality ratios (results shown above in Tables 5-27 through 5-29) typically rely upon comparisons of the mortality experience in an exposed population group compared to that in the general population. However, the comparison population may not always be appropriate due to differences in general health status (e.g., the healthy worker effect) and differences in exposure to other risk factors for a specific disease (e.g., smoking history). The lack of comparability between the study population and the comparison population can lead to confounding by other measured or unmeasured characteristics that may be statistically associated with both the exposure of interest and the endpoint. The Cox proportional hazards model controls for such potentially confounding characteristics by using a comparison group from within the study population (i.e., internal controls). Internal controls are a statistically appropriate comparison group because they are expected to be more similar in potentially confounding characteristics to the remainder of the cohort, thereby controlling for both measured and unmeasured confounding and helping ensure that comparisons are more statistically valid.

5.4.3.3.1. ***Lung cancer mortality analysis in the Libby worker cohort.*** As described in the previous section, quantitative exposure-response relationships for lung cancer mortality were evaluated using the Cox proportional hazards model. Cox proportional hazards models of this type require the specification of a timescale. Age is typically the time-related variable with the strongest relationship to cancer mortality and was used as the timescale in these analyses. Use of age as the timescale in a time-varying Cox proportional hazards model controls for age as a risk factor by design rather than by parametric modeling and effectively rules out age as a potential confounder. Individual covariates available to EPA in the complete analytic data set compiled from the NIOSH data were evaluated for their ability to explain lung cancer mortality. These included gender, race, birth year, age at hire, and various exposure-related variables including TWA workplace intensity of exposure in fibers/cc, job type, and the start and stop date of each different job. These data allowed for the computation of cumulative exposure, cumulative exposure with application of a half-life, and RTW cumulative exposure, with and without application of a half-life (see Section 5.4.2.5). Each exposure metric was also lagged by 0, 10, 15, or 20 years. The use of a lag period aims to account for the latency period between the onset of lung cancer (which occurs some time before clinical diagnosis) and lung cancer mortality.

All lung cancer mortality analyses were conducted using SAS software version 9.1 (SAS, Cary, NC). EPA fit the extended Cox proportional hazards model (Tableman and Kim, 2004; Kleinbaum and Klein, 1996), which included both time-independent factors such as gender, race, and date of birth, as well as time-dependent measures of LAA exposure over the entire time course of each individual's lifetime from his or her date of hire until death or loss to follow-up. The inclusion of date of birth in these analyses controls for potential birth cohort effect, which is strongly related to smoking patterns as people of different generations develop different smoking rates.

EPA's analyses of time-dependent exposure data included goodness-of-fit testing of the proportionality assumption for the Libby worker cohort. Because Cox proportional hazard models rely on the assumption that the hazard rate among the exposed is proportional to the hazard rate among the unexposed, it is important to evaluate the model against this assumption. Therefore, analyses of extended Cox proportional hazards models tested this assumption using a Wald test on the model interaction term between the LAA exposure metric and the timescale (i.e., age). As a general rule, a nonzero slope that is either increasing or decreasing indicates a violation of the proportional hazards assumption. Wald tests for the complete cohort consistently showed that the interaction term was a statistically significant predictor of lung cancer mortality ($p < 0.05$) and was interpreted as evidence that the hazards did not remain proportional over time. The cause of the lack of proportionality is unknown, but several likely explanations are discussed in Section 5.4.3.4 below and in the discussion of uncertainties in Section 5.4.6.1.

5.4.3.4. *Rationale for Analyzing the Subcohort of Libby Workers After 1959*

Several possible explanations exist for the finding that duration of exposure was the best fitting exposure metric for mesothelioma mortality, as well as the finding of the lack of proportionality of hazards in the lung cancer mortality modeling.

- Duration of exposure, but not department code or job category, was known for 706 of 991 (71%) workers hired from 1935 to 1959. The same exposure concentration had been estimated for almost all of these workers, likely resulting in a particularly large measurement error for exposure in approximately one-third of the total cohort of 1,871 workers. Assigning the same exposure concentration to so many of the workers hired before 1960, regardless of job, likely resulted in significant exposure misclassification and may explain the superior fit for duration of exposure in modeling of mesothelioma mortality relative to the other exposure metrics based on measured exposures.

- Even where the job category was identified, few exposure data exist prior to 1968. For the majority of job locations (23 of 25), no exposure measurements were available prior to 1967, and so exposures were estimated based on employee interviews (conducted in 1982) to determine what was known about major changes in operations between 1935 and 1967. For two job locations, dust-to-PCM extrapolations are based on measurements taken in the late 1960s; thus, extrapolating from the mid 1960s to the early 1960s is likely to be more certain than extrapolating further back in time. Random error in these exposure measurements would also generally attenuate the strength of association between exposure and observed effect during the earlier years of mine operation, and thus, a greater degree of measurement error in the earlier years could have resulted in the lack in proportionality of the hazard ratios for lung cancer over time. A greater degree of measurement error in the earlier years could also provide an explanation for the worse fit of the mesothelioma models that incorporated these exposure measures.

- Another explanation for the lack of proportional hazards in modeling lung cancer mortality may be that this cohort has an anomalous age structure due to the hiring of much older individuals during the time of the Second World War. Among those workers in the cohort hired prior to 1960, 9% were older than 50 years at the time of hire, and 22% were older than 40 years. Among those workers hired in 1960 or afterwards, only 4% were older than 50 years, and 14% were older than 40 years. Older workers differ from younger workers in several potentially important ways that could alter their response to exposures. Older workers were born in a different era, with different nutritional and public health standards, which may influence mortality patterns.

- The lack of proportional hazards in modeling lung cancer mortality may also be a reflection of confounding or effect modification, which can change in magnitude over time. The most likely candidate for confounding or effect modification is smoking. NIOSH records show that of the 1,871 workers in the full Libby workers cohort, 1,121 workers (60%) were missing smoking status data, while 750 (40%) had data with values "*S*" (Smoker), "*Q*" (Former Smoker), or "*N*" (Nonsmoker). Given this high percentage of missing values, EPA did not consider these smoking data to be adequate for use in the evaluation of confounding or effect modification. Effect modification by age is another possibility and may also explain 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 lung cancer risk in a cohort of asbestos exposed workers; however, similar two-stage clonal expansion modeling of lung cancer risk in the same cohort of workers was unable to replicate that finding, which may be due to the reliance of this methodology on additional assumptions which EPA does not have a basis for making (see discussion of two-stage modeling in Section 5.4.3.3).

- Smoking rates and patterns among the subcohort of workers hired after 1959 are likely to have been more similar because smoking rates change more slowly over shorter periods of time than over longer ones. This restriction in time period of hiring would also result in less variation by birth year cohort, which is strongly related to smoking patterns as people of different generations develop different smoking rates. 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. Further discussion of the relevance of smoking can be found in the section on uncertainties (see Section 5.4.6).

When the assumption of proportionality is not met, the potential influence of confounding factors in the full-cohort analysis of lung cancer mortality is of concern. Additionally, the lack of job category information for 71% of the workers hired prior to 1960 and greater measurement error in early exposures may result in significant random exposure measurement error, which may bias the observed exposure-response relationships towards the null.

Although duration of exposure was the best exposure metric for modeling mesothelioma mortality in the full cohort, it does not allow quantitatively estimating an exposure-response relationship to support IUR. In addition, violation of the underlying statistical assumptions adversely affected modeling of lung cancer mortality in the full cohort. Therefore, EPA chose to undertake a subcohort analysis of workers hires after 1959.

While it is generally true that the use of more data is an advantage in statistical analyses because it allows for the computation of more statistically precise effect estimates, this advantage could not be realized, because of the difficulty in deriving risks from the full cohort analysis (see next section on uncertainties remaining in the subcohort). The reasons stated in Section 5.4.2 for choice of Libby worker cohort data over other study populations are still valid for the subcohort. In particular, (1) these workers were directly exposed to LAA, (2) detailed work histories and job-specific exposure estimates are available to reconstruct estimates of each individual's occupational exposure experience with only nine workers completely missing job and department codes during the period of relatively high average time-weighted estimated exposure intensity, (3) the subcohort is still sufficiently large and has been followed for a sufficiently long period of time for cancer to develop (i.e., cancer incidence) resulting in mortality, and (4) the broad range of exposure experiences in the subcohort provided an information-rich data set.

EPA initially examined the fit of these models using several exposure metrics to predict mortality from mesothelioma and found that in this subcohort, the exposure metrics that included

information on exposure concentration provided superior statistical fits to the exposure metrics based only on employment duration. In this same subcohort, the assumptions of the Cox proportional hazards model for analysis of lung cancer were also satisfied for the modeling of time-varying exposure.

On the other hand, there are quantitative uncertainties related to the choice of the subcohort. First of all, the numbers of cases of both lung cancer and mesothelioma are lower than in the whole cohort. Second, the follow-up of subcohort, while in excess of 40 years, may not be sufficiently long to encompass all potential lung cancer, especially, mesothelioma mortality related to LAA exposures. Third, the subcohort is younger and overall mortality is lower than in the full cohort. However, the choice of the subcohort is appropriate because of the superior exposure information based on a higher percentage of estimated exposures from actual measurements as opposed to inferred exposure values. The higher percentage of actual measurements allows a more accurate dose-response evaluation [see the discussion in Lenters et al. (2012) and Lenters et al. (2011)] on the impact the quality of the exposure information has on estimates of dose-response relationships [see Bateson and Kopylev (2014)].

5.4.3.5. *Results of the Analysis of Mesothelioma Mortality in the Subcohort*

Of the 880 workers hired after 1959, 230 (26%) had died by December 31, 2006. The number of mesothelioma deaths in the subcohort is seven (two deaths coded in ICD-10 and five deaths coded in ICD-9). The mesothelioma death rate of 2.47 per 10,000 person-years for the subcohort is similar to the mesothelioma death rate of 2.68 per 10,000 person-years for the full cohort (18 mesothelioma deaths), with a difference of less than 10%.

Tables 5-30 to 5-32 show the mesothelioma mortality rate by duration of exposure, age of first exposure, and TSFE. As in the full cohort, both duration of exposure and TSFE show a relationship with mesothelioma mortality rate. However, unlike the full cohort, where there was no relationship with age at first exposure, in the subcohort, ages greater than 25 may be associated with higher risk than those below 25. EPA again evaluated the potential for overdispersion of the counts of mesothelioma deaths. In the subcohort, mean and variance of exposure are 7.95×10^{-3} and 7.90×10^{-3}, respectively. Therefore, as in the full cohort, overdispersion is very unlikely.

Table 5-30. Mesothelioma mortality rate in the subcohort of employees hired after 1959 shown by duration of exposure (yr)

	Duration			
	0–1 yr	**1–2 yr**	**2–5 yr**	**5+ yr**
Deaths/PY	1/14,942	0/4,129	1/4,614	5/4,669
Rate × 10^{-4}	0.7	0	2.2	10.7

Table 5-31. Mesothelioma mortality rate in the subcohort of employees hired after 1959 shown by age at first exposure

	Age		
	15–25 yr old	**25–35 yr old**	**35+ yr old**
Deaths/PY	1/14,104	4/9,029	2/5,222
Rate × 10^{-4}	0.7	4.4	3.8

Table 5-32. Mesothelioma mortality rate in the subcohort of employees hired after 1959 shown by time since first exposure (TSFE)

	Time since first exposure			
	<15 yr	**15–25 yr**	**25–35 yr**	**35+ yr**
Deaths/PY	0/12,954	2/8,155	3/5,731	2/1,514
Rate × 10^{-4}	0	2.5	5.2	13.2

It is important to note that these marginal analyses, as well as the marginal analyses in the full cohort (see Section 5.4.3.2), do not specifically include the quantitative effects of the exposure—only the timing of exposure. Therefore, these marginal analyses provide an incomplete understanding of the quantitative exposure-response relationship. To more fully understand the effect of the timing of exposure, the quantitative effect of exposure must be modeled. Unlike the full cohort where personal exposure information is mostly missing, subcohort personal exposure information is available. Therefore, EPA next investigated the overall fit of different exposure models and then tabulated and represented graphically the mesothelioma mortality rate as predicted by several models that include personal exposure information.

Table 5-33 shows the relative fit of various exposure metrics for mesothelioma mortality in the subcohort hired after 1959, including only those exposure metrics with information weights greater than 0.01. Information weights are computed from the DICs (Burnham and Anderson, 2002), and are commonly used in Bayesian analyses. Information weights are

computed by first assessing the differences between the best DIC and each of the others ($\Delta\ DIC_i$) (see eq 5-14).

$$DIC\ w_i = \exp\left(-\frac{1}{2}\Delta\ DIC_i\right) \Big/ \sum_{r=1}^{R} \exp\left(-\frac{1}{2}\Delta\ DIC_i\right) \tag{5-14}$$

where

R is the number of models and
$DIC\ w_i$ is information weight of the i^{th} model.

Table 5-33. Comparison of model fit of exposure metrics for mesothelioma mortality in the subcohort hired after 1959.[a] Only the model fits with information weights greater than 0.010 are shown.[b]

Exposure metric	Lag(yr)	DIC	Information weight
CE with 5-yr half-life	15	70.6	0.428
CE with 5-yr half-life	10	72.8	0.143
CE with 10-yr half-life	10	73.9	0.082
CE with 10-yr half-life	15	74.0	0.078
CE with 10-yr half-life	0	74.5	0.061
CE with 5-yr half-life	0	75.0	0.047
CE with 15-yr half-life	10	75.7	0.033
CE with 15-yr half-life	0	76.0	0.029
CE with 15-yr half-life	15	76.1	0.028
CE with 20-yr half-life	10	76.7	0.020
CE with 20-yr half-life	0	77.0	0.017
CE with 20-yr half-life	15	77.2	0.016

[a]Because one of mesothelioma deaths occurred in less than 20 yr from start of the exposure, lag 20 metrics assigned no exposure to this case, and the very poor fit of lag 20 metrics is a result.
[b]As discussed in Section 5.4.2.4, models with lag 0 were not considered further in derivation of unit risks.

Metrics with higher DICs and lower information weights indicate a poorer model fit and are not included in Table 5-33. The other exposure metrics that were evaluated included those metrics used in the full cohort analysis (duration of exposure, TSFE, age at death or censoring, RTW metrics, and CE with lag metrics), but none of these metrics fit as well as the metrics in Table 5-33.

The two metrics with cumulative exposure lagged 15 and 10 years, both with 5-year half-life, provided the two best fits as indicated by their lower DIC values and higher information weights (see Table 5-33). Cumulative exposures lagged 10 or 15 years, both with 10-year

half-life, provided the next two best fits according to DIC values, but models including each of these metrics exhibited noticeably lower information weights than the best metric. All metrics in Table 5-33 contain a decay term and have the same number of parameters in their corresponding model, allowing for a direct comparison of the DIC values and information weights.

For models from the amphibole asbestos literature, in the subcohort hired after 1959, the DIC value for mesothelioma using the Peto metric (see eq 5-11) is substantially higher (DIC = 98.4) than for any of the metrics in Table 5-33. This indicates that the metric of exposure used in the previous IRIS IUR (U.S. EPA, 1988a) does not provide as good a fit for the LAA worker cohort as the other metrics of exposure in Table 5-33. Setting the power term on time since first exposure (k in eq 5-11) in the IRIS IUR (U.S. EPA, 1988a) metric to the values of 2 and 4, as suggested by U.S. EPA (1986a), continues to yield substantially higher DIC values compared to the fit values of the exposure metrics in Table 5-33 (DIC = 89.2 and 107.9, respectively). For the Peto model with clearance, increasing the power term in the Peto model with clearance to $k = 3.9$ with decay $\lambda = 0.068$ and $k = 5.4$ with decay $\lambda = 0.015$ decreased DIC slightly from the standard Peto model itself (DIC = 95.4 and 95.3, respectively). Using CE instead of C in decay models, as discussed in Berry et al. (2012), made the fit much worse, as measured by DIC. The fit also degraded when using the Berry et al. (2012) models of the form (C or CE) × $(T - 5)^k$.

Next, EPA considered which covariates should be added to the model with the exposure metric that provided the best fit. The addition of covariates "age at death or censoring" and "TSFE" did not improve the fit, as measured by DIC (results not shown).

As discussed above, EPA tabulated the mesothelioma rates for the two best fitting metrics in Table 5-33 and for alternative models proposed in the amphibole asbestos literature (i.e., Peto model and Peto model with clearance) in Tables 5-34 to 5-38. These tables show information by quintiles for each metric of exposure.

The first two tables (see Tables 5-34, 5-35) show a dose-response relationship between mesothelioma deaths and values of each exposure metric—while the mesothelioma data are sparse, higher values of metric correspond to higher rate of mesothelioma. Tables 5-36 to 5-38 show a somewhat less clear dose-response relationship for the Peto model and the Peto model with clearance, as the relationship between metric and rate appears to be somewhat parabolic.

Table 5-34. Mesothelioma mortality rate in the subcohort of employees hired after 1959 for the cumulative exposure (CE) with 15-year lag and 5-year half-life

	CE with 15-yr lag and 5-yr half-life				
	0–0.024	**0.024–0.094**	**0.094–0.27**	**0.27–0.97**	**0.97+**
Deaths/PY	1/4,858	0/5,975	0/5,827	0/5,494	6/5,751
Rate × 10^{-4}	2.1	0	0	0	10.4

Table 5-35. Mesothelioma mortality rate in the subcohort of employees hired after 1959 for the cumulative exposure (CE) with 10-year lag and 5-year half-life

	CE with 10-yr lag and 5-yr half-life				
	0–0.015	**0.015–0.05**	**0.05–0.15**	**0.15–0.55**	**0.55+**
Deaths/PY	1/5,315	0/5,626	0/5,953	1/5,995	5/5,465
Rate × 10^{-4}	1.9	0	0	1.7	9.1

Table 5-36. Mesothelioma mortality rate in the subcohort of employees hired after 1959 for the Peto model

	Peto metric				
	0–130	**130–760**	**760–3,530**	**3,530–18,070**	**18,070+**
Deaths/PY	1/4,585	0/5,460	0/5,639	4/5,943	2/6,727
Rate × 10^{-4}	2.2	0	0	6.7	3.0

Table 5-37. Mesothelioma mortality rate in the subcohort of employees hired after 1959 for the Peto model with power k = 3.9 and decay λ = 6.8%/yr

	Peto metric with power k = 3.9 and decay λ = 6.8%/yr				
	0–311	**311–1,837**	**1,837–7,400**	**7,400–35,330**	**35,330+**
Deaths/PY	1/4,515	0/5,531	0/5,718	4/5,988	2/6,603
Rate × 10^{-4}	2.4	0	0	6.7	3.0

Table 5-38. Mesothelioma mortality rate in the subcohort of employees hired after 1959 for the Peto model with power k = 5.4 and decay λ = 15%/yr

	Peto metric with power k = 5.4 and decay λ = 15%/yr				
	0−2,883	**2,883−17,029**	**17,029−67,762**	**67,762−287,614**	**287,614+**
Deaths/PY	1/4,492	0/5,588	0/5,710	4/5,941	2/6,624
Rate × 10^{-4}	2.2	0	0	6.7	3.0

To further illustrate the fit of the Peto model to the Libby mesothelioma data, the frequency of the values of exposure computed using the Peto method and two best-fitting exposure metrics, which were CE with 5-year half-life and 10- or 15-year lag, were plotted and the mesothelioma cases were noted (see Figures 5-6 to 5-8). These figures provide more information than Tables 5-34 through 5-36. The histograms show in a relative scale the frequency of occurrence of each value of the specific exposure metric, thereby revealing the complete distribution and showing where exposure values of the cases were. In these figures, the exposure metric has been transformed to the natural log scale which yields a more normalized distribution. The figures show how the exposure values of the mesothelioma deaths relate to the exposure values of the subcohort of workers hired after 1959. Better fitting models are expected to show higher exposure values for the mesothelioma cases relative to those who did not die from mesothelioma, while poorer fitting models are expected to show mesothelioma cases scattered with equivalent density to the distribution as a whole and, thus, closer to the center of the distribution of exposure metric.

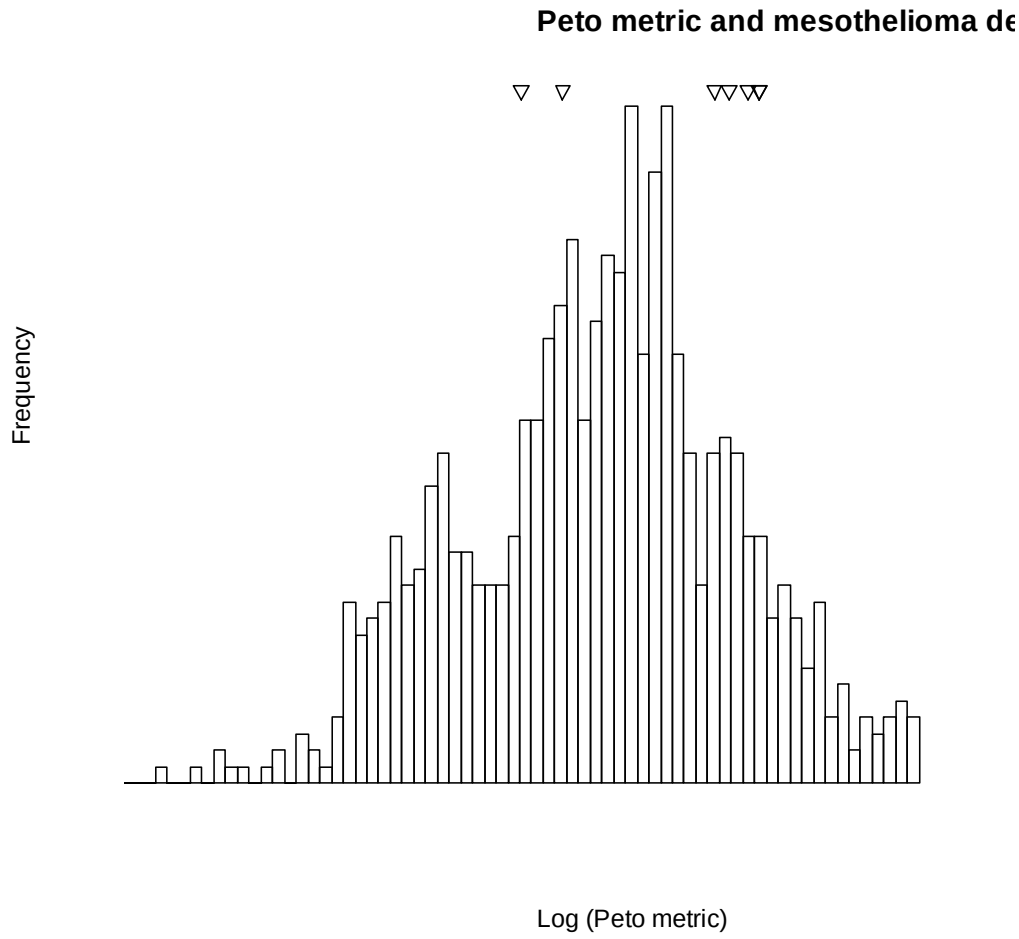


Figure 5-6. Distribution of values of the Peto metric and Peto metric values of mesothelioma deaths (shown as inverted triangles) in the subcohort of employees hired after 1959.

From comparing Figures 5-6 (above) and Figures 5-7, and 5-8 (below), exposure values of the mesothelioma deaths based on the Peto exposure metric are clearly closer to the center of the distribution and, therefore, more like the values of those that did not die of mesothelioma. Thus Peto exposure metric does not reveal a higher likelihood of death from mesothelioma compared to the other exposure metrics. This is consistent with what was observed in Tables 5-34 through 5-38—the Peto model does not fit the subcohort data as well as CE metrics with decay fit. For the CE-based exposure metrics (see Figures 5-7 and 5-8), unlike the Peto exposure metric (see Figure 5-6), mesothelioma deaths are concentrated at high values of the exposure metrics and not as close to the center of the distribution.

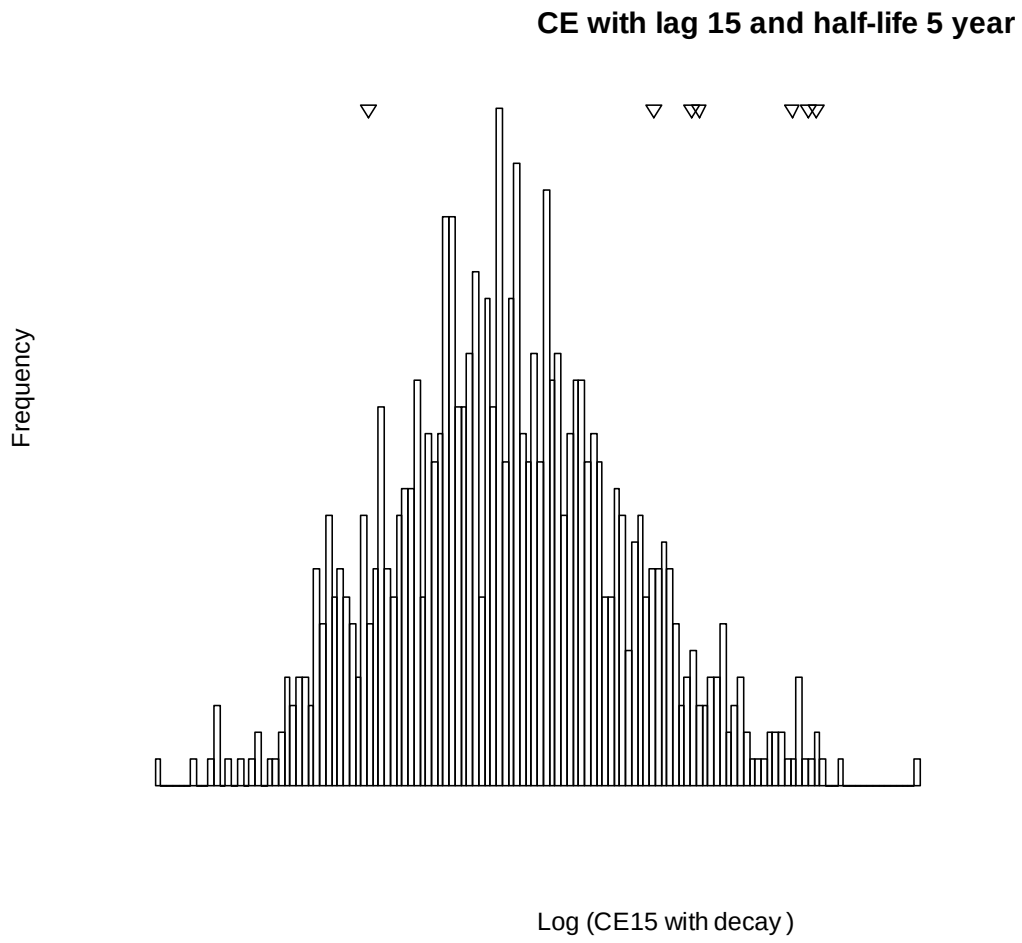


Figure 5-7. Distribution of observed values of cumulative exposure (CE) with 15-year lag and 5-year half-life and CE with 15-yr lag and 5-yr half-life values of mesothelioma deaths (shown as inverted triangles) in the subcohort of employees hired after 1959.

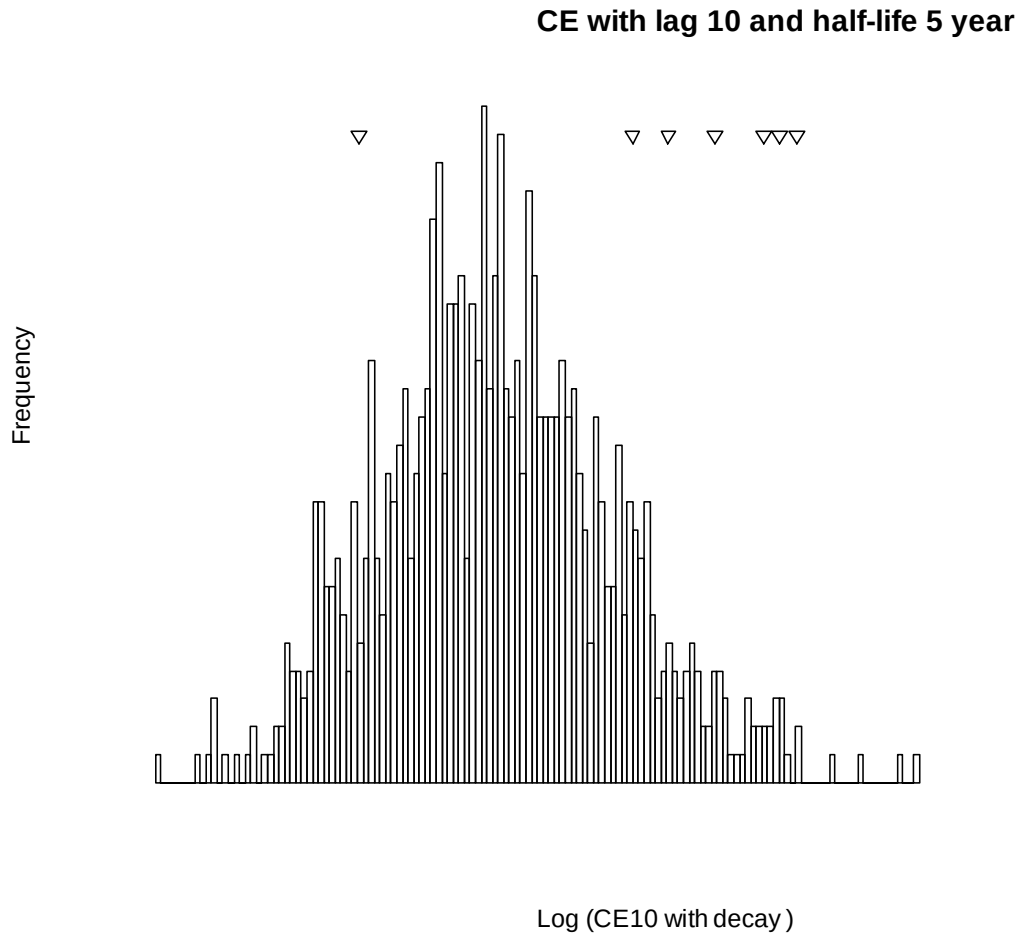


Figure 5-8. Distribution of observed values of cumulative exposure (CE) with 10-year lag and 5-year half-life and CE with 10-yr lag and 5-yr half-life values of mesothelioma deaths (shown as inverted triangles) in the subcohort of employees hired after 1959.

As discussed above and seen in Tables 5-34 through 5-38 and Figures 5-6 through 5-8:

1) While TSFE by itself, without personal exposure information, shows a clear relationship with increases in mesothelioma rates with increasing TSFE (see Table 5-32), adding information on concentration of fibers to the model (as the Peto model does) appears to degrade the fit (compare Table 5-36 to Table 5-32). The amphibole cohorts (amosite and crocidolite), which were used to derive the Peto model and the Peto model with clearance had little, if any, personal exposure data. Therefore, those models were predominantly based on the power of TSFE and demonstrated a good fit to the exposure timing data from those cohorts. Lack of good exposure data, and in particular personal exposure information, was a limitation of these analyses. In the case of the Libby workers subcohort, personal exposure data is available and when personal exposure is taken into account, the models do not appear to fit as well.

2) The tabular fit of the best models from Table 5-33 (see Tables 5-34 to 5-35) compared to the fit in Tables 5-36 to 5-38, demonstrates somewhat better alignment for the subcohort. The tabular results are consistent with overall model fit statistics.

Comparing the relative fits of the empirical models based on individual-level exposure estimates (but just seven cases) with those literature-based models (Peto and Peto with clearance based on hundreds of cases but little actual individual-level exposure data) reveals uncertainties related to model selection. While there is understandable uncertainty in using empirical models based on a small number of cases, there is also uncertainty in applying literature-based models based on different type of amphibole asbestos without individual-levels exposure estimates. This uncertainty is discussed below in the section describing the derivation of the IUR (see Section 5.4.5.3). As described in Section 5.4.2.5, only metrics with nonzero lag were retained for derivation of unit risks. Table 5-39 shows KM (slope) and credible intervals for all metrics retained from Table 5-33.

Table 5-39. Mesothelioma mortality exposure metrics fits, slopes per day, and credible intervals in the subcohort of employees hired after 1959

Exposure metric	Lag yr	DIC	Slope × 10^{-5}	90% Credible interval for slope × 10^{-5}
CE—5-yr half-life	15	70.6	20.6	(10.2, 34.3)
CE—5-yr half-life	10	72.8	31.1	(15.2, 50.8)
CE—10-yr half-life	10	73.9	9.93	(5.00, 16.3)
CE—10-yr half-life	15	74.0	7.78	(3.72, 12.9)
CE—15-yr half-life	10	75.7	6.17	(3.04, 10.1)
CE—15-yr half-life	15	76.1	5.30	(2.63, 8.69)
CE—20-yr half-life	10	76.7	4.71	(2.34, 7.71)
CE—20-yr half-life	15	77.2	4.27	(2.12, 6.98)

Table 5-40 shows fits (DIC), KM (slope), and credible intervals for the Peto model and the Peto model with clearance (note that these slopes are not directly comparable with those in Table 5-39 because of difference in the units of time due to the use of different powers).

Table 5-40. Peto model and Peto model with clearance fits, slopes per year, and credible intervals in the subcohort of employees hired after 1959

Power (k)	Decay	DIC	Slope × 10^{-8}	90% Credible interval for slope × 10^{-8}
5.4	0.15	95.3	0.09	(0.04, 0.15)
3.9	0.068	95.4	0.66	(0.34, 1.09)
3	No	98.4	1.06	(0.52, 1.72)

Issues related to uncertainty in the choice of exposure metric are described further in the section on the derivation of the combined IUR of mesothelioma and lung cancer (see Section 5.4.5.3).

5.4.3.6. *Results of the Analysis of the Lung Cancer Mortality in the Subcohort*

EPA based its final analyses for lung cancer mortality on the subset of workers hired after 1959. Thus, this analysis is based on 32 deaths from lung cancer[25] (ICD-8: 2 deaths with the code 162.1; ICD-9: 1 death with the code 162.2, 20 deaths with the code 162.9; ICD-10: 9 deaths with the code C349) out of 230 total deaths that occurred in the subcohort of 880 workers.

Tables 5-41 to 5-43 show lung cancer mortality rates by duration of exposure, age of first exposure, and TSFE. As in the full cohort, duration of exposure, age at first exposure, and TSFE all show relationships with lung cancer mortality rate.

[25]Note that in the full cohort, it was unclear whether cases of tracheal cancer were included in the definition of lung cancer as many of the recorded ICD codes on death certificates did not provide sufficient detail to distinguish tracheal cancer cases from lung cancer cases. However, among the subcohort of workers hired after 1959, all the deaths from the broader category of cancers of the lung, bronchus, and trachea did provide sufficient detail to show that no deaths occurred from tracheal cancer.

Table 5-41. Lung cancer mortality rate in the subcohort of employees hired after 1959 shown by duration of exposure (yr)

	Duration			
	0–1 yr	**1–2 yr**	**2–5 yr**	**5+ yr**
Deaths/PY	13/14,942	5/4,129	2/4,614	12/4,669
Rate × 10^{-4}	8.7	12.1	4.3	25.7
White male deaths/white male PY	12/13,779	5/3,848	2/4,251	12/4,601
White male rate × 10^{-4}	8.7	13.0	4.7	26.1
White male $SMR_{Montana}$	1.4	2.0	0.7	4.1
White male $SMR_{United\ States}$	1.1	1.7	0.6	3.4

SMR standardized to white male lung cancer mortality rates obtained from NCI (2012).

Table 5-42. Lung cancer mortality rate in the subcohort of employees hired after 1959 shown by age at first exposure

	Age		
	15–25 yr old	**25–35 yr old**	**35+ yr old**
Deaths/PY	1/14,104	12/9,029	19/5,222
Rate × 10^{-4}	0.7	13.3	36.4

SMR not computed due to lack of comparable rates.

Table 5-43. Lung cancer mortality rate in the subcohort of employees hired after 1959 shown by time since first exposure (TSFE)

	Time since first exposure			
	<15 yr	**15–25 yr**	**25–35 yr**	**35+yr**
Deaths/PY	4/12,954	11/8,155	13/5,731	4/1,514
Rate × 10^{-4}	3.1	13.5	22.7	26.4
White male deaths/white male PY	4/12,054	11/7,560	12/5,404	4/1,461
White male rate × 10^{-4}	3.3	14.6	22.2	27.4
White male $SMR_{Montana}$	0.5	2.3	3.5	4.3
White male $SMR_{United\ States}$	0.4	1.9	2.9	3.5

SMR standardized to white male lung cancer mortality rates obtained from NCI (2012).

As noted in Section 5.4.3.5, these marginal analyses do not specifically include the effects of the exposure as well as both the duration and the TSFE. Therefore, EPA investigated the overall fit of different exposure models and tabulated the results of several models that include personal exposure information.

All multivariate Cox proportional hazards models with time-varying exposures were initially fit, using one exposure metric at a time, to the subcohort hired after 1959 with covariates for gender, race, and date of birth. Lung cancer mortality was modeled using CE and RTW exposure, where each metric was potentially modified by four different half-lives (5, 10, 15, or 20 years). Each of these exposure metrics was also evaluated with four different lag periods to allow for cancer latencies of 0, 10, 15, or 20 years. In all, 40 multivariate exposure-response models were evaluated for the adequacy of the exposure metric to fit the epidemiologic data. Each model and the comparative model fit statistics are presented in Table 5-44.

Table 5-44. Model fit comparison for different exposure metrics and lung cancer mortality associated with LAA, controlling for age, gender, race, and date of birth. Results ordered at left by exposure metric and at right by model fit.

Ordered by exposure metric			Ordered by model fit				
Exposure metric	Lag (yr)	AIC	Exposure metric	Lag (yr)	AIC	Multivariate model *p*-value[a]	Exposure *p*-value
CE	0	361.610	CE—10-yr half-life	10	358.400	0.0071	0.0009
CE	10	361.073	CE—5-yr half-life	10	358.502	0.0075	0.0010
CE	15	363.124	CE—15-yr half-life	10	358.777	0.0084	0.0015
CE	20	364.964	CE—20-yr half-life	10	359.122	0.0098	0.0022
CE—20-yr half-life	0	361.123	CE—5-yr half-life	15	359.910	0.0138	0.0032
CE 20-yr half-life	10	359.122	CE—10-yr half-life	15	360.543	0.0181	0.0079
CE—20-yr half-life	15	361.533	CE	10	361.073	0.0227	0.0188
CE—20-yr half-life	20	364.703	CE—20-yr half-life	0	361.123	0.0232	0.0155
CE—15-yr half-life	0	361.382	CE—15-yr half-life	15	361.129	0.0232	0.0162
CE—15-yr half-life	10	358.777	CE—15-yr half-life	0	361.382	0.0258	0.0184
CE—15-yr half-life	15	361.129	CE—20-yr half-life	15	361.533	0.0276	0.0254
CE—15-yr half-life	20	364.588	RTW 5-yr half-life	0	361.593	0.0283	0.0309
CE—10-yr half-life	0	362.169	CE	0	361.610	0.0285	0.0307
CE—10-yr half-life	10	358.400	CE—10-yr half-life	0	362.169	0.0360	0.0358
CE—10-yr half-life	15	360.543	RTW 10-yr half-life	0	362.283	0.0378	0.0588
CE—10-yr half-life	20	364.342	RTW 15-yr half-life	0	362.714	0.0452	0.0863
CE—5-yr half-life	0	364.225	RTW 20-yr half-life	0	362.973	0.0503	0.1084
CE—5-yr half-life	10	358.502	CE	15	363.124	0.0535	0.1215
CE—5-yr half-life	15	359.910	RTW 5-yr half-life	10	363.224	0.0558	0.1343
CE—5-yr half-life	20	363.644	CE—5-yr half-life	20	363.644	0.0662	0.1751
RTW	0	363.869	RTW	0	363.869	0.0726	0.2397
RTW	10	364.835	RTW 10-yr half-life	10	364.041	0.0778	0.2810
RTW	15	364.990	CE—5-yr half-life	0	364.225	0.0838	0.2908
RTW	20	364.502	RTW 15-yr half-life	10	364.336	0.0876	0.3733
RTW 20-yr half-life	0	362.973	CE—10-yr half-life	20	364.342	0.0878	0.3661
RTW 20-yr half-life	10	364.477	RTW 20-yr half-life	10	364.477	0.0927	0.4314
RTW 20-yr half-life	15	365.011	RTW	20	364.502	0.0936	0.5307
RTW 20-yr half-life	20	364.628	CE—15-yr half-life	20	364.588	0.0969	0.4815
RTW 15-yr half-life	0	362.714	RTW 20-yr half-life	20	364.628	0.0985	0.5763
RTW 15-yr half-life	10	364.336	RTW 15-yr half-life	20	364.662	0.0998	0.5909

Table 5-44. Model fit comparison for different exposure metrics and lung cancer mortality associated with LAA, controlling for age, gender, race, and date of birth. Results ordered at left by exposure metric and at right by model fit. (continued)

Ordered by exposure metric				Ordered by model fit				
Exposure metric	Lag (yr)	AIC		Exposure metric	Lag (yr)	AIC	Multivariate model *p*-value[a]	Exposure *p*-value
RTW 15-yr half-life	15	365.001		CE—20-yr half-life	20	364.703	0.1014	0.5530
RTW 15-yr half-life	20	364.662		RTW 10-yr half-life	20	364.719	0.1021	0.6188
RTW 10-yr half-life	0	362.283		RTW 5-yr half-life	15	364.768	0.1041	0.6021
RTW 10-yr half-life	10	364.041		RTW 5-yr half-life	20	364.831	0.1067	0.6884
RTW 10-yr half-life	15	364.962		RTW	10	364.835	0.1069	0.6586
RTW 10-yr half-life	20	364.719		RTW 10-yr half-life	15	364.962	0.1124	0.8173
RTW 5-yr half-life	0	361.593		CE	20	364.964	0.1125	0.8204
RTW 5-yr half-life	10	363.224		RTW	15	364.990	0.1136	0.8809
RTW 5-yr half-life	15	364.768		RTW 15-yr half-life	15	365.001	0.1141	0.9100
RTW 5-yr half-life	20	364.831		RTW 20-yr half-life	15	365.011	0.1146	0.9599

CE = Cumulative exposure with or without exponential decay modeled with different half-lives.
RTW = Residence time-weighted exposure with or without exponential decay with different half-lives.
[a]Likelihood ratio test (overall model fit where $p < 0.05$ indicated an adequate fit).

The assumptions of the Cox proportional hazards model were reevaluated for the subcohort. Restricting the cohort addressed each of the previously listed potential explanations for the lack of hazard proportionality (see Section 5.4.3.3). First, measurement error for exposures is likely to have been smaller after 1959 for several reasons. One reason is that 706 workers were removed from the analysis because job category and department code information were missing during all of their employment prior to 1960. Also, beginning in 1968, fiber concentrations by PCM analysis of site-specific air samples were available for all location operations to inform the JEM.

Second, prior to 1968, the exposure intensity for 23 of 25 location operations was estimated based on assumptions informed by employee interviews in the early 1980s. It is likely the uncertainty of these assumptions increased the farther back in time that exposures were estimated, making the earliest exposure estimates (1940s and 1950s) less certain than those only a few years before fiber count data were available. Further, between 1956 and 1967,

dust-to-PCM extrapolation data were used to estimate exposures in the dry mill based on measurements taken in the late 1960s. Although there is some uncertainty in the conversion ratio selected by Amandus et al. (1987b), dust-to-fiber conversions are likely to be less uncertain than extrapolations further back in time to the 1950s and 1940s, where only one air sample for dust was available in 1944. Thus, the potential attenuation effect of nondifferential measurement error is likely to be reduced by examining the post-1959 cohort alone compared to the entire cohort.

Third, smoking rates among this more narrowly defined subcohort are likely to have been more homogeneous; thus, restricting analysis to this subcohort would help to limit any potential confounding due to smoking.

Finally, EPA conducted goodness-of-fit testing of the extended Cox proportional hazards model as applied to the subcohort hired post-1959. There was no evidence to reject the hypothesis of proportionality, and the exposure models demonstrated adequate fits to the data, with statistically significant effect estimates. In each of the Cox proportional hazards model analyses with time-varying exposures—across all the exposure metrics and across all the lag lengths—no violations of the assumption of proportionality of hazards were found.

As the exposure-response models cannot strictly be considered to be nested, a standard measure of fit called the AIC (Burnham and Anderson, 2002) was used for comparison of goodness of fit across models based on the same data set. In their text on model selection, Claeskens and Hjort (2008) state that "…for selecting a model among a list of candidates, AIC is among the most popular and versatile strategies." Claeskens and Hjort (2008) also state that the model yielding the smallest AIC is judged the best fitting and it is a common practice in environmental epidemiology to simply select the single model with the best statistical fit (i.e., the lowest AIC) among the models evaluated. While large differences in AIC values can reveal important differences in model fit, small differences are less conclusive. For example, in a set of models differing in AIC by two or fewer units, each can be considered to have a substantially similar level of empirical support [(Burnham and Anderson, 2002); p. 70].

Table 5-44 shows the models and exposure metrics ordered by fit. Of interest is whether there are models with distinct exposure metrics that adequately fit these data (as measured by statistical significance of the model *p*-value) and then whether a measure of relative fit exists among these adequately fitting models. Of the 40 exposure-response metrics, 14 demonstrated an adequate fit to the data as measured by the overall model fit, with the standard likelihood ratio test being statistically significant ($p < 0.05$), as well as having statistically significant exposure metrics ($p < 0.05$). However, note that only the nine models that demonstrated adequate model and exposure metric fit and incorporated a lag period to account for lung cancer mortality latency were advanced for potential use in developing a unit risk. While metrics that did not include an adjustment for lag on the exposure metric to account for cancer mortality latency were fit to these data for the sake of completeness, they were dropped from further consideration because

they implicitly assume no passage of time between the initiation of cancer, subsequent promotion of that cancer, and mortality.

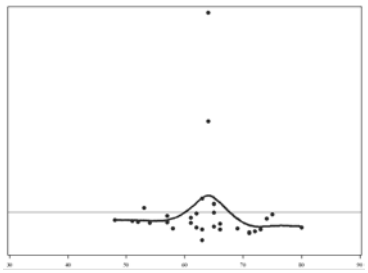
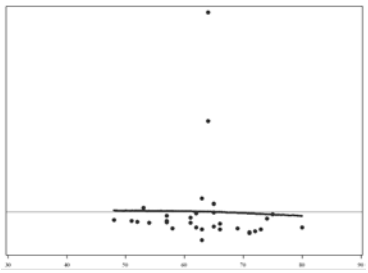
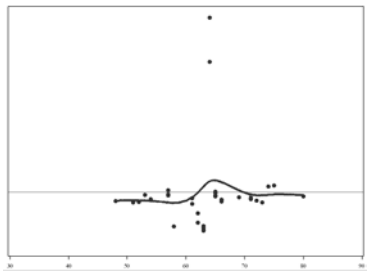
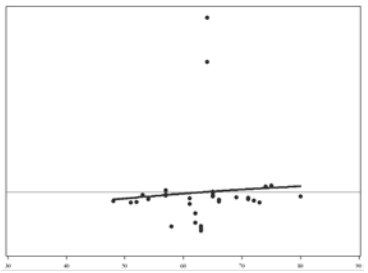
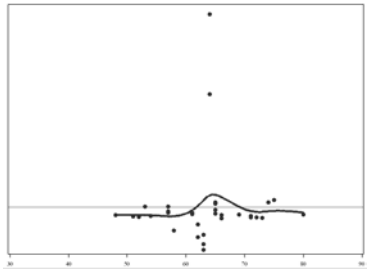
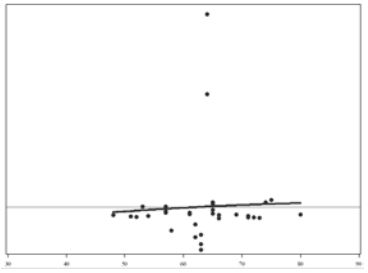
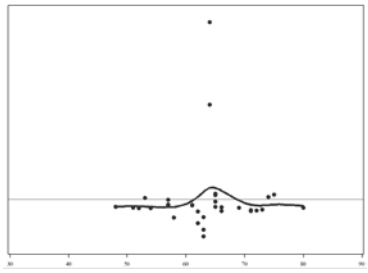
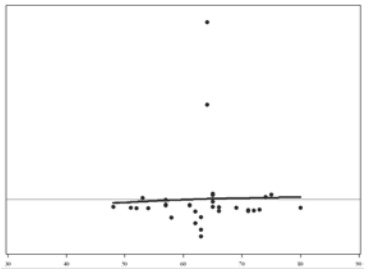
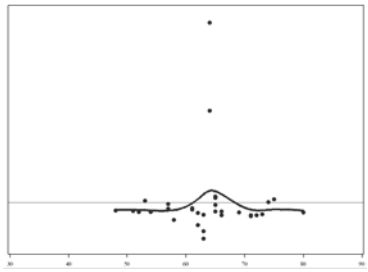
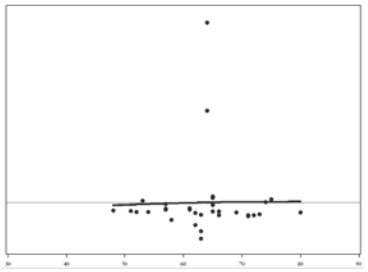
Several general patterns were discernible with respect to which exposure metric(s) best predicted lung cancer mortality when comparing AICs for relative model fit. The data show that lagging exposure by 10 years best predicts lung cancer mortality compared to other lags. This trend is seen across both the cumulative exposure without decay and the various half-life cumulative exposure metrics where a 10-year lag of exposure best predicts lung cancer mortality for all cumulative exposure metrics compared to other lags. Metrics with 15-year lags were generally the next best in terms of fit. Another conclusion is that the models that included RTW exposure metrics, regardless of half-life or lag, did not fit as well as the models that employed cumulative exposure with different half-lives and lags.

Among the 40 exposure metric models that were evaluated, the exposure model with the lowest AIC value was for cumulative exposure with a 10-year half-life for decay and a 10-year lag for cancer mortality latency and had a model *p*-value based on the likelihood ratio test of 0.0071 (see Table 5-44). This multivariate model controlled for age, gender, race, and date of birth. This model estimated a KL (slope) of 1.26×10^{-2} per fiber/cc-yr based on a 365-day calendar year,[26] and the 95th percentile upper bound on this parameter was 1.88×10^{-2} per fiber/cc-yr. The *p*-value for the LAA regression coefficient (slope) was <0.001, indicating that this parameter was statistically significantly greater than zero. Table 5-45 shows the slopes and confidence intervals for all retained metrics from Table 5-44. Figure 5-9 shows the model residuals (in this case, the Schoenfeld residuals for Cox models) for the retained models in Table 5-45. Patterns in such residuals such as an increasing or decreasing slope overall can indicate lack of fit. Attention is directed at the pattern of residuals with respect to age at death (the *x*-axis). None of the plots appears to show a meaningful deviation from a linear function of age which indicates a lack of interaction between the model-predicted effect of exposure on lung cancer mortality risk and age. That is, the risk of lung cancer mortality does not appear to vary by age within the subcohort of workers at the Libby facility. There is no indication of a systematic lack of fit across these models excepting the nonlinear departure in the center of each residual plot which appears to be random and is minimized with the pattern in the residuals if smoothed out to a greater extent. The model fit residuals are consistent with the similarity of the AIC values in demonstrating similar model fit.

[26]The two-sided 90% confidence interval is (6.00×10^{-3}, 1.88×10^{-2}).

Table 5-45. Lung cancer mortality exposure metrics fits, slopes, and confidence intervals (CI) for all retained metrics from Table 5-44. Subset of lung cancer models with lagged exposures that yielded statistically significant model fit (p <0.05) and exposure metric fit (p <0.05) to the epidemiologic data.

Exposure metric	Lag yr	AIC	Slope	SE	Exposure p-value	90% CI for the slope
CE—10-yr half-life	10	358.400	0.0126	0.0038	0.0009	(0.0063, 0.0188)
CE—5-yr half-life	10	358.502	0.0179	0.0055	0.0010	(0.0089, 0.0269)
CE—15-yr half-life	10	358.777	0.0106	0.0033	0.0015	(0.0052, 0.0160)
CE—20-yr half-life	10	359.122	0.0095	0.0031	0.0022	(0.0044, 0.0146)
CE—5-yr half-life	15	359.910	0.0155	0.0052	0.0032	(0.0069, 0.0241)
CE—10-yr half-life	15	360.543	0.0115	0.0043	0.0079	(0.0044, 0.0186)
CE	10	361.073	0.0058	0.0025	0.0188	(0.0017, 0.0099)
CE—15-yr half-life	15	361.129	0.0097	0.0040	0.0162	(0.0031, 0.0163)
CE—20-yr half-life	15	361.533	0.0087	0.0039	0.0254	(0.0023, 0.0151)

Exposure Metric	Less smoothing	More smoothing
CE—no half-life; 10-yr lag		
CE—5-yr half-life; 10-yr lag		
CE—10-yr half-life; 10-yr lag		
CE—15-yr half-life; 10-yr lag		
CE—20-yr half-life; 10-yr lag		

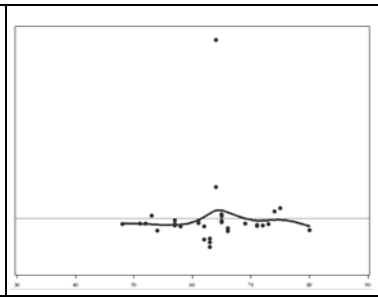
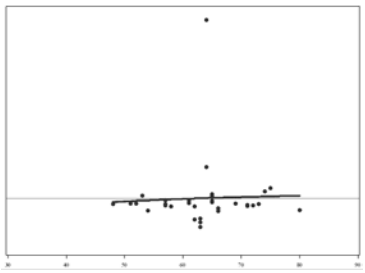
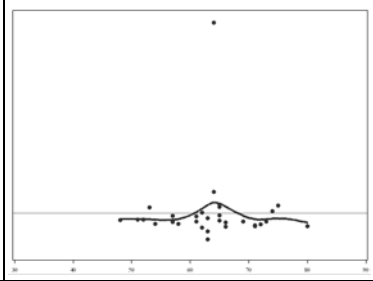
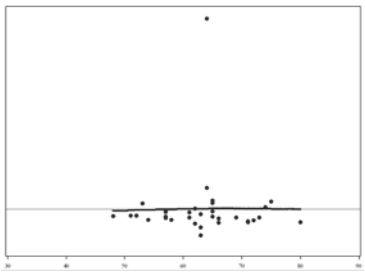
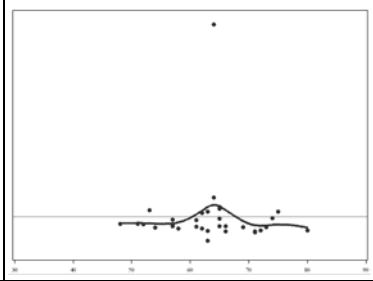
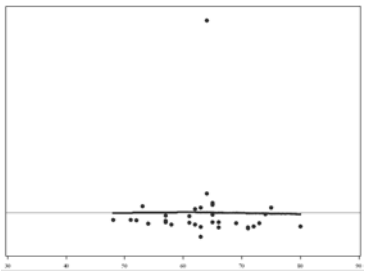
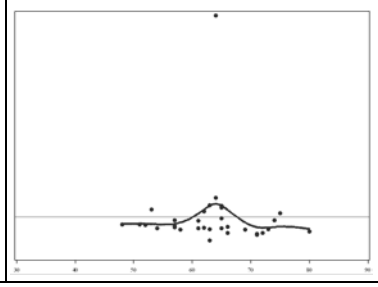
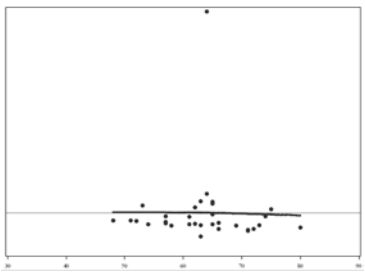
CE—5-yr half-life; 15-yr lag		
CE—10-yr half-life; 15-yr lag		
CE—15-yr half-life; 15-yr lag		
CE—20-yr half-life; 15-yr lag		

Figure 5-9. Regression diagnostics showing model fit based on the Schoenfeld residuals with two levels of nonparametric smoothing (using cubic splines) to show any patterns of departures from the model predicted values. In each plot, age at lung cancer mortality is shown against the model residuals. The *x*-axis shows the age of death while the *y*-axis shows the scaled residuals (predicted minus observed) according to the scale of the specific exposure metric.

According to the model results presented in Table 5-44, there were multiple exposure metrics that predicted lung cancer mortality and exhibited statistically significant effect estimates. Several other metrics were considered to fit nearly as well as the model with the smallest AIC because their AIC values were within two units of the exposure model with the lowest AIC, a proximity that can be considered to be a range that cannot clearly differentiate among models (Burnham and Anderson, 2002). As each of the other exposure metrics was based on a different configuration of the same exposure data, the different slopes (KLs) are not directly comparable, but all adequately fitting lagged models also produce statistically significant slopes for the exposure-response relationship (p <0.05). Of particular note are the results of the cumulative exposure model with a 10-year lag for latency but without a decay function because this model showed the lowest AIC among nondecay models.

The AIC values for models that included lag and/or half-life adjustments to the exposure metrics were not penalized in the regression analyses for using these extra parameters because these factors were not represented as covariates but rather were embedded in the computation of the exposure metric. While these results were obtained using each instance of lag and/or half-life terms in separate model fit, it may be appropriate to mathematically penalize the AICs for inclusion of these additional parameters. AIC values, as typically computed by regression software, include the addition of a penalty for model complexity as measured by the number of parameters that are fit in the regression model (thereby increasing the AIC). In the AIC calculations presented in Table 5-44, the models are treated as having the same number of parameters because each model represents the same individual's time-varying exposures in a different way but with a single exposure parameter in the regression models. For that reason, the models are equally penalized in the software's AIC calculation. However, because an argument can be made that exposure metrics that do not include a decay function, with an explicit half-life term, are implicitly more parsimonious (simpler), a comparison of the AICs is not straightforward. If the decay model fits were penalized for the inclusion of the decay function in the computation of the exposure metric, then with such an adjustment, the relative fit of the CE models would be somewhat improved in terms of their comparison with the values in Table 5-44 (AICs are generally penalized two units for each additional parameter).

Table 5-45 displays the lagged exposure-response models and metrics with adequate model fit (p <0.05) to the epidemiologic data that were further considered. The units of the slopes are fibers/cc-yr. These slopes and confidence intervals represent calendar year continuous environmental exposure as described above and define the "Exposed Hazard Rate" in the life-table procedure when multiplied by the exposure level (see Appendix G for details). The plots in Figure 5-9 do not suggest a meaningful difference in model fits among the nine different parameterizations of exposure with adequate fit.

As presented in Table 5-45, the CE model with 10-year half-life and lag provided an adequate fit to the data based on the likelihood ratio test (p <0.05) and had the lowest AIC value.

The cumulative exposure model with a 10-year lag also yielded a statistically adequate fit to these data ($p < 0.05$), as did several decay models with a 15-year lag. These results demonstrate reasonable uncertainty in the metric of exposure such that no single exposure model can be definitively selected based on goodness of fit alone. Issues related to uncertainty in the choice of exposure metric are described further in the section explaining the derivation of the combined IUR of mesothelioma and lung cancer (see Section 5.4.5.3).

5.4.3.7. *Sensitivity Analysis of the Influence of High Exposures in Early 1960s on the Model Fit in the Subcohort*

As discussed in Section 5.4.2.5, the comparison of model fit among various exposure metrics is an empirical process and does not necessarily reflect a specific biological or other factor as an underlying cause for model fit. Although data do not exist to evaluate biological bases for model fit, other potential factors can be explored where data allow. For example, because of concerns that very high (>100 fibers/cc) 8-hour TWA exposures during 1960−1963 (see Table 5-21) could have influenced the relative fit of the various exposure metrics, EPA conducted a sensitivity analysis of the impact on the relative model fit of reducing all estimated exposure intensities for 1960−1963 by 50%.

For modeling mesothelioma mortality on this revised data set, one change occurred in the relative fit of 3rd and 4th best fit decay models, but the observation that exposure metrics including decay fit better than exposure metrics without decay was unchanged (see Table 5-46). However, the fit of all the metrics decreased slightly, with each DIC increased between 0.3 and 1.1. The metrics without decay and RTW metrics had DIC values higher than those in Table 5-46. The revised data set DIC for the model used in IRIS IUR (U.S. EPA, 1988a) was 97.9.

Table 5-46. Sensitivity analysis of model fit comparison for different exposure metrics and mesothelioma mortality associated with LAA. Estimated exposure intensities for all jobs during 1960−1963 were reduced by 50%.

Exposure metric	Lag (yr)	All workers hired after 1959 (*n* = 880). Based on seven mesothelioma deaths (as shown in Table 5-33).	All workers hired after 1959 (*n* = 880). Based on seven mesothelioma deaths. Exposures during 1960−1963 at 50%.
		DIC	DIC
CE—5-yr half-life	15	70.6	71.2
CE—5-yr half-life	10	72.8	73.9
CE—10-yr half-life	10	73.9	74.9
CE—10-yr half-life	15	74.0	74.6
CE—15-yr half-life	10	75.7	76.4
CE—15-yr half-life	15	76.1	76.7
CE—20-yr half-life	10	76.7	77.3
CE—20-yr half-life	15	77.2	77.7

CE = Cumulative exposure with exponential decay modeled with different half-lives.

For modeling lung cancer mortality on this revised data set, no difference was present in the order of the relative fit between the same exposure metrics that fit the subcohort of workers hired after 1959 and those exposures estimated by Amandus et al. (1987b) for 1960−1963 (see Table 5-47). The metrics based on the revised data set fit marginally better based on AIC.

Table 5-47. Sensitivity analysis of model fit comparison for different exposure metrics and lung cancer mortality associated with LAA, controlling for age, gender, race, and date of birth. Estimated exposure intensities for all jobs during 1960−1963 were reduced by 50%. Lung cancer models presented include those with statistically significant multivariate model *p*-value and nonzero lag in exposure.

Exposure metric	Lag (yr)	All workers hired after 1959 (*n* = 880) based on 32 deaths from lung cancer (as shown in Table 5-44)			All workers hired after 1959 (*n* = 880) based on 32 deaths from lung cancer. Exposures during 1960−1963 at 50%.		
		AIC	Multivariate model *p*-value	Exposure *p*-value	AIC	Multivariate model *p*-value	Exposure *p*-value
CE—10-yr half-life	10	358.400	0.0071	0.0009	357.644	0.0051	0.0004
CE—5-yr half-life	10	358.502	0.0075	0.0010	357.781	0.0054	0.0005
CE—15-yr half-life	10	358.777	0.0084	0.0015	357.966	0.0059	0.0006
CE—20-yr half-life	10	359.122	0.0098	0.0022	358.283	0.0068	0.0009
CE—5-yr half-life	15	359.910	0.0138	0.0032	359.456	0.0113	0.0025
CE—10-yr half-life	15	360.543	0.0181	0.0079	360.167	0.0154	0.0067
CE	10	361.073	0.0227	0.0188	360.238	0.0159	0.0086
CE—15-yr half-life	15	361.129	0.0232	0.0162	360.810	0.0203	0.0138
CE—20-yr half-life	15	361.533	0.0276	0.0254	361.245	0.0244	0.0217

CE = Cumulative exposure with or without exponential decay modeled with different half-lives.

This sensitivity analysis reduces some of the potential uncertainty in the results that may have been attributed to exposure measurement error specific to the 1960−1963 time period when some of the estimated exposures were particularly high.

5.4.3.8. *Additional Analysis of the Potential for Confounding of Lung Cancer Results by Smoking in the Subcohort*

In the full cohort analysis, the proportional hazard assumption was not found to hold, and one of the reasons for this failure was the possible presence of confounding by smoking, which altered the proportionality of the hazard rate in the exposed workers compared to the baseline hazard rate over time. Confounding, which can bias observed results when there is an uncontrolled variable that is correlated with both the explanatory variable and the outcome variable, is a distinct concept from effect-measure modification (e.g., synergy), which might reflect different observed effects of exposure to LAA among smokers as compared to nonsmokers. The extent of effect-measure modification cannot be assessed without adequate data on smoking; however, the potential for effect-measure modification is discussed in Section 5.4.6.

As an additional check on the potential for confounding, a novel method was evaluated to test for confounding by smoking in occupational cohorts that do not have data on smoking. A method has been described by Richardson (2010) to determine if an identified exposure relationship with lung cancer is confounded by unmeasured smoking in an occupational cohort study. Richardson (2010) demonstrated that an exposure of interest (i.e., LAA) can be used to predict an outcome other than lung cancer such as COPD, which is known to be caused by smoking, but not thought to be related to the exposure of concern.[27] If a positive relationship is identified where no causal association is suspected, this would suggest that smoking and the exposure metric (LAA) were positively correlated and that the identified exposure-response relationship was, in fact, confounded by smoking. EPA implemented this methodology to model the potential effects of LAA on the risk of COPD mortality (n = 18) on the subcohort of workers hired after 1959. Using the exposure metric defined as cumulative exposure with a 10-year lag, the extended Cox proportional hazards model with time-varying exposures estimated a slope (beta) for COPD of −0.056 per fiber/cc-yr based on a 365-day calendar year. The p-value for the coefficient (slope) was 0.102, indicating that this parameter was not statistically significantly different from zero. Using the exposure metric defined as cumulative exposure with a 10-year half-life for decay and a 10-year lag for cancer latency, the extended Cox proportional hazards model with time-varying exposures estimated a slope (beta) of −0.135 per fiber/cc-yr based on a 365-day calendar year. The p-value for the coefficient (slope) was 0.116, indicating that this parameter was not statistically significantly different from zero.

Summarizing these findings, EPA used the method described by Richardson (2010) to evaluate whether exposures to LAA predicted mortality from COPD as an indication of potential confounding by smoking and found a nonsignificant negative relationship, which was inconsistent with confounding by smoking in the subcohort of workers hired after 1959.

5.4.4. Exposure Adjustments and Extrapolation Methods

The estimated exposures based on the JEM and work histories are discussed in Section 5.4.2.5. Note that all potency estimates (i.e., KM or KL) presented with units of fibers/cc-yr are for calendar year and not for occupational year, so no additional adjustment is needed to address this difference as may have been found in other evaluations based on occupational epidemiology cohort analyses. Adjustments for differences in breathing rates and the number of hours of exposure in an occupational (8-hour) day as compared to a whole (24-hour) day are not incorporated directly into the slope but rather applied in the derivation of the central risk and unit risk estimates.

[27] Richardson (2010) cited literature with possible associations between asbestos and COPD which, if true, would have explained a positive association among the Libby workers cohort but should not detract from the use of the Richardson method as applied to these Libby workers, where a negative association is found.

5.4.5. Inhalation Unit Risk (IUR) of Cancer Mortality

The derivation of the unit risk estimates, defined as the lifetime risk of mortality from either mesothelioma or lung cancer from chronic inhalation of LAA at a concentration of 1 fiber/cc of air, is presented in the following subsections.

5.4.5.1. *Unit Risk Estimates for Mesothelioma Mortality*

Computational details of the methodology and tables for deriving the lifetime unit risk for mesothelioma mortality are presented in Appendix G. For mesothelioma, the life-table procedure involves applying the absolute rates of mesothelioma mortality estimated in the Libby workers to the age-specific survival distribution of the general population to compute the age-specific risks of mesothelioma mortality expected at specific LAA exposure concentrations. The modeling analysis presented above showed that metrics including lag and half-life parameters provided the best empirical fit to the Libby worker subcohort data. Although there is uncertainty in applying these models for occupational mortality to estimate risks for different exposure levels and time patterns (see Section 5.4.6), following the recommendations of the *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a), a linear low-dose extrapolation below the POD was used because the MOA for LAA for mesothelioma is largely unknown. Lifetime unit risk estimates from the Peto model and the Peto model with clearance are presented in Table 5-48.

Table 5-48. Unit risks for the Peto model and Peto model with clearance

Model	Power	Decay	DIC	Central risk estimate	Unit risk
Peto with clearance	5.4	0.15	95.3	0.015	0.025
	3.9	0.068	95.4	0.035	0.058
Peto	3	No	98.4	0.117	0.191

The mesothelioma unit risks for model results presented in Table 5-39 and discussed in Section 5.4.3.5 are presented in Table 5-49. All of the metrics in Table 5-49 are CE metrics lagged 10−15 years (the fit of 20-year lag models was much worse because one of seven mesothelioma deaths occurred before 20 years; lags longer than 15 years are possible, and this is an uncertainty described in Section 5.4.6). Issues related to uncertainty in the choice of exposure metric are described further in the section on the derivation of the combined IUR of mesothelioma and lung cancer (see Section 5.4.5.3).

Table 5-49. Mesothelioma mortality exposure metrics unit risks for the subcohort hired after 1959

Exposure metric	Lag yr	DIC	Central risk estimate	Unit risk
CE—5-yr half-life	15	70.6	0.032	0.053
CE—5-yr half-life	10	72.8	0.054	0.088
CE—10-yr half-life	10	73.9	0.028	0.047
CE—10-yr half-life	15	74.0	0.020	0.032
CE—15-yr half-life	10	75.7	0.022	0.036
CE—15-yr half-life	15	76.1	0.017	0.027
CE—20-yr half-life	10	76.7	0.020	0.032
CE—20-yr half-life	15	77.2	0.015	0.025

5.4.5.1.1. ***Adjustment for mesothelioma underascertainment.*** For mesothelioma, the undercounting of cases (underascertainment) is a particular concern given the limitations of the ICD classification systems used prior to 1999. In practical terms, this means that some true occurrences of mortality due to mesothelioma are missed on death certificates and in almost all administrative databases such as the National Death Index. Even after the introduction of a special ICD code for mesothelioma with the introduction of ICD-10 in 1999, detection rates are still imperfect (Camidge et al., 2006; Pinheiro et al., 2004), and the reported numbers of cases typically reflect an undercount of the true number.

Kopylev et al. (2011) reviewed the literature on this underascertainment and developed a general methodology to account for the likely numbers of undocumented mesothelioma deaths using the Libby worker cohort as an example. Because the analysis of mesothelioma mortality was based on absolute risk, it was possible to compensate for mesothelioma underascertainment in the Libby worker subcohort. Kopylev et al. (2011) considered analyses when mesothelioma type (i.e., pleural and peritoneal) is unknown and when it is known. As the number of peritoneal mesotheliomas is partially known in the Libby worker subcohort, the method for known proportion of pleural and peritoneal mesothelioma deaths is briefly described here.

Selikoff and Seidman (1992) provided information on the likelihood that individuals who have been diagnosed as having mesothelioma will have that disease recorded (in some field) on their death certificate. Their results are based on histopathological analysis (Ribak et al., 1991) of a very large cohort of insulators, with more than 450 mesothelioma cases. Despite medical advances, diagnosis of mesothelioma is still very challenging, and histopathology is still a standard diagnostic tool today [e.g., Mossman et al. (2013)]. Using their results on the most common misdiagnoses of mesothelioma (mesothelioma diagnosed as lung, colon, and pancreatic cancers; and conversely, other diseases misdiagnosed as mesothelioma) and likelihoods of corresponding misdiagnoses, Kopylev et al. (2011) conducted a simulation study randomly

creating a new data set with the number of mesothelioma deaths simulated in the full Libby cohort to match the Selikoff and Seidman (1992) results. That simulated data set included 24 mesothelioma cases that were obtained using the underascertainment estimate of 37% derived from Selikoff and Seidman (1992). The full cohort was used for the simulation study because of the larger number of mesothelioma cases and because limitations of exposure information is not relevant for that analysis. Using the Poisson model and MCMC simulation similarly to that described in Section 5.1.3.1, Kopylev et al. (2011) calculated the mean of underascertainment of risk and its 90% confidence interval to be 1.39 and (0.80; 2.17).

This method to adjust for underascertainment was applied to the Libby workers subcohort; mesothelioma mortality-adjusted unit risks are listed in Table 5-50.

Table 5-50. Mesothelioma unit risks for the subcohort hired after 1959 adjusted for underascertainment

Exposure metric	Lag yr	DIC	Adjusted central risk estimate	Adjusted unit risk
CE—5-yr half-life	15	70.6	0.044	0.074
CE—5-yr half-life	10	72.8	0.075	0.122
CE—10-yr half-life	10	73.9	0.039	0.065
CE—10-yr half-life	15	74.0	0.028	0.044
CE—15-yr half-life	10	75.7	0.031	0.050
CE—15-yr half-life	15	76.1	0.024	0.038
CE—20-yr half-life	10	76.7	0.028	0.044
CE—20-yr half-life	15	77.2	0.022	0.035

Similarly, for the subcohort data, the Peto model and the Peto model with clearance unit risks are presented in Table 5-51.

Table 5-51. Mesothelioma unit risks for the subcohort hired after 1959 based on the Peto model and the Peto model with clearance adjusted for mesothelioma underascertainment

Model	Power	Decay %	DIC	Adjusted central risk estimate	Adjusted unit risk
Peto with clearance	5.4	0.15	95.3	0.021	0.035
	3.9	0.068	95.4	0.049	0.086
Peto	3	No	98.4	0.163	0.265

5.4.5.2. *Unit Risk Estimates for Lung Cancer Mortality*

Computational details of the methodology and tables for deriving the unit risk for lung cancer mortality are presented in Appendix G. For lung cancer, the life-table procedure involves application of the hazard rates of lung cancer mortality estimated in the Libby workers to the age-specific background rates of lung cancer in the general population (accounting for the age-specific survival distribution of the general population) to compute the age-specific risks of lung cancer mortality expected at specific LAA exposure concentrations. Although there is uncertainty in applying these models for occupational mortality to the estimation of risks for different exposure levels and time patterns (see Section 5.4.6), following the recommendations of the *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a), a linear low-dose extrapolation below the POD was used because the MOA for LAA for lung cancer is undetermined. The nine exposure-response models shown in Table 5-45 all had reasonably similar goodness of fits. No single model stands out as statistically superior; however, there is a range of quality of fit within the set that could be considered adequate. The lung cancer mortality unit risks are shown in Table 5-52.

Table 5-52. Unit risks for subset of lung cancer models with lagged exposures that yielded statistically significant model fit ($p < 0.05$) and exposure metric fit ($p < 0.05$) to the epidemiologic data

Exposure metric	Lag	AIC	Exposure *p*-value	Central risk estimate (based on EC_{01})	Unit risk (based on LEC_{01})
C—10-yr half-life	10	358.400	0.0009	0.0260	0.0389
CE—5-yr half-life	10	358.502	0.0010	0.0195	0.0293
CE—15-yr half-life	10	358.777	0.0015	0.0300	0.0455
CE—20-yr half-life	10	359.122	0.0022	0.0326	0.0501
CE—5-yr half-life	15	359.910	0.0032	0.0167	0.0260
CE—10-yr half-life	15	360.543	0.0079	0.0231	0.0375
CE	10	361.073	0.0188	0.0399	0.0679
CE—15-yr half-life	15	361.129	0.0162	0.0258	0.0434
CE—20-yr half-life	15	361.533	0.0254	0.0280	0.0486

LEC_{01} = 95% lower confidence limit of the exposure concentration associated with a 1% increased risk.

Using the results of the exposure model with the lowest AIC value (i.e., cumulative exposure with a 10-year half-life for decay and a 10-year lag for cancer latency) alone, the 95% lower confidence limit of the exposure concentration associated with a 1% increased risk (LEC_{01}) yielded a lifetime unit risk of 0.0389 per fiber/cc. The value of the risk that would

correspond to the measure of central tendency involves EC_{01} rather than LEC_{01}. The EC_{01} yielded a lifetime central estimate of 0.0260 per fiber/cc.

Using the results of the exposure model based on cumulative exposure with a 10-year lag for cancer latency, the LEC_{01} for the adult-only exposures was determined to be 0.191 fiber/cc. This LEC_{01} yielded a lifetime unit risk of 0.0679 per fiber/cc. The EC_{01} for the adult-only exposures was determined to be 0.325 per fiber/cc. When divided into a POD of 1%, this EC_{01} yielded a lifetime central estimate of 0.0399 per fiber/cc.

The resulting unit risks in Table 5-52 ranged from 0.0260 to 0.0679 per fiber/cc. This shows that the unit risk (i.e., 0.0389 per fiber/cc) based on the exposure metric with the lowest AIC value (i.e., cumulative exposure with a 10-year half-life for decay and a 10-year lag for cancer latency) is in the center of this range, and is thus statistically robust. However, because this estimate is in the middle of the range, it does not capture the uncertainty across metrics with similar goodness of fit. As noted (see Section 5.4.3.6., an argument can be made that the CE metric with a 10-year lag and no half-life is implicitly more parsimonious (simpler) because it was not explicitly adjusted to include decay, although this metric is mathematically equivalent to CE metric with a 10-year lag and an infinitely long decay half-life. Conceptually, the AIC values are penalized for increased model complexity (thereby increasing the AIC). The CE metric with a 10-year lag does fit these data—both statistically and by examination of the residuals. Further, the CE metric is a simpler and more straightforward metric, and has an extensive tradition of use in the epidemiologic literature and in the practice of risk assessment.

5.4.5.3. *Inhalation Unit Risk (IUR) Derivation for Combined Mesothelioma and Lung Cancer Mortality*

For mesothelioma, the exposure-response models developed by EPA using personal exposure data on the subcohort (see Table 5-50) provided better fit to the subcohort data than the Peto model and the Peto model with clearance that have been proposed in the asbestos literature (see Table 5-51). These variations of the Peto model have been shown to predict mesothelioma mortality more precisely than the original Peto model in a large crocidolite-exposed cohort of 6,908 workers with 329 mesothelioma deaths from Wittenoom, Australia (Berry et al., 2012)—specifically, the best fitting models for that cohort was the Peto model with a power $k = 3.9$ and decay rate of $\lambda = 0.068$ (approximately 10-year half-life) and Peto model with a power $k = 5.4$ and decay rate of $\lambda = 0.15$ (approximately 5-year half-life).

The exposure-response models developed by EPA using personal exposure data on the subcohort (see Table 5-50) show estimated lifetime unit risks of 0.074 and 0.122 per fiber/cc. The two Peto models with different clearances and powers of k show lifetime unit risks of 0.086 and 0.035 per fiber/cc, respectively (see Table 5-51). The results of the two different approaches to modeling, the first based only on the LAA data and the second based on a much larger population of workers exposed to another but different amphibole asbestos, reveal a relatively

small degree of uncertainty in the derivation of the mesothelioma lifetime unit risk. Therefore, EPA selected the model derived directly from the Libby data with the strong support of the model that best fit the mesothelioma risk in a much larger cohort of amphibole-exposed workers. EPA's selected model based on cumulative exposure with a 10-year lag and 5-year half-life yielded a lifetime unit risk for mesothelioma of 0.122 per fiber/cc which encompasses other three risk estimates. Table 5-53 shows the combined IUR for LAA for mesothelioma and lung cancer based on the selected mesothelioma model, the two best-fitting mesothelioma models from the epidemiologic literature (the Peto model with clearance), as well as the combined IUR for LAA based on Peto model.

Table 5-53. Estimates of the combined central estimate of the unit risk for mesothelioma and lung cancer and the combined upper-bound lifetime unit risks for mesothelioma and lung cancer risks (the Inhalation Unit Risk for LAA) for different combination of mesothelioma and lung cancer models.[a,b] Primary IUR value in bold.

Lung cancer	Mesothelioma	Combined central estimate (per fiber/cc)	Combined upper bound (per fiber/cc)
Selected IUR based directly on the Libby data			
CE10	CE10 5-yr half-life	0.115	**0.169**
Best models from the epidemiologic literature (Peto model with clearance)			
CE10	Peto with clearance Decay rate of 6.8%/yr Power of time = 3.9	0.089	0.135
CE10	Peto with clearance Decay rate of 15%/yr Power of time = 5.4	0.061	0.092
Alternative model from the epidemiologic literature (Peto model)			
CE10	Peto No decay Power of time = 3	0.203	0.308

[a]Note that for the IUR values for LAA shown in this table, the fiber concentration are presented here as continuous lifetime exposure in fibers/cc where exposure measurements are based on analysis of air filters by PCM. Current analytical instruments used for PCM analysis have resulted in a standardization of minimum fiber width considered visible by PCM between 0.2 and 0.25 µm. Historical PCM analysis (1960s and early 1970s) generally had less resolution, and fibers with minimum widths of 0.4 or 0.44 µm were considered visible by PCM (Amandus et al., 1987b; Rendall and Skikne, 1980). Methods are available to translate exposure concentrations measured in other units into PCM units for comparison.
[b]While this assessment is informed by studies of other types of asbestos, it is not a complete toxicity review of other amphiboles or of chrysotile asbestos.

For lung cancer, this assessment selected the upper bound among the lung cancer lifetime unit risks from the plausible exposure metrics (regardless of the small residual differences in quality of fit). Because there were few metrics with unit risks higher than the best fitting metric's unit risk for lung cancer mortality endpoint, this method effectively selects the highest lifetime unit risk among those considered for the lung cancer mortality endpoint. Based on the selected model for lung cancer mortality using the cumulative exposure with a 10-year lag in the Libby subcohort data yields a central unit risk estimate of 0.040 per fiber/cc and upper-bound lifetime unit risk of 0.0680 per fiber/cc.

Once the cancer-specific lifetime unit risks are selected, the two are then combined. It is important to note that this estimate of overall potency describes the risk of mortality from cancer at either of the considered sites and is not just the risk of both cancers simultaneously. Because each of the unit risks is itself an upper-bound estimate, summing such upper-bound estimates across mesothelioma and lung cancer mortality is likely to overpredict the overall risk. Therefore, following the recommendations of the *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a), a statistically appropriate upper bound on combined risk was derived in order to gain an understanding of the overall risk of mortality resulting from mesothelioma and from lung cancer.

Because the estimated risks for mesothelioma and lung cancer mortality were derived using Poisson and Cox proportional hazards models, respectively, it follows from statistical theory that each of these estimates of risk is approximately normally distributed. For independent normal random variables, a standard deviation for a sum is easily derived from individual standard deviations, which are estimated from confidence intervals: standard deviation = (unit risk – central risk) ÷ $Z_{0.95}$, where $Z_{0.95}$ is a standard normal quantile equal to 1.645. For normal random variables, the standard deviation of a sum is the square root of the sum of the squares of individual standard deviations.

As shown in Table 5-50, the upper bound of the selected mesothelioma mortality unit risks was 0.122 per fiber/cc (highest adjusted unit risk value). The associated central estimate of risk was 0.075 per fiber/cc for mesothelioma mortality. Table 5-52 shows the upper bound of the selected lung cancer mortality unit risk was 0.068 per fiber/cc (highest unit risk value based on LEC_{01}). The associated central estimate of risk was 0.040 per fiber/cc for lung cancer mortality.

It is important to mention here that the assumption of independence of the estimated risks for mesothelioma and lung cancer mortality (note above) is a theoretical assumption, as there is insufficient 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 the 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 calculated by $[1 - \min(p1,p2)]/(1 - p1 \times p2)$ and the upper limit is $\min(1,2 - p1 - p2)/(1 - p1 \times p2)$. Substituting the risk of lung cancer ($p1$) is 0.040 and the risk of mesothelioma ($p2$) is 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.

In order to combine the unit risks, first obtain an estimate of the standard deviation of the sum of the individual unit risks as:

$$\sqrt{[\,[[(0.122 - 0.075) \div 1.645]^2 + (0.068 - 0.040) \div 1.645]^2\,]} = 0.033 \text{ per fiber/cc} \quad (5\text{-}15)$$

Then, the combined central estimate of risk of mortality from either mesothelioma or lung cancer is 0.040 + 0.075 = 0.115 per fiber/cc, and the combined IUR is $0.115 + 0.033 \times 1.645 = 0.169$ per fiber/cc.

To illustrate the uncertainty in the selected IUR, Table 5-53 shows central risks and upper bounds for the combined IUR for selected metrics for each cancer (CE10 for lung cancer and CE10 with 5-year half-life for mesothelioma) and for selected lung cancer model (CE10) with other mesothelioma models suggested in the literature from Tables 5-51. The selected IUR does address issues of model uncertainty because a higher risk is only given by the Peto model, but the Peto model tends to overestimate mortality from mesothelioma in asbestos cohorts with long follow-up [e.g. Barone-Adesi et al. (2008) and Berry et al. (2012)].

Age-dependent adjustment factor

As discussed in Section 4.7.1.1, there is no chemical-specific information for LAA, or general asbestos, that would allow for the computation of a chemical-specific age-dependent adjustment factor for assessing the risk of exposure that include early-life exposures.

The review of mode-of-action information in this assessment (see Section 4.6.2.2) concluded that the available information on the mode of action by which LAA causes lung cancer or mesothelioma is complex and a mode of action is not established at this time. Thus, in accordance with 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 for substances that act through a mutagenic mode of action is not recommended.

5.4.5.3.1. ***Comparison with other published studies of Libby workers cohort.*** For lung cancer, two alternative analytic approaches to the use of EPA's extended Cox proportional hazards models are considered here for the calculation of a unit risk of lung cancer mortality. All of the choices are based on different analyses of the Libby worker cohort; however, inclusion criteria

differ among the analyses as does the length of mortality follow-up. Each of the two alternative approaches has two options to estimate the slope of the exposure-response relationship in place of the regression slope estimated from the Cox proportional hazards model.

The first approach would be to use the published categorical results based on Sullivan (2007), which offers two options: (1) estimate a slope to those categorical data or (2) use the slope estimated in a published reanalysis of categorical data of the Sullivan (2007) cohort by Berman and Crump (2008). The second approach would be to use the published regression results of other researchers who modeled the underlying continuous data. There are two options under this approach: (1) use the slope estimated by Larson et al. (2010b) or (2) use the slope estimated by Moolgavkar et al. (2010).

For comparison purposes, the lung cancer unit risk from these alternatives is computed; however, as all analyses are based upon different subsets of the Libby workers cohort and used different analytic methods, the results are not necessarily interchangeable. Table 5-54 summarizes lung cancer risks derived from these studies.

Table 5-54. Lung cancer regression results from different analyses of cumulative exposure in the cohort of workers in Libby, MT. All analyses used NIOSH-collected exposure data but used different cohort definitions, lengths of follow-up, and lengths of exposure lags to account for cancer latency.

Lung cancer analysis	Cohort definition	Follow-up	Lung cancer cases/*N*	Slope per fibers/cc-yr $\times 10^{-3}$ (calendar yr)	Risk based on upper confidence limit (UCL) on the slope (per fibers/cc)
This current assessment	Hired post-1959 Exposures 1960−1982	2006	32/880	5.8	0.068
Sullivan (2007)	Still alive post-1959 White males Exposures 1960−1982	2001	99/1,672	4.2	0.037
Moolgavkar et al. (2010)[a]	Still alive post-1959 White males Exposures 1960−1982	2001	95/1,662	1.69	0.011
Berman and Crump (2008)[b]	Still alive post-1959 White males Exposures 1960−1982	2001	93/1,672	3.96	0.079
Larson et al. (2010b)	Full cohort Exposures 1935−1993	2006	98/1,862	1.61	0.010

[a]Reanalysis of Sullivan (2007).
[b]Sullivan (2007) and reanalysis of Sullivan (2007) state slightly different number of lung cancers. It is impossible to reconcile these numbers from published information.

The first alternative analytical approach to estimating the extra risk from a linear regression of individual mortality data was to use a technique that is standard in EPA cancer risk assessments (U.S. EPA, 2005a) when individual-level data are not available. This approach used a weighted linear regression of standardized risk ratio (SRR) estimators for lung cancer mortality in white males, as calculated in the NIOSH cohort analysis (Sullivan, 2007), with categorical cumulative exposure and a 15-year lag. The Sullivan (2007) analysis was based only on those workers who had not died or been lost to follow-up before January 1, 1960 (in contrast to employment beginning after January 1, 1960), because the NIOSH software program (Life-Table Analysis System) used for this analysis only has statistics on external comparison rates for asbestosis (one of the primary outcomes of interest in the Sullivan (2007) analysis) beginning in 1960. The SRR analysis involves internal comparisons of lung cancer mortality rates in the higher exposure categories to the lung cancer mortality rates in the lowest exposure category. The weights used for the SRRs were the inverses of the variances. Midpoints of the exposure intervals were used, and for the unbounded interval, the midpoint was assumed to be twice the starting point of that interval.

Using this approach, a regression coefficient of 4.2×10^{-3} per fiber/cc-yr (standard error [SE] = 7.7×10^{-4} per fiber/cc-yr, $p = 0.03$) was obtained from the weighted linear regression of the categorical SRR results. Because the data from Sullivan (2007) were already adjusted for the length of an occupational year (240 days) to the length of a calendar year (365 days), only the standard adjustment for inhaled air volume was performed. The concentration estimate obtained using this regression modeling and the life-table analysis procedure was LEC_{01} = 0.272 fiber/cc, resulting in the lung cancer unit risk of 0.0368 per fiber/cc.

The Berman and Crump (2008) reanalysis was based on the Sullivan (2007) summary results except the authors used a lag of 10 years [personal communication with Sullivan in 2008 as cited by Berman and Crump (2008)]. They fit the IRIS IUR (U.S. EPA, 1988a) lung cancer model to aggregate data using an extra multiplicative parameter α. In this model, the relative risk at zero exposure is α rather than 1 (unity). With $\alpha = 1$, their model did not fit, and with α estimated, the fit was satisfactory. Berman and Crump (2008) chose the central estimate of the slope from the fit with α estimated, but constructed an "informal" 90% confidence interval by the union of two confidence intervals (this upper bound is shown in Table 5-54). This was done to address uncertainty in the estimated parameter α, similar to what is done in this current assessment with estimated lag and decay. Note also that Berman and Crump (2008) provided a UF to adjust for several sources of uncertainty in exposures, resulting in an upper-bound risk of 0.3162.

The second alternative analytic approach to estimating the extra risk of lung cancer from a Cox regression with time-dependent covariates of individual mortality data was to use the results published by Larson et al. (2010b), with cumulative exposure and a 20-year lag. This analysis of lung cancer mortality was based on the full cohort of 1,862 workers, updated until

2006 and using the same model form as the current EPA analysis (the extended Cox proportional hazards model). Larson et al. (2010b) reported a regression coefficient of 1.06×10^{-3} per fiber/cc-yr (SE = 3.1×10^{-4} per fiber/cc-yr, $p = 0.0006$).[28] EPA assumed that the cumulative exposures reported by Larson et al. (2010b) were based on years of occupational exposure (240 days per year) during a 365-day calendar year. In order to account for exposure on every day of the year for a calculation of unit risk, an adjustment for exposures during the length of an occupational year (240 days) to the length of an calendar year (365 days) and an adjustment for the volume of inhaled air were performed to match EPA's analyses. The concentration estimate obtained using the Larson et al. (2010b) regression modeling and the life-table analysis procedure was LEC_{01} = 1.26 fibers/cc, resulting in a lung cancer unit risk of 0.0103 per fiber/cc.

Moolgavkar et al. (2010) also used the Cox proportional hazards model with time-dependent covariates for analysis of the Sullivan (2007) cohort with a 15-year lag. The parameter in this study estimates 1.11×10^{-3} per fiber/cc-yr (SE = 2.5×10^{-4} per fiber/cc-yr), which is very close to the Larson et al. (2010b) value, and therefore, the lung cancer unit risk based on their analysis would be very close to the Larson et al. (2010b) value. Comparison with McDonald et al. (2004) is difficult because in that article, outcome is defined as respiratory cancer (ICD-9 160−165), which is more expansive than other researchers' definitions of the outcome as lung cancer, and their subcohort of 406 white men employed before 1963 was exposed during a time period when exposure assessment was less reliable and more likely to include significant exposure-measurement error. Nonetheless, the parameter estimate resulting from the Poisson analysis by McDonald et al. (2004) was 3.6×10^{-3} per fiber/cc-yr.

The differences in the results in Table 5-54 appear to be mostly attributable to the time periods of analysis and various degrees of exposure measurement error corresponding to these time periods rather than the analytic approach. EPA based their analyses on the exposures that occurred after 1959, while the Sullivan (2007), Larson et al. (2010b), and Moolgavkar et al. (2010) analyses were based on the cohort including those hired before 1960, and McDonald et al. (2004) included only workers hired before 1964. The small discrepancy between observed lung cancer deaths between this current assessment and Larson et al. (2010b), described in Section 4.1.1.1, is unlikely to play a role in the difference among risk estimates. Moreover, for the subcohort hired after 1959, all deaths are included in the Larson et al. (2010b) lung cancer counting rules.

As explained in detail in the discussion on uncertainty in the exposure assessment (see Section 5.4.6), there were only several measurements from the 1950s and one from 1942, and most of the exposure estimation for the early years of the cohort's experience was based on

[28]Note that EPA results based on the subcohort hired after 1959 were from the same model form but based on the cumulative exposure with a 10-year lag and had a slope of 5.81×10^{-3} per fiber/cc-yr (SE = 2.48×10^{-3} per fiber/cc-yr, $p = 0.018$).

estimates of the ratio of dust to fibers estimated in the late 1960s and extrapolated backwards in time for several decades. Moreover, 706 of the workers hired before 1960 (not necessarily short-term workers) did not have estimated exposure measurements associated with their positions, leading to a much larger measurement error. These limitations in the underlying exposure assessment for the years before 1968 likely resulted in exposure measurement error that could have attenuated the analytic regression results [see the discussion in Lenters et al. (2012) and Lenters et al. (2011)] on the impact the quality of the exposure information has on estimates of dose-response; also Bateson and Kopylev (2014), thereby yielding a smaller effect estimate for the whole cohort compared to the subcohort hired after 1959.

None of the approaches used by McDonald et al. (2004), Sullivan (2007), or Larson et al. (2010b) could have been appropriately used for the unit risk of mesothelioma because these approaches are not based on absolute risk metrics of association, which the current assessment considers to be the relevant metric of association. Berman and Crump (2008) did not evaluate the risk of mesothelioma. Moolgavkar et al. (2010) used an absolute risk model for mesothelioma. These results are summarized in Table 5-55. The upper-bound results for the full cohort presented by Moolgavkar et al. (2010) are about 80% of the U.S. EPA (1988a) estimate of the mesothelioma slope factor, leading to an approximately 80% estimate of the mesothelioma unit risk as dependence is linear in the mesothelioma slope factor (see eq 5-11). This is very close to the current assessment's estimate based on the subcohort, which is also about 80% of the U.S. EPA (1988a) estimate of mesothelioma risk. Duration of exposure, but neither department code nor job category, was known for 706 of 991 (71%) workers hired from 1935 to 1959. Because of that limitation, duration of employment is the best metric for the full cohort, and it does not support exposure-response estimation.

Table 5-55. Mesothelioma analysis results from different analyses of cumulative exposure in the Libby workers cohort. All analyses used NIOSH-collected exposure data but different cohort definitions, lengths of follow-up, and lengths of exposure lags to account for cancer latency.

Mesothelioma analysis	Cohort definition	Follow-up	Mesothelioma cases/*N*	Mesothelioma risk (absolute risk model) (per fiber/cc)
This current assessment	Hired post-1959 Exposures 1960−1982	2006	7/880	Upper Bound = 0.122 Central = 0.075
Sullivan (2007)	Still employed post-1959 White males Exposures 1960−1982	2001	15/1,672	No estimates of absolute risk
Moolgavkar et al. (2010)[a]	Still employed post-1959 White males Exposures 1960−1982	2001	15/1,662	Upper Bound ≈ 0.13 Central ≈ 0.08
Larson et al. (2010b)	Full cohort Exposures 1935−1993	2006	19/1,862	No estimates of absolute risk
Berman and Crump (2008)[a]	Still employed post-1959 White males Exposures 1960−1982	2001	15/1,672	No estimates provided

[a]Reanalysis of Sullivan (2007).

5.4.6. Uncertainties in the Cancer Risk Values

Uncertainties in the derivation of the IUR are important to consider. This assessment does not involve extrapolation from high doses in animals to low doses in humans. It is based on a well-documented and well-studied cohort of workers with adequate years of follow-up to evaluate mesothelioma and lung cancer mortality risks with PODs within the range of the data. The discussions below explore uncertainty in the derivation of the IUR to provide a comprehensive and transparent context for the resulting cancer mortality risk estimates.

5.4.6.1. *Sources of Uncertainty*

Sources of uncertainty in this assessment include:

1) *Uncertainty in low-dose extrapolation,*
2) *Uncertainty in exposure assessment, including analytical measurements uncertainty,*
3) *Uncertainty in model form,*
4) *Uncertainty in selection of exposure metric,*
5) *Uncertainty in assessing mortality corresponding to other cancer endpoints,*

6) *Uncertainty in control of potential confounding in modeling lung cancer mortality,*

7) *Uncertainty due to potential effect modification,*

8) *Uncertainty due to length of follow-up,*

9) *Uncertainty in use of life-tables to calculate cancer mortality inhalation unit risks,*

10) *Uncertainty in combining of risks to derive a composite cancer inhalation unit risk (IUR), and*

11) *Uncertainty in extrapolation of findings in adults to children.*

5.4.6.1.1. ***Uncertainty in low-dose extrapolation.*** A common source of uncertainty in quantitative cancer risk assessments generally derives from extrapolating from high doses in animals to low doses in humans. Compared to assessments based on animal data, the uncertainty from low-dose extrapolation in this assessment, which uses occupational epidemiology data, is considered to be lower for the following reasons. The NIOSH worker cohort developed by Sullivan (2007) includes 410 workers employed less than 1 year among the 880 workers hired on or after January 1, 1960. Although short-term workers on average experience a mean exposure intensity per day worked greater than workers employed more than a year (Sullivan, 2007), the cohort nevertheless includes many short-term workers with relatively low cumulative occupational exposures. Further, inclusion of salaried workers in the NIOSH cohort (Sullivan, 2007) adds many workers with lower workplace exposure. Thus, while occupational exposure concentrations may be generally higher than typical ongoing environmental concentrations, the low-dose exposures in this occupational database may be more representative of nonoccupational exposures.

While many occupational epidemiology studies are based on relatively high exposure levels that are beyond the range of common environmental exposures, many in the Libby worker cohort experienced exposures that were near or below the PODs derived from the life-table analysis (i.e., the estimated PODs are in the range of the observed data). The POD for the selected lung cancer mortality exposure metric was 0.191 fiber/cc. The POD for the selected mesothelioma mortality exposure metric was 0.106 fiber/cc. Among the workers hired after 1959 who had at least 1 year of occupational exposure (n = 470; 20 lung cancer deaths), there were 19 (4%) with average occupational exposure concentrations of less than 0.3 fiber/cc, including one lung cancer death (5%).

Although data might have been modeled down to a very low cumulative exposure level, the *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a) recommends defining a POD for low-dose extrapolation to increase the stability of the IUR estimate at lower exposures where fewer cancers might be expected. Thus, the uncertainty associated with low-dose extrapolation is somewhat mitigated because the linear extrapolation from the dose associated with the POD

from the life-table analyses of each cancer endpoint was encompassed within the observed data range. Nonetheless, some uncertainty remains in the extrapolation from occupational exposures to lower environmental exposures when using a POD.

5.4.6.1.2. ***Uncertainty in exposure assessment.*** Accurate exposure assessment is generally considered to be a major challenge for occupational epidemiologic studies and is a challenge well recognized by the NIOSH investigators (Amandus et al., 1987b). As stated previously in Section 5.4.3.3, while it is generally true that the use of more data is an advantage in statistical analyses because it allows for the computation of more statistically precise effect estimates, this advantage in precision may be offset by a negative impact on the accuracy of the effect estimate if an increase in sample size is accompanied by greater exposure misclassification or other biases. In this case, EPA decided to base this LAA-specific human health risk assessment upon the mortality experience of workers hired on or after January 1, 1960. EPA's use of the subcohort analysis is based on the belief that it is important to accurately estimate the true underlying exposure-response relationships by relying on the most accurate exposure data. The use of this subcohort greatly reduces the uncertainty in exposure error compared to evaluations based on the full cohort. More specifically:

a) Job category and department codes were completely unknown for 706 of the 991 workers' jobs from 1935 to 1959 (71% of the cohort for this time period). These workers had the same estimated exposure concentration (66.5 fibers/cc) for all years without this information. Examination of the post-1959 cohort removes this significant source of exposure misclassification (only 9 of 880 subcohort workers did not have department code and job category information).

b) Using the more recently hired cohort minimizes the uncertainty in estimated worker exposures based on the JEM, which was informed by air sampling data available in 1956 and later years. Although uncertainties still exist in the task-specific exposure estimates from 1960−1967, uncertainty in the assessment of earlier exposure levels is considerably greater.

c) Exposure measurements were collected from the area samples and represented exposures for all the workers with the same job code. Statistically, this causes the Berkson measurement error effect, which is described later in this section.

As EPA exposure-response modeling for mesothelioma and lung cancer mortality is based on the post-1959 subcohort, the remaining discussion of uncertainty in exposure measurement will address these data.

5.4.6.1.2.1. ***Sources of uncertainty in job history information.*** Worker exposures for EPA exposure-response modeling were calculated based on job histories and the JEM from 1960 through 1982 (see Figure 5-5). Overall, there is little uncertainty in the job history information.

Regarding exposure estimation for the occupational cohort, the NIOSH investigators (Amandus et al., 1987b) conducted a detailed retrospective exposure assessment to estimate the individual worker exposures. NIOSH used extensive occupational exposure data to construct the time-specific JEM, spanning decades (Amandus et al., 1987b). These data were reabstracted from the workers' employment records for quality assurance (Sullivan, 2007). NIOSH records on work histories and job-specific exposure extended from the 1930s through May 1982. However, the vermiculite mining and milling operation continued on for several years, and some workers were retained through 1993 for plant close-out activities. Only 148 members of the post-1959 cohort (n = 880) were employed as of the May 1982 employment records when the cohort was enumerated by NIOSH (Sullivan, 2007). Because exposure concentrations in 1982 (see Table 5-21) were generally below 1 fiber/cc with only two locations having concentrations of 1.2 fibers/cc, it is unlikely that these workers' exposures were significantly underestimated.

Sources of uncertainty in exposure intensity for the identified location operations

The available exposure data that inform the JEM include over 4,000 air samples, the majority of which were collected after 1967 (see Table 4-1). All of the job location exposure estimates (see Table 5-21) from 1968−1982 were directly informed from air samples collected on membrane filters and analyzed for fibers by PCM. The availability of site-and task-specific air samples for these years provides a good basis for the exposure estimates. However, some uncertainties exist in estimating asbestos exposures using air samples analyzed by PCM.

1) PCM analysis does not determine the mineral or chemical make-up of the fiber: The PCM method defines and counts fibers based on the size (length, width, and aspect ratio) of the particle without regard for the material that makes up the particle being viewed. The PCM method was developed for use in occupational environments where asbestos was present, and the nature of the fibers should be further evaluated to confirm the fibers viewed under PCM are asbestos. McGill University researchers evaluated the fibers collected on membrane filters in the early 1980s and confirmed the presence of asbestos fibers in the tremolite-actinolite solution series consistent with the LAA (McDonald et al., 1986a). NIOSH researchers confirmed the presence of tremolite asbestos in bulk dust samples but not in air samples from the facility (Amandus et al., 1987b). Although less specific to fibers, 60−80% of the airborne dust in the mills in 1968 was tremolite, further supporting the presence of asbestos in the air (based on State of Montana air sampling, and x-ray diffraction analysis by the Public Health Service [correspondence, October 17, 1968]). However, although the presence of mineral fibers in the actinolite-tremolite series was confirmed in the work environment, it is possible that fibers were also counted by PCM from other materials (such as textiles from clothes and packaging materials). Therefore, it is unknown from these data what proportion of the counted PCM fibers were mineralogically asbestos and what proportion were other materials present in the air workplace.

2) PCM defines fibers as particles with an aspect ratio of 3:1 or greater. There is an ongoing debate in the literature on asbestos toxicity regarding the influence of aspect

ratio on relative toxicity. Specifically, in mining environments, it has been speculated that a larger proportion of low aspect ratio fibers from mineral dusts may significantly impact the apparent cancer potency of the measured PCM fibers in those environments (Berman, 2010; U.S. EPA, 1988a). Few data are available to understand fiber morphology and fiber aspect ratios in the Libby cohort working environment. Considering the post-1959 cohort, PCM fiber size distribution and aspect ratio data only exist for a set of eight air samples (599 fibers) collected from the wet mill and screening operations and analyzed by the NIOSH researchers (Amandus et al., 1987b). For these air samples, over 96% of the fibers viewed by PCM had an aspect ratio greater than 10:1 [see Table 4-2 (Amandus et al., 1987b)].[29] However, because these samples were provided by the company in the early 1980s, they do not represent conditions in the old wet mill or dry mill operations, which were significantly dustier environments (Amandus et al., 1987b). It is possible that prior to IH modifications in 1974, the dry and old wet mills generated proportionally more mineral dusts than the screening plant and new wet mill operations after IH modifications. No data are available for the mining environment, which would also be expected to generate a range of mineral dusts. Therefore, there is a significant uncertainty about the size and aspect ratio of fibers included in PCM fiber counts for the majority of the post-1960 workers cohort, but it is not possible to judge the direction or magnitude of such uncertainty.

3) The resolution of visible PCM fibers: Current analytical instruments used for PCM analysis have resulted in a standardization of minimum fiber width considered visible by PCM between 0.2 and 0.25 µm. Historical PCM analysis (1960s and early 1970s) generally had less resolution, and fibers with minimum widths of 0.4 or 0.44 µm were considered visible by PCM (Amandus et al., 1987b; Rendall and Skikne, 1980). McDonald et al. (1986a) compared fibers viewed by PCM and TEM and estimated that approximately one-third of the total fibers could be viewed by PCM. Because 38% of the fibers were <5 µm in length, this implies approximately 30% were not viewable by optical microscopy for other reasons, such as width. However, it is unknown what proportion of that 30% would be viewed with the minimum width resolution of 0.25 µm for later optical microscopy. It is likely that early PCM counts were underestimated relative to the later data for the cohort but by less than a factor of 2.

Before 1968, no air sampling data were available for 23 of the 25 job location operations (see Table 4-2), and the exposure estimates were extrapolated from later air sampling data. Amandus et al. (1987b) recognized there was significant uncertainty in the extrapolation of available air sampling data to previous time periods. The researchers considered major changes in operations and interviewed employees in the early 1980s regarding previous years of operation. The assumptions used to make these extrapolations are clearly stated for each of the plant operations. For four operations, high and low estimates of pre-1968 exposures were provided based on different sets of exposure assumptions (see Table 5-21). For ore loading,

[29]Although Amandus et al. (1987b) report the sizing of PCM fibers, the details of the methodology are not given regarding how these fibers were identified. No method is cited, and it is unclear if the sizing was done by PCM or TEM for fibers in the reported size categories.

there were negligible differences in the exposure estimates for the period from 1960−1967 (10.7 versus 9 fibers/cc). For drilling, the river dock, and the bagging plant, there were 3.4-, 2.6-, and 2.8-fold differences, respectively, between the high and low estimates of exposure between 1960 and 1968.

Dry mill exposures between 1960 and 1968 were informed by air sampling for total dust collected in the dry mill facility from 1956−1969 (where total dust was collected by midget impingers). Amandus et al. (1987b) derived a conversion factor of 4.0 fibers/cc per mppcf to apply to the two location operations in the dry mill during these years. A range of conversion factors was considered for the dry mill depending on how the dust and fiber air samples (PCM) were grouped and averaged (1.2 to 11.5 fibers/cc per mppcf). A subset of dust and fiber samples available over the same time period (1967−1968) resulted in a ratio of 8.0 fibers/cc per mppcf. In contrast, a ratio of 1.9 fibers/cc resulted when total dust samples from 1969 were compared with fiber samples from 1970. However, both of these subsets had limited numbers of samples available. Therefore, the conversion factor of 4.0 fibers/cc per mppcf was selected based on using the maximum samples available over a time period when the dry mill exposures were considered similar: dust samples (1965−1969) and fiber samples (1967−1971).

5.4.6.1.2.2. ***Sources of uncertainty in the calculation of the job-exposure matrix (JEM).*** The exposures in the JEM (see Figure 5-5) were calculated from the exposure intensities of the various task-specific exposure intensities shown by job location operation (see Table 5-21). The uncertainties in the exposure intensity for the job location operations will impact the JEM. Additionally, for each of the job categories in the JEM, NIOSH researchers defined which tasks (job location operations) were conducted and for what proportion of the work day. A TWA exposure for each job category across time was calculated based upon these assumptions and the task-specific exposure estimates. There is a measure of uncertainty in these assumptions for each job category. Additionally, there is interindividual variation within the job categories. These uncertainties are common to exposure reconstruction for epidemiological cohorts.

5.4.6.1.2.3. ***Uncertainty in the exposure metric.*** The PCM measurement is the available exposure metric for analysis of the Libby worker cohort at this time. Currently, there is no optimal choice of the best dose metric for asbestos, in general, and for LAA, in particular. Uncertainties related to PCM analytical method are discussed in Section 2. Briefly, PCM cannot distinguish between asbestos and nonasbestos material or differentiate among specific types of asbestos. Further, due to limitations of this methodology, PCM does not take into account fibers shorter than 5 µm in length.

5.4.6.1.2.4. ***Evaluation of the effects of uncertainties in exposure measurement.*** An understanding of the effects of exposure measurement error on the risks estimated from

epidemiologic analyses is important to place these possible exposure measurement errors in context. The effect of exposure measurement error on estimates of the risk of mesothelioma or lung cancer mortality attributable to exposure depends upon the degree to which that error may be related to the likelihood of the outcome of interest (mesothelioma or lung cancer mortality). Exposure measurement error that is similar among workers who died of lung cancer, and those who did not die of lung cancer, is termed nondifferential exposure measurement error. Exposure measurement error that is associated with the outcome (error that is differential with respect to disease status) can cause bias in an effect estimate towards or away from the null, while nondifferential exposure error typically results in bias towards the null (Rothman and Greenland, 1998). From the above evaluation of uncertainties, there is no indication that the uncertainties in job history information, exposure estimates for specific tasks, or calculation of the JEM would be differential based on the cancer health outcome data. Therefore, these uncertainties 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).

Generally speaking, if the exposure concentrations estimated by NIOSH were systematically too high, then the associated risks of exposure estimated in the regression analysis would be low because the same actual risk would be spread across a larger magnitude of exposure. Similarly, if the exposure concentrations estimated by NIOSH were systematically too low, then the associated risks of exposure estimated in the regression analysis would be too high. From the above evaluation, the majority of the sources of uncertainty are not systematic. There are a few areas of uncertainty that may be classified as biased:

1) High- and low-exposure estimates for four job location operations were provided between 1960 and 1967. Amandus et al. (1987b) chose the high estimates of exposure for these job location operations when calculating the JEM. Therefore, there will be a bias towards the high end for the job categories informed by these data. There was a 1.1- to 3.4-fold difference between the high and low estimates. This difference will be less pronounced where these exposure concentrations are averaged with other job location operations in the JEM, and across multiple jobs (as was the case for the majority of the workers; see Figure 5-5).

2) Current PCM analysis would count more fibers relative to early PCM methods based on minimum fiber width resolution. For example, Amandus et al. (1987b) used a minimum width cutoff of 0.44 µm in their review of PCM fibers in the 1980s, which may have resulted in as much as a twofold underestimate compared to current PCM methods with a width resolution of 0.25 µm or less. Additionally, as PCM methodology has developed over time, it is unknown when PCM results from company records would be considered relatively standard to a minimum width resolution between 0.2 and 0.25 µm. Also, prior to standardization of PCM to 0.25-µm minimum width, there was interlaboratory variability as well. Therefore, the

size distribution of PCM fibers (e.g., minimum width) reported in the JEM may have changed over time. Although theoretically a systematic bias, given the years for which PCM data are available, this is likely an insignificant effect.

3) Asbestos was a contaminant of vermiculite that was the primary object of production. Mine, old dry mill, and wet mill ambient air may have contained material other than asbestos that could have contributed to PCM fiber count. The exposures in the old dry and wet mills and mine location may have included a greater proportion of dust to fibers than tasks using the ore and refined vermiculite after the new wet mill became operational. It is possible there is a systematic overcount of fibers in the dusty environment due to interference from nonmineral fragments. This likely affects the exposure intensity for 23 of 25 job location operations within the mine and old dry mill. Estimated exposures from job categories that include these operations may be biased upwards.

Nondifferential measurement error in a continuous exposure can be of the classical or Berkson type and typically arises in environmental and occupational settings as a mixture of the two forms (Zeger et al., 2000). Classical measurement error occurs when true exposures are measured with additive error (Carroll et al., 2006) and the average of many replicate measurements, conditional on the true value, equals the true exposure (Armstrong, 1998). This error is statistically independent of the true exposure being measured and attenuates true linear effects of exposure, resulting in effect estimates in epidemiologic studies that are biased towards the null (Heid et al., 2004; Zeger et al., 2000; Armstrong, 1998). Such errors occur, for example, when the mean values of multiple local air samples are used.

Berkson measurement error is independent of the surrogate measure of exposure (Heid et al., 2004; Berkson, 1950) and is present when the average of individuals' true exposures, conditional on the assigned measurement, equals the assigned measurement. Berkson measurement error can arise from the use of local area mean sampled exposures to represent the individual exposures of people in that area—even when the estimated area mean is equal to the true underlying mean (i.e., no classical measurement error). Examples of random variability in personal behavior that may produce Berkson measurement error in personal exposure estimates include the volume of air breathed per day among the workers and the effectiveness of an individual's nasal filtration at removing contaminants. In general, Berkson measurement error is not thought to bias effect estimates but rather increases their standard errors (Zeger et al., 2000). However, some epidemiologic studies have suggested that Berkson measurement error can produce a quantitatively small bias towards the null in some analyses (Bateson and Wright, 2010; Kim et al., 2006; Reeves et al., 1998; Burr, 1988). Uncertainties in the levels and time course of asbestos exposure for the Libby workers also adds uncertainty in evaluating the relative fit of different exposure metrics.

5.4.6.1.2.5. ***Exposure to other kinds of asbestos and residential exposure.*** Another source of uncertainty in the estimation of exposures in the Libby workers cohort is the potential contribution of nonoccupational or residential exposures as well as exposures to other kinds of asbestos in employment before or after working in Libby.

Many of the workers resided in Libby, MT before and/or after their employment at the mining and milling facilities ended. The vermiculite from the mine had been used at numerous sites around the town including baseball fields around the expansion plant, high- and middle-school tracks, attic and wall insulation in homes, and as a soil amendment in gardens (U.S. EPA, 2010a, 2001). Exposure to asbestos could have occurred among individuals outside of the workplace, particularly through activities with the potential of stirring up soil or other materials that had been mixed with the vermiculite (Weis, 2001). The results of community sampling indicated that even 10 years after mill operations ceased, asbestos fiber concentrations in the air could exceed OSHA standards established for the protection of workers during some activities (Weis, 2001).

Therefore, the workers' actual personal exposures as the sum of occupational and nonoccupational exposures are likely to have been underestimated by the use of estimated Libby-related occupational exposure alone. The difficulty stems from the lack of data on residential exposures and lack of information on pre- and postemployment residence of the Libby workers. Nonoccupational exposures were likely to have been smaller in magnitude than the occupational exposures, but workers may have lived in and around Libby, MT for many more years than they were exposed occupationally. The effect of residential exposure could be more prominent for workers with lower occupational exposure who resided in Libby for a long time. Whitehouse et al. (2008) has reported several cases of mesothelioma among residents of the Libby, MT region who were not occupationally exposed. However, because the report by Whitehouse et al. (2008) details only the cases and does not define or enumerate the population from which those cases were derived, computed relative risks from nonoccupational exposures were not available. ATSDR (2000) reported higher relative risks of mesothelioma among the population of Libby, MT, including former workers residing in Libby, but did not provide relative risk for nonoccupational exposure. Instead, the ATSDR (2000) report on mortality grouped cases among the former workers with nonoccupationally exposed cases. Therefore, it is not clear what the magnitude of the contribution of workers' nonoccupational exposures was to their overall risk.

Some of the occupational workers with lower exposures, such as short-term workers, may have either been high school or college students working during the summer or may have been transient workers who may not have stayed for a long time in Libby. It is interesting to note that the lung cancer rates by age at first exposure show very low rates for those first exposed before age 25 (see Table 5-42). Sullivan (2007) analyzed differences between short- and long-term workers and reported little difference among the groups except for age at hire. As the short-term

workers were younger on average, this supported the suggestions that some of the short-term workers may have been college students working during the summer. This population of short-term workers is not well defined; however, while it is possible that short-term transient workers could potentially have been exposed to other kinds of asbestos or other lung carcinogens in their non-Libby occupational career, which might have affected their pre- and post-Libby risk profile for asbestos exposure, lung cancer rates for those with less than 1 year of exposure are in line with those with less than 5 years of exposure (see Table 5-27). While their occupational histories other than working in Libby are unknown, it is very unlikely that they include exposures of the magnitude that were encountered in the Libby mine and mill. The impact of these uncertainties on regression slopes is difficult to evaluate. However, the slope may be somewhat underestimated, as an observed increase in risk would be attributed to a larger exposure differential than might have been present due to the addition of nonoccupational exposures. There will also be a downward bias from random exposure measurement error with lower occupational exposure affected disproportionately; however, the magnitude of this bias would be expected to be small.

5.4.6.1.2.6. ***Conclusion regarding uncertainty in exposure assessment.*** Overall, there are likely to be multiple sources of uncertainty attributable to exposure measurement error. It is possible that systematic error may have been introduced into the exposure intensities assigned to several of the job location operations discussed above. In each case, these errors in estimating exposures were overestimates, which in general, might lead to underestimations of risk for lung cancer, but the results are unclear for the risk of mesothelioma. The magnitude of the potential overestimates of drilling and dry and old wet mill exposures is uncertain. The dust-to-fiber conversion ratio applied to the dry mill during 1960−1967 could be an over- or underestimate by as much as twofold, as Amandus et al. (1987b) derived a conversion factor of 4.0 fibers/cc per mppcf, but subsequent samples available during 1967−1968 resulted in a ratio of 8.0 fibers/cc per mppcf, while samples from 1970 yielded a ratio of 1.9 fibers/cc. Random error in the measurement of dust or fibers would likely have produced an underestimation of risk. There is no known bias in the assumptions to extrapolate exposure to pre-1968 location operations outside of the dry mill, and random bias would also likely have produced an underestimation of risk.

5.4.6.1.3. ***Uncertainty in model form.*** For mesothelioma mortality, the Poisson model is commonly used for rare outcomes and has been applied by McDonald et al. (2004) to model mesothelioma risk in the Libby worker cohort. For lung cancer mortality, the Cox proportional hazards model is a well-established method that is commonly used in cohort studies, including by Larson et al. (2010b) and Moolgavkar et al. (2010) for the Libby worker cohort, because this type of survival analysis takes into account differences in follow-up time among the cohort.

Larson et al. (2010b) conducted Poisson analyses and reported that their lung cancer results using this different model form were similar to those from their extended Cox proportional hazards models, but those results were not shown.

Both of these model forms allow for the evaluation and control of important potential confounding factors such as age, gender, and race, and for the modeling of exposure as a continuous variable. Both model forms yielded exposure-response results with good fit to the occupational exposure data. The default assumption of the extended Cox proportional hazards model as well as the Poisson model is that all censoring (due to death or loss to follow-up) is assumed to be independent of exposure to the LAA. However, exposure to LAA may cause death from other causes such as asbestosis or nonmalignant respiratory disease (Larson et al., 2010b), which is referred to as dependent censoring. The concern is that the observation of lung cancer mortality may be precluded by mortality from other causes.

In the cohort of 880 workers hired after 1959, 32 died of lung cancer, while 10 died of asbestosis, and 21 died of nonmalignant respiratory disease. The mean length of follow-up from the date of hire until death for the workers who died of lung cancer was 24.9 years. However, the mean length of follow-up for the workers who died of asbestosis or nonmalignant respiratory disease was 30.4 years, so it does not appear that early deaths from other causes associated with exposure to the LAA (Larson et al., 2010b) would have precluded many cases of lung cancer. This implies that any potential bias in the lung cancer risk estimates due to dependent competing risks is small.

With respect to mesothelioma mortality, note that the exposure-response modeling is limited by the number of deaths. However, dependent censoring, as described above, is not accounted for in the Poisson model and likely causes a downward bias in the estimation of risk. The mean length of follow-up for the workers who died of mesothelioma was 30.1 years, and there is some evidence that early deaths from other exposure-related causes precluded an individual's risk of death from mesothelioma; only lung cancer exhibited a shorter average follow-up time compared to mesothelioma, and in 419 cases of mesothelioma, mesothelioma and lung cancer were never coidentified (Roggli and Vollmer, 2008).

5.4.6.1.4. ***Uncertainty in selection of exposure metric.*** There is uncertainty about what metric should be used for modeling exposure to LAA. This current assessment evaluated models proposed in the asbestos literature for modeling mesothelioma and models that include unlagged and lagged cumulative exposure with and without a half-life of various lengths, and RTW exposure with and without a half-life. In the analysis of comparative model fit based on the empirical data, lagged cumulative exposure with a half-life provided the best fits for both mesothelioma and lung cancer mortality associated with LAA. However, evaluation of 20-year lag and longer lag times for mesothelioma was not possible, as the earliest mesothelioma death happened less than 20 years from the start of the exposure; hence, exposure was zeroed out, and

the fit of any model with 20-year lag was very poor. Latency time for mesothelioma may be as long as 60−70 years [e.g., Bianchi and Bianchi (2009)], so the precise lag time is uncertain.

In evaluating the data on lung fiber burden, Berry et al. (2009) estimated the range of the half-life for crocidolite to be between 5 and 10 years. That range is consistent with the finding of a 5- to 10-year half-life with 10−15 years lag that provided the best fit to the Libby workers cohort mesothelioma mortality data. Similarly, recent publications indicate that the relative risk of lung cancer due to asbestos exposure declines 15−20 years after the cessation of exposure to asbestos (Magnani et al., 2008; Hauptmann et al., 2002). The marginally best fit for the Libby workers cohort lung cancer mortality data was for CE models with a 5- to 20-year half-life and 10-year lag. However, the precise lag and half-life times are somewhat uncertain. Sensitivity analysis that excluded people with high exposure during 1960−1963 (see Section 5.4.3.6.4) provides further evidence that distinguishing between various lags and decays may be difficult with these data. A limitation of this sensitivity analysis is the decrease in the number of cases, especially for mesothelioma. Resolving this uncertainty would require longer follow-up time, which would allow for a subcohort analysis of workers hired in 1967 or afterwards (when exposure estimates began to be based on PCM measurements) until a sufficient number of cases would be available for additional analysis.

These simulated decay models were derived mathematically to approximate underlying biological processes that are not well understood, and are based on maximizing the likelihood for the workers cohort and may not necessarily apply to the environmental exposure patterns. Nonetheless, while the mode of action for carcinogenicity is unknown, the models incorporating a half-life in the exposure metric were clearly preferable for mesothelioma mortality, and the goal of the regression modeling effort was to identify the best fitting exposure model for the Libby worker cohort.

Table 5-53 illustrates uncertainty in the IUR due to exposure metric selection. The quantitative uncertainty is about threefold.

5.4.6.1.5. ***Uncertainty in assessing of mortality corresponding to other cancer endpoints.***
There is evidence that other cancer endpoints may also be associated with exposure to the commercial forms of asbestos. IARC concluded that there was sufficient evidence in humans that commercial asbestos (chrysotile, crocidolite, amosite, tremolite, actinolite, and anthophyllite) was causally associated with lung cancer and mesothelioma, as well as cancer of the larynx and the ovary (Straif et al., 2009). Among the entire Libby workers cohort, only two deaths were found to be due to laryngeal cancer, and there were no deaths from ovarian cancer among the 24 deaths of 84 female workers. The lack of sufficient number of workers to estimate risk of ovarian cancer is an uncertainty in an overall cancer health assessment.

The remaining uncertainties attributed to assessing mortality corresponding to the cancer endpoints are considered to be low.

5.4.6.1.6. ***Uncertainty in control of potential confounding in modeling lung cancer mortality.*** It is well known that smoking is a strong independent risk factor for lung cancer and may have a synergistic effect with asbestos exposure (Wraith and Mengersen, 2007). In contrast, smoking is not considered a risk factor for mesothelioma (Selikoff and Lee, 1978; Anderson et al., 1976).

As an important potential confounder of the lung cancer mortality analysis, the possible effect of smoking on the estimated risk of lung cancer mortality associated with exposure to LAA needs to be evaluated to the fullest extent possible. This consideration was discussed in Amandus and Wheeler (1987) and in Section 4.1.1.3.

Additionally, W.R. Grace and Co. instituted a smoking ban on the property in 1979 (Peacock, 2003), which may have affected smoking habits, reporting of smoking habits, or both. About 30% of the subcohort was still employed in 1979 and all of the post-1959 cohort had been terminated by May 1982, so the effect of a workplace smoking ban on cohort smoking history may explain the higher proportion of former smokers in the Amandus and Wheeler (1987) data. Lung cancer risks in ex-smokers decrease over time compared to lung cancer risks in continued smokers. A reduction of smoking in the Libby worker population may lead to fewer observations of lung cancer deaths in later years of the cohort study than would have occurred in the absence of the smoking restrictions. Changes in smoking behavior during the course of the epidemiological observation period would lead to changes in the observed time course of lung cancer death rates. This issue is related to potential effect modification of lung cancer mortality described in Section 5.4.6.1.7.

Without high-quality individual-level data on smoking that could be used to control for potential confounding, it is still possible to comment upon the likelihood and potential magnitude of confounding and the impact any confounding would be expected to have on the lung cancer mortality risk estimates. Confounding can be controlled for in a number of ways including by modeling and by restriction. Restriction of the study population can reduce any potential confounding by making the resulting population more similar. For instance, there can be no confounding by gender when a study population is restricted to only men. This assessment restricted the study population to those workers hired after 1959. Smoking habits have changed over time, and it can reasonably be assumed that the range of smoking habits among those hired after 1959 is less variable than that among the whole cohort, particularly because of the narrower range of birth cohorts represented in this subcohort. This should have the effect of reducing some of the potential for confounding. Analytic examinations of potential confounding are discussed below.

Richardson (2010) describes a method to determine if an identified exposure relationship with lung cancer is confounded by unmeasured smoking in an occupational cohort study. EPA implemented this methodology to model the potential effects of LAA on the risk of COPD mortality on the subcohort of workers hired after 1959 (see Section 5.4.3.8). Summarizing these findings, EPA used the method described by Richardson (2010) to evaluate whether exposures to

LAA predicted mortality from COPD as an indication of potential confounding by smoking and found a statistically nonsignificant negative relationship, which was inconsistent with confounding by smoking.

5.4.6.1.7. ***Uncertainty due to potential effect modification.*** Among the 32 deaths from lung cancer in workers hired after 1959 that were used to estimate the unit risk of lung cancer mortality (see Section 5.4.5.2), data on smoking listed 16 as smokers, 4 as former smokers, and 12 of the 32 had missing data. Thus, data to support an estimate of the risk of LAA among known nonsmokers were not available.

It is theoretically possible that the risk of lung cancer mortality estimated in this current assessment is a reflection of a positive synergy between smoking and asbestos, and that the adverse effect of LAA among the potentially nonsmoking workers has been overestimated. The unit risk of the lung cancer estimate herein and the combined mesothelioma and lung cancer mortality IUR would then be health protective for any population that had a lower prevalence of smoking than that of the Libby worker cohort. However, if the smoking ban did diminish the effect of smoking, then any overestimation would be somewhat mitigated.

5.4.6.1.8. ***Uncertainty due to length of follow-up.*** There is some potential uncertainty regarding the length of follow-up for cancer mortality, even more so with the restriction of the cohort to those workers hired after 1959. The hire dates among this subset of the cohort ranged from January 1960 to November 1981 (the mean date of hire was May 1971). Follow-up continued until the date of death or December 31, 2006, whichever occurred first. Therefore, the range of follow-up was from 25 to 46 years, with a mean of more than 35 years.

However, for mesothelioma mortality, the length of the latency period is considerably longer. Suzuki and Yuen (2001) reviewed 1,517 mesothelioma cases from 1975 through 2000 and was able to estimate the latency for 800. Suzuki and Yuen (2001) reported 17% of cases had a latency of less than 30 years with 52% of cases with a latency of less than 40 years. Bianchi and Bianchi (2009) estimated the mesothelioma latency in 552 cases and reported mean latency periods of 35 years among insulators, 46 years among various industries, and 49 years among shipyard workers.

According to the results of Suzuki and Yuen (2001) and of Bianchi and Bianchi (2009) a mean length of follow-up of 35 years may only have captured half of all eventual mesothelioma mortality cases among the Libby workers hired after 1959. If this were so, then the unit risk of mesothelioma mortality could be larger than was estimated from existing data, suggesting continued examination.

5.4.6.1.9. ***Uncertainty in use of life-tables to calculate cancer mortality inhalation unit risk (IUR).*** The life-table procedure computes the extra risk of death from birth up to 85 years of age, in part, because this is how national cancer incidence and mortality rate data that are one basis of the life-tables are made available [see SEER (2010)], Table 15.10, age-specific U.S. death rates). Because the prevalence of cancer mortality is a function of increasing age, this cut-off at age 85 ignores a small additional risk of lung cancer mortality among a small percentage of people who have the higher background risk. This has the effect of slightly underestimating the IUR that would be derived if the life-table were extended for an additional period of time, accounting for longer life spans. Extension of the life-table analysis to people over the age of 85 requires an additional assumption. Assuming that having attained the age of 85 years, the additional life expectancy is 5 years, then the lung cancer mortality unit risk based on the LEC_{01} would be somewhat larger—on the order of 5−10%—slightly more than the additional mesothelioma mortality risk if the life-tables were extended.

5.4.6.1.10. ***Uncertainty in combining of risk for composite cancer inhalation unit risk (IUR).*** For the purpose of combining risks, it is assumed that the unit risks of mesothelioma and lung cancer mortality are normally distributed. Because risks were derived from a large epidemiological cohort, this is a reasonable assumption supported by the statistical theory. EPA conducted a bounding analysis and showed that the related uncertainty is very low.

5.4.6.1.11. ***Uncertainty in extrapolation of findings in adults to children.*** The analysis of lung cancer mortality specifically tested the assumption that the relative risk of exposure is independent of age within the observed age range of the occupational subcohort hired after 1959 and did not find evidence of age dependence, although such a dependence among a working-age study population has been reported in another asbestos-exposed cohort (Richardson, 2009). However, note that no comparable data are available to estimate the lifetime risk from early life exposures. Note that default age-dependent adjustment factors (ADAFs) are not recommended because a mutagenic MOA was not identified.

5.4.6.2. ***Summary***

Section 5.4.6.1 details the several sources of uncertainty in the assessment of the cancer exposure-response relationships and the use of those data to derive the inhalation unit risk. The text that follows summarizes the primary sources of uncertainty and, where possible, the expected direction of effect on the exposure-response risk estimates and the inhalation units risk.

1) Uncertainty in low-dose extrapolation (see Section 5.4.6.1.1)

- There remains some uncertainty in the extrapolation of risks based on occupational exposure to environmental exposure levels but this uncertainty is

considered to be low as the lower range of occupational exposure overlaps with expected environmental exposure levels.

2) *Uncertainty in exposure assessment, including analytical measurements uncertainty (see Section 5.4.6.1.2)*

- The JEM was based on the "high" exposure estimate for each job according to Amandus et al. (1987b) and to some extent this could be an overestimate of exposure. The associated cancer risk would be somewhat underestimated resulting in a somewhat underestimated IUR.

- The JEM was largely based on estimated fiber concentration using PCM measurement (with some extrapolations in time), and because PCM may count all long and thin objects as fibers, these measurement could overestimate the true LAA fiber concentrations leading to an overestimate of exposure and a somewhat underestimated cancer risk resulting in a somewhat underestimated IUR.

- PCM measurements in the era of NIOSH measurements in Libby used a lower resolution, and therefore, included only somewhat thicker fibers thereby counting fewer fibers than would have been counted by later PCM standards. These earlier measurement could underestimate the true LAA fiber concentrations leading to an underestimate of exposure and an overestimate of cancer risk resulting in a somewhat overestimated IUR.

- The PCM measurement is the available exposure metric for analysis of the Libby worker cohort at the time of this assessment. Currently, there is no optimal choice of the best dose metric for asbestos, in general and in particular, for LAA. Uncertainties related to PCM analytical method are discussed in Section 2 and such uncertainties cannot be related to the IUR at the time of this assessment.

- Random measurement error in the assignment of exposures could have the effect of underestimating the risk of lung cancer mortality as that measure of risk is based on a relative measure. The effect would be to somewhat underestimate the risk of lung cancer resulting in a somewhat underestimated unit risk for lung cancer. It is unclear what the impact of such measurement error would be on the absolute risk of mesothelioma.

- Exposure to other kinds of asbestos and residential exposure to LAA may have caused workers' actual personal exposures (as the sum of occupational and nonoccupational exposures) to have been underestimated by the use of estimated Libby occupational exposure information alone. This could underestimate the true LAA fiber exposures leading to an overestimate of the associated cancer risk resulting in a somewhat overestimated IUR.

3) *Uncertainty in model form (see Section 5.6.4.1.3)*

- For mesothelioma, the Poisson model is the standard epidemiologic form and it is considered to be the most appropriate model form for rare health outcomes; therefore, uncertainty is considered to be low. For lung cancer mortality, the Cox proportional hazards model is the standard epidemiologic form. It is considered

to be the most appropriate model form for health outcomes with time-varying exposure data, and thus, uncertainty is considered to be low.

4) *Uncertainty in selection of exposure metric (see Section 5.6.4.1.4)*

- There is uncertainty about what metric should be used for modeling exposures to LAA. Table 5-53 illustrates the uncertainty in the IUR due to exposure metric selection. The quantitative uncertainty is about threefold.

5) *Uncertainty in assessing mortality corresponding to other cancer endpoints (see Section 5.6.4.1.5)*

- The lack of sufficient numbers of workers to estimate the risk of other cancers potentially related to LAA exposure is an uncertainty of unclear direction but is considered to be low due to the rarity of those cancers.

6) *Uncertainty in control of potential confounding in modeling lung cancer mortality (see Section 5.4.6.1.6)*

- The uncertainty in control of potential confounding by smoking is considered to be low, as the described sensitivity analysis did not show evidence of potential confounding.

7) *Uncertainty due to potential effect modification (see Section 5.4.6.1.7)*

- Smoking was not considered to be related to LAA exposure, and therefore, smoking is not considered to be a likely effect modifier of cancer risk. Age has been shown to be a potential effect modifier of lung cancer risk but there was no evidence of this relationship in the subcohort.

8) *Uncertainty due to length of follow-up (see Section 5.4.6.1.8)*

- There is uncertainty related to the limited follow-up for cancer mortality, and it is possible that with subsequent mortality follow-up the IUR could change in a direction that is unknown.

9) *Uncertainty in the use of life-tables to calculate cancer mortality IUR (see Section 5.4.6.1.9)*

- The life-table procedure computes the extra risk of death from birth to 85 years of age. If the life-tables were extended from 85 to 90 years to account for longer life spans, the selected lung cancer mortality unit risk (Table 5-52 shows this as 0.068) would be somewhat larger, about 5−10%, and the selected mesothelioma unit risk (Table 5-50 shows this as 0.122) would be slightly less (about 3%). Taking both effects into consideration, the uncertainty in the IUR is considered to be low.

10) *Uncertainty in combining of mortality risks to derive a composite cancer mortality inhalation unit risk (IUR) (see Section 5.4.6.1.10)*

- EPA assumed that the cancer risks were independent, conducted a bounding analysis and showed the related uncertainty to be very low.

11) Uncertainty due to extrapolation of findings in adults to children (see Section 5.4.6.1.11)

- There is uncertainty in the assumption that risks are independent of age and that children are at the same exposure-related risk as adults. The lack of published information on cancer risks associated with exposures during childhood remains an uncertainty of unclear magnitude.

6. MAJOR CONCLUSIONS IN THE CHARACTERIZATION OF HAZARD AND EXPOSURE RESPONSE

Libby Amphibole asbestos (LAA),[30] present in vermiculite ore from the mine near Libby, MT, is a complex mixture of amphibole fibers—both mineralogically and morphologically (see Section 2.2). The mixture primarily includes winchite, richterite, tremolite, magnesio-riebeckite, magnesio-arfvedsonite, and edenite (84:11:6:1:1:1) amphibole minerals that exhibit a range of fiber morphologies [e.g., asbestiform, acicular, prismatic (Meeker et al., 2003)]. Given the exposure potential to LAA—and its characteristic mineral composition—a hazard characterization and cancer exposure-response assessment are presented.

As discussed in Section 1, no RfC for asbestos currently exists, and the EPA IRIS IUR for asbestos is based on a synthesis of 14 epidemiologic studies that included occupational exposure to chrysotile, amosite, or mixed mineral fibers (chrysotile, amosite, and crocidolite) (U.S. EPA, 1988a). Some uncertainty exists in applying the resulting IUR to environments and minerals not included in the studies considered for the asbestos IUR derivation (U.S. EPA, 1988a). Published mortality studies on the worker cohorts exposed to LAA have become available since the derivation of the IRIS asbestos IUR [i.e., McDonald et al. (2004), McDonald et al. (1986a), Amandus and Wheeler (1987), Sullivan (2007), Larson et al. (2010b), and Dunning et al. (2012)]. This assessment documents noncancer and cancer health effects from inhalation exposure to LAA. Neither an oral slope factor nor an oral reference dose for Libby Amphibole asbestos were derived in this assessment. Oral exposure was not assessed because inhalation is the primary route of concern and oral exposure data for Libby Amphibole asbestos is lacking.

6.1. HUMAN HAZARD POTENTIAL

6.1.1. Exposure

Several different groups of humans have the potential for exposure to fibers from vermiculite mined in Libby, MT, and hence the potential for exposure to the LAA associated with this material. These groups include not only the former workers at the mine and mill site, but also residents in the community of Libby, MT, as well as workers at other locations who processed the vermiculite product. When the mine in Libby, MT, was active, miners, mill workers, and those working in the processing plants were exposed to vermiculite ore, silica dust, and amphibole structures released to air from the ore during the mining and processing operations (Meeker et al., 2003; Amandus et al., 1987b; McDonald et al., 1986a). In some cases, workers may have inadvertently transported contaminated materials from the workplace to

[30]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.

vehicles, homes, and other establishments, typically on the clothing, shoes, and hair. This transported material may have resulted in "take-home exposure" for the workers, their families, and other coresidents. The magnitude of these historic take-home exposures was not measured, so the levels at which individuals in the home might have been exposed are unknown.

While some vermiculite concentrate was exfoliated and used in Libby, MT, most of the concentrate was transported to expansion plants at other locations across the country where it was exfoliated and distributed. A review of company records from 1964−1990 indicates that more than 6 million tons of vermiculite concentrate was shipped to over 200 facilities outside of Libby, MT (ATSDR, 2008). Because expanded vermiculite from Libby was widely used in numerous consumer and construction products in the United States, even people not associated with Libby or other communities with expansion plants may also have the potential for exposure to LAA (see Table 2-2). Vermiculite from Libby, MT was most notably used as attic insulation (vermiculite added insulation or VAI) under the brand name Zonolite (Versar, 2003), and as a soil amendment for gardening, as a fireproofing agent, and in the manufacturing of gypsum wallboard. Residents living in communities near the expansion plants may also have been subjected to some of the same LAA exposure pathways as was the Libby community. The 2008 ATSDR Summary Report observed that individuals in a community with a vermiculite expansion and processing plant could have been exposed to LAA by breathing airborne emissions from the facility or by inhalation exposure to contaminants brought into the home on workers' clothing or from outdoor sources (ATSDR, 2008).

6.1.2. Fiber Toxicokinetics

Although oral and dermal exposure to fibers does occur, inhalation is considered the main route of human exposure to mineral fibers, and therefore, has been the focus of more fiber toxicokinetic analyses in the literature. As with other forms of asbestos, exposure to LAA is presumed to be through all three routes of exposure; however, this assessment specifically focuses on the inhalation pathway of exposure. Generally, fiber deposition in the respiratory tract is fairly well defined based on fiber dimensions and density, although the same cannot be said for fiber translocation to extrapulmonary sites (e.g., pleura). The deposition location within the pulmonary and extrapulmonary tissues plays a role in the clearance of the fibers.

Fiber clearance from the respiratory tract can occur through physical and biological mechanisms. Limited mechanistic information is available on fiber clearance mechanisms in general, and no information specific to clearance of LAA fibers is available. Fibers have been observed in various pulmonary and extrapulmonary tissues following exposure, suggesting translocation occurs to a variety of tissues. Studies have also demonstrated that fibers may be cleared through physical mechanisms (coughing, sneezing) or through dissolution of fibers.

Multiple fiber characteristics (e.g., dimensions, density, and durability) play a role in the toxicokinetics and toxicity of fibers. The literature examining a variety of fiber determinants and

their role in disease is extensive, with a focus on fiber length, width, and durability; however, these studies are often contradictory, making conclusions difficult for fibers in general. This is in part due to the variety of fibers analyzed, inadequate study design, and/or lack of information on fiber dimensions in earlier studies. However, due to the importance in understanding the role of these fiber determinants in the biological response, careful attention has been paid to these fiber characteristics when analyzing research studies on LAA and asbestiform tremolite, an amphibole fiber that comprises part of LAA (see Appendix D). No toxicokinetic data are currently available specific to LAA or its components (e.g., winchite, richterite, tremolite, magnesio-riebeckite, magnesio-arfvedsonite, and edenite). When available, fiber characteristic data are presented in the discussion of each study in relation to the toxic endpoints described.

6.1.3. Noncancer Health Effects in Humans and Laboratory Animals

The predominant noncancer health effects observed following inhalation exposure to LAA are on the lungs and pleural lining surrounding the lungs. These effects have been observed primarily in studies of exposed workers and community members, and are supported by laboratory animal studies. Recent studies have also examined other noncancer health effects following exposure to LAA, including autoimmune effects and cardiovascular disease; this research base is currently not as well developed as that of respiratory noncancer effects. Adequate data are not available to differentiate the health effects of the predominant mineralogical forms composing LAA. Although the adverse effects of asbestiform tremolite are reported in the literature, the contribution of asbestiform winchite and asbestiform richterite to the aggregate effects of LAA has not been determined.

Noncancer health effects identified in humans following inhalation exposure to LAA include pleural abnormalities, asbestosis, and reduced lung function, as well as increased mortality from noncancer causes. Two cohorts of workers exposed to LAA have been studied: workers at the mine and related operations in Libby, MT and employees in the O.M. Scott plant in Marysville, OH, where the vermiculite ore was exfoliated and used as an inert carrier in lawn care products. Radiographic assessments of study participants in both cohorts identified abnormalities consistent with asbestos-related disease, specifically pleural effects and small interstitial opacities [indicative of interstitial fibrosis (Rohs et al., 2008; Amandus et al., 1987a; McDonald et al., 1986b; Lockey et al., 1984)]. These studies provided quantitative exposure estimates and were considered suitable for exposure-response analysis to support an RfC derivation. Additionally, five cohort mortality studies of Libby, MT workers identified an increased risk of mortality from noncancer causes, including asbestosis and other nonmalignant respiratory disease (Larson et al., 2010b; Sullivan, 2007; McDonald et al., 2004; Amandus and Wheeler, 1987; McDonald et al., 1986a) and cardiovascular disease (Larson et al., 2010b).

ATSDR conducted health screening of community members in and around Libby, MT (including past workers), and identified an increase in radiographic abnormalities with an

increased number of exposure pathways (Peipins et al., 2004a; Peipins et al., 2003; ATSDR, 2001b). Other researchers have also used these data to identify the increased prevalence of respiratory symptoms in children (Vinikoor et al., 2010) and to evaluate the prevalence of radiographic abnormalities and reduced lung function in nonworker participants (Weill et al., 2011). Radiographic abnormalities were more prevalent in mine/mill workers versus other exposure categories (i.e., household contacts, 'dusty trades', and community-only exposures) (Weill et al., 2011). Prevalence of pleural effects increased with age and within each exposure group. Decreased pulmonary function (as percentage of the predicted forced vital capacity) was reported for participants with radiographic abnormalities (Weill et al., 2011). A nested case-control study based on ATSDR community health screening also identified a potential for increased prevalence of autoimmune disease (Noonan et al., 2006), and other experimental work has examined mechanistic steps relating to autoimmunity (Marchand et al., 2012; Pfau et al., 2005). Further development of this area of research could provide additional insights into the range of health effects possibly linked to LAA.

Laboratory animal and mechanistic studies of LAA are consistent with the noncancer health effects observed in workers exposed to LAA in Libby, MT and Marysville, OH, as well as exposed community members. Pleural fibrosis was increased in hamsters after intrapleural injections of LAA (Smith, 1978). More recent studies have demonstrated increased collagen deposition and inflammation consistent with fibrosis following intratracheal instillation of LAA fibers in mice and rats (Cyphert et al., 2012b; Cyphert et al., 2012a; Padilla-Carlin et al., 2011; Shannahan et al., 2011a; Shannahan et al., 2011b; Smartt et al., 2010; Putnam et al., 2008). Pulmonary fibrosis, inflammation, and granulomas were observed after tremolite inhalation exposure in Wistar rats (Bernstein et al., 2005b; Bernstein et al., 2003) and intratracheal instillation in albino Swiss mice (Sahu et al., 1975). Davis et al. (1985) also reported pulmonary effects after inhalation exposure in Wistar rats, including increases in peribronchiolar fibrosis, alveolar wall thickening, and interstitial fibrosis.

Limited research is available on noncancer health effects occurring outside the respiratory system and pleura. Sullivan (2007) and Larson et al. (2010b) examined cardiovascular disease-related mortality in the cohort of exposed workers from Libby (see Section 4.1). Mechanistic studies have examined the potential role of iron and the associated inflammation for both respiratory and cardiovascular disease (Shannahan et al., 2012a; Shannahan et al., 2012c; Shannahan et al., 2012b; Shannahan et al., 2012d; Shannahan et al., 2011b). Recent studies in the Libby, MT community examined the association between asbestos exposure and autoimmune disease (Noonan et al., 2006) or autoantibodies and other immune markers [(Pfau et al., 2005) see Table 4-15]. Mechanistic studies examining the role of LAA exposure in autoimmune disease have shown limited effects but did observe an increase in autoantibodies in the serum of exposed animals (Salazar et al., 2013; Salazar et al., 2012). These results are supported by recent in vitro studies demonstrating increased autoantibodies to

mesothelial cells, leading to collagen deposition (Serve et al., 2013). These recent studies have examined the association between asbestos exposure and autoimmune disease; additional research in this area could enhance understanding of this potential mode of action for noncancer effects (Salazar et al., 2013; Serve et al., 2013; Rasmussen and Pfau, 2012; Salazar et al., 2012; Blake et al., 2008; Pfau et al., 2008; Hamilton et al., 2004). Limitations in the number, scope, and design of these studies make it difficult to reach conclusions about the role of asbestos exposure in either cardiovascular disease or autoimmune disease.

Limited in vitro studies have demonstrated oxidative stress following LAA exposures in various cell types (Duncan et al., 2014; Duncan et al., 2010; Hillegass et al., 2010; Pietruska et al., 2010; Blake et al., 2007). LAA fibers increased intracellular ROS in both murine macrophages and human epithelial cells (Duncan et al., 2010; Blake et al., 2007). The role of surface iron on inflammatory marker gene expression and inflammasome activation was shown to be increased following exposure to LAA in human epithelial cells [(Duncan et al., 2014; Shannahan et al., 2012a; Shannahan et al., 2012c; Shannahan et al., 2012b; Shannahan et al., 2012d; Shannahan et al., 2011b; Duncan et al., 2010; Pietruska et al., 2010) see Table 4-18]. Tremolite studies also demonstrate cytotoxicity in various cell culture systems (see Table 4-22). However, evidence is currently insufficient to establish the noncancer MOA for LAA.

6.1.4. Carcinogenicity in Humans and Laboratory Animals

There is convincing evidence of a causal association between exposure to LAA and mesothelioma and lung cancer in workers from the Libby, MT vermiculite mining and milling operations as well as workers from the Marysville, OH plant (Larson et al., 2010b; Sullivan, 2007; McDonald et al., 2004; Amandus et al., 1988; Amandus and Wheeler, 1987; McDonald et al., 1986a). Whitehouse et al. (2008) documented 11 mesothelioma cases in nonworkers exposed to LAA in Libby, MT. Increased lung cancer and mesothelioma deaths are also reported for worker cohorts exposed to other forms of amphibole fibers (amosite and crocidolite) (de Klerk et al., 1989; Seidman et al., 1986; Henderson and Enterline, 1979). These findings are consistent with the increased cancers reported for communities exposed to various rocks and soils containing tremolite fibers (Hasanoglu et al., 2006; Sichletidis et al., 1992b; Baris et al., 1987; Langer et al., 1987; Baris et al., 1979; Yazicioglu, 1976). Although potency, fiber dimension, and mineralogy differ among amphiboles, these studies are supportive of the hazard identification of LAA fibers described in this assessment.

Although experimental data in animals and data on toxicity mechanisms are limited for LAA, tumors were observed in tissues similar to those seen in humans (e.g., mesotheliomas, lung cancer) indicating that the existing data are consistent with the cancer effects observed in humans exposed to LAA. Smith (1978) reported increased incidence of mesotheliomas in hamsters after intrapleural injections of LAA. Additionally, studies in laboratory animals (rats and hamsters) exposed to tremolite via inhalation (Bernstein et al., 2005b; Bernstein et al., 2003; Davis et al.,

1985), intrapleural injection (Roller et al., 1997, 1996; Davis et al., 1991; Wagner et al., 1982; Smith et al., 1979), or implantation (Stanton et al., 1981) have shown increases in mesotheliomas and lung cancers. The tremolite used in these studies was from various sources and varied in fiber content and potency (see Section 4.2, Appendix D).

The available mechanistic information suggests LAA induces effects that may play a role in carcinogenicity (see Section 4.2, Appendix D). Several in vitro studies have demonstrated oxidative stress and genotoxicity following LAA exposures in various cell types (Duncan et al., 2010; Hillegass et al., 2010; Pietruska et al., 2010; Blake et al., 2007). LAA increased intracellular ROS in both murine macrophages and human epithelial cells (Duncan et al., 2010; Blake et al., 2007). Additionally, surface iron, inflammatory marker gene expression, inflammasome, and aneugenic micronuclei were increased following exposure to LAA in human epithelial cells (Duncan et al., 2010; Pietruska et al., 2010). Tremolite studies demonstrate cytotoxic and clastogenic effects (e.g., micronucleus induction and chromosomal aberrations) of the fibers in various cell culture systems.

6.1.5. Susceptible Populations

Certain segments of the general population could be more susceptible to adverse health effects from exposure to LAA. In general, factors that may contribute to increased susceptibility from environmental exposures include lifestage, gender, race/ethnicity, genetic polymorphisms, health status, and lifestyle (e.g., smoking). However, little data exist to address the potential of increased susceptibility to cancer or noncancer effects from exposure to the LAA.

Most occupational studies of workers exposed to LAA have examined the effects only in men because this group represents the vast majority of workers in these settings (Moolgavkar et al., 2010; Sullivan, 2007; McDonald et al., 2004; Amandus et al., 1988; Amandus et al., 1987b; Amandus and Wheeler, 1987; Amandus et al., 1987a; McDonald et al., 1986a; McDonald et al., 1986b). The analysis presented here includes all workers; however, there were few women in the cohort, and therefore, no determination can be made regarding increased susceptibility to lung cancer or mesothelioma by gender. Gender-related differences in exposure patterns, physiology, and dose-response are some of the factors that may contribute to gender-related differences in risk from asbestos exposure (Smith, 2002). The limited data available from community-based studies (ATSDR, 2000) do not provide a basis for drawing conclusions regarding gender-related differences in carcinogenic effects from LAA. Racial diversity among the workers in the studies examining LAA exposure is also limited, and data on ethnic groups are absent, precluding the ability to examine racial and ethnicity-related differences in the mortality risks within the Libby, MT worker cohort. Finally, the potential modifying effects of genetic polymorphisms, preexisting health conditions, nutritional status, and other lifestyle factors have not been studied sufficiently to determine their potential contribution to variation in risk in the population.

6.1.6. Mode-of-Action Information

Research on multiple types of elongate mineral fibers supports the role of multiple modes of action following exposure to LAA. Of the MOAs described in Section 4.4, the evidence that chronic inflammation, genotoxicity and cytotoxicity, and cellular proliferation may all play a role in the carcinogenic response to LAA is only suggestive (see Table 4-23). In vitro studies provide evidence that amphibole asbestos is capable of eliciting genotoxic and mutagenic effects in mammalian respiratory cells; however, direct evidence linking mutagenicity to respiratory cells following inhalation exposure is lacking. Results of the in vivo studies described here are consistent with the hypothesis that some forms of amphibole asbestos act through a MOA dependent on cellular toxicity, based on the observations that cytotoxicity and reparative proliferation occur following subchronic exposure and that bronchiolar tumors are produced at exposure levels that produce cytotoxicity and reparative proliferation. However, dose-response data in laboratory animal studies for damage/repair and tumor development are limited due to the limited number of inhalation studies that used multiple doses of fibers. Although evidence is generally supportive of a MOA involving chronic inflammation or cellular toxicity and repair, there is insufficient evidence to establish a MOA; thus, a linear approach is used to calculate the inhalation cancer unit risk in accordance with the default recommendation of the 2005 *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a). It is possible that multiple MOA discussed above, or an alternative MOA, may be responsible for tumor induction.

6.1.7. Weight-of-Evidence Descriptor for Cancer Hazard

Under the EPA *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a), LAA is *carcinogenic to humans* following inhalation exposure based on epidemiologic evidence that shows a convincing association between exposure to LAA fibers and increased lung cancer and mesothelioma mortality (Larson et al., 2010b; Moolgavkar et al., 2010; Sullivan, 2007; McDonald et al., 2004; Amandus and Wheeler, 1987; McDonald et al., 1986a). These results are further supported by animal studies that demonstrate the carcinogenic potential of LAA fibers and tremolite fibers in rodent bioassays (see Section 4.1, 4.2, Appendix D). As LAA is a durable mineral fiber of respirable size, this weight-of-evidence descriptor is consistent with the extensive published literature that documents the carcinogenicity of amphibole fibers [as reviewed in (Aust et al., 2011; Broaddus et al., 2011; Bunderson-Schelvan et al., 2011; Huang et al., 2011; Mossman et al., 2011)].

EPA's *Guidelines for Carcinogenic Risk Assessment* (U.S. EPA, 2005a) indicate that for tumors occurring at a site other than the initial point of contact, the weight of evidence for carcinogenic potential may apply to all routes of exposure that have not been adequately tested at sufficient doses. An exception occurs when there is convincing information (e.g., toxicokinetic data) that absorption does not occur by other routes. Information on the carcinogenic effects of LAA via the oral and dermal routes in humans or animals is absent. The increased risk of lung

cancer and mesothelioma following inhalation exposure to LAA has been established by studies in humans, but these studies do not provide a basis for determining the risk from other routes of exposure. Mesothelioma occurs in the pleural and peritoneal cavities, and therefore, is not considered a portal-of-entry effect. However, the role of indirect or direct interaction of asbestos fibers in disease at these extrapulmonary sites is still unknown. There is no information on the translocation of LAA to extrapulmonary tissues following either oral or dermal exposure, and limited studies have examined the role of these routes of exposure in cancer. Therefore, LAA is considered *carcinogenic to humans* by the inhalation route of exposure.

6.2. EXPOSURE-RESPONSE

6.2.1. Noncancer/Inhalation

There were three potential candidate studies for the derivation of the RfC—two of these were occupationally exposed cohorts, that is, the Libby worker cohort (Larson et al., 2012a) and the Marysville worker cohort (Rohs et al., 2008) and the third was of community residents in Minneapolis, MN [Minneapolis cohort; (Alexander et al., 2012)]. Each of these studies provided individual exposure estimates and documented increased hazard of pleural effects. As detailed in Section 5.2.1, each of the available studies has strengths and weaknesses. The cohort of Marysville, OH workers [Lockey et al. (1984) and the follow-up by Rohs et al. (2008)] was selected as the principal cohort over the Libby worker cohort for several reasons: (1) lack of confounding by residential and community exposure; (2) availability of information on important covariates (e.g., BMI); (3) an exposure-response relationship defined for lower cumulative exposure levels (particularly the workers hired in 1972 or later and evaluated in 2002−2005); (4) adequate length of follow-up; (5) use of more recent criteria for evaluating radiographs (ILO, 2002); (6) availability of high-quality exposure estimates based on numerous industrial hygiene samples and work records (see Section 5.2.1 for details); and (7) availability of data on TSFE matched to the exposure data. The study of Libby workers (Larson et al., 2012a) had many of these same attributes (e.g., adequate follow-up and high-quality exposure estimates), but exposure levels were generally higher in this group compared to the Marysville workers, and the Libby workers may have experienced greater levels of undocumented “take home” and other nonoccupational exposure for which TSFE data were more uncertain. The main limitation in the study of Minneapolis community residents (Alexander et al., 2012) was relatively lower quality exposure information; exposure estimates were based on a small number of total dust measurements from stack emissions combined with air dispersion modeling, and the authors estimate that the individual exposure estimates are likely to have an order of magnitude of uncertainty. Thus, the study of Marysville workers (Rohs et al., 2008) was selected as the principal study for RfC derivation.

The MOA for LPT and the results of other asbestos epidemiology studies could potentially inform noncancer modeling decisions and suggest exposure metrics to use in

modeling. However, the conclusion of Section 3 of this assessment is that the data are not sufficient to establish a MOA for the pleural and/or pulmonary effects of exposure to LAA. A general understanding of the biology and epidemiology of pleural health endpoints suggests that the timing of exposure, the exposure intensity, and the duration of exposure may be important explanatory variables and these variables were carried forward for modeling using three exposure metrics called "mean exposure" or "mean concentration" (C), "cumulative exposure" (CE), and "residence time-weighted exposure" (RTW).

LPT was selected as the critical effect from among the noncancer radiographic endpoints evaluated in the principal study for derivation of the RfC, with a BMR of 10% extra risk. LPT was selected because it is the study endpoint that generally appears soonest after exposure and at the lowest levels of exposure (i.e., is deemed the most sensitive endpoint). LPT is a pathological change associated with decreased pulmonary function, and thus is considered an appropriate adverse effect for deriving the RfC (see Section 5.2.2.3 and Appendix I).

The RfC is derived based on data from the Marysville workers who were evaluated in 2002−2005 and hired in 1972 or later. These workers were selected due to the greater certainty in their exposure assessment. BMC modeling was used to derive the POD. Statistical models were evaluated based on biological and epidemiological considerations (see Section 5.2.2.6.1) and EPA's Benchmark Dose Technical Guidance (U.S. EPA, 2012). Considerations included (1) the nature of the data set (i.e., cross-sectional, dichotomous health outcome data), (2) ability to estimate the effect of exposure and of covariates, (3) appropriate inclusion of a plateau term representing theoretical maximal prevalence of the outcome, and (4) appropriate estimation of the background rate of the outcome. A number of models were evaluated, and the Dichotomous Hill model with the plateau parameter fixed at a literature-derived value of 85% was selected for the derivation of a POD and sensitivity analyses. This model had very similar fit to others evaluated and was thought to provide the greatest flexibility and ability to determine sensitivity of model results to various assumptions. EPA considered several exposure metrics informed by general biology and the epidemiologic literature, including mean exposure intensity, cumulative exposure (which incorporates duration of exposure), and RTW exposure (which incorporates TSFE by weighting more heavily exposures occurring in the more distant past).

Another important feature of the exposure-response analysis is the ability to include effects of TSFE in the modeling. TSFE has been shown in the literature to be important in evaluating risk of LPT, and studies have shown that prevalence of LPT can increase with increasing TSFE, even after exposure has ceased. EPA evaluated TSFE as a predictor in the primary analytic group of workers hired after 1972 and evaluated in 2002−2005, but found that TSFE was not significantly associated with LPT in this group—likely due to the very low variability in TSFE for this particular population. Thus, EPA used a hybrid modeling approach to "borrow" information on the effect of TSFE from a larger subset of the Marysville workers with greater variability in TSFE. The model was fit in the group of all workers evaluated in

2002−2005 (regardless of hire date), including both LAA exposure and TSFE as predictors. The regression coefficient corresponding to TSFE was then set as a fixed parameter in the model for the primary analytic group of workers hired in 1972 or later. In this hybrid modeling, mean exposure was used due to its superior model fit compared to cumulative exposure. RTW exposure was not used since TSFE was included as a separate covariate (to avoid collinearity of predictors). Using this modeling approach (details in Section 5.2.2.6.2), the resulting BMC_{10} under these modeling assumptions is 0.0.0923 fiber/cc; the corresponding lower 95% confidence limit of the BMC_{10} ($BMCL_{10}$) is 0.026 fiber/cc.

The RfC is obtained by applying uncertainty factors as needed. Two default UFs and one data-informed UF have been applied for a composite UF of 300 (intraspecies uncertainty factor, $UF_H = 10$; database uncertainty factor, $UF_D = 3$; data-informed subchronic-to-chronic uncertainty factor, $UF_S = 10$) (see Section 5.2.5). As shown below, the chronic RfC is 9×10^{-5} fiber/cc for LAA, calculated by dividing the POD by a composite UF of 300:

$$\begin{aligned} \text{Chronic RfC} &= \text{POD} \div \text{UF} \\ &= 0.026 \text{ fiber/cc} \div 300 \\ &= 8.67 \times 10^{-5} \text{ fiber/cc, rounded to } 9 \times 10^{-5} \text{ fiber/cc} \end{aligned} \quad (6\text{-}1)$$

Note that for the primary RfC as well as for all the alternative RfCs, the fiber concentration are presented here as continuous lifetime exposure in fibers/cc, where exposure measurements are based on analysis of air filters by PCM. Current analytical instruments used for PCM analysis have resulted in a standardization of minimum fiber width considered visible by PCM between 0.2 and 0.25 µm. Historical PCM analysis (1960s and early 1970s) generally had less resolution, and fibers with minimum widths of 0.4 or 0.44 µm were considered visible by PCM (Amandus et al., 1987b; Rendall and Skikne, 1980). Methods are available to translate exposure concentrations measured in other units into PCM units for comparison.

While this assessment is informed by studies of other types of asbestos, it is not a complete toxicity review of other amphiboles or of chrysotile asbestos.

EPA conducted RfC derivation from the same subcohort with alternative definitions of the health endpoint (see Section 5.2.3.1 and 5.2.3.2). The chronic RfC value for "any pleural thickening" (APT) was also 9×10^{-5} fiber/cc and the same value was derived for "any radiographic change" (ARC). Although EPA based the primary value of the RfC on the model based on mean exposure, Section 5.2.4 illustrates an alternative derivation of an RfC of 1×10^{-4} fiber/cc from the same cohort with an alternative exposure metric of cumulative exposure. EPA also conducted alternative modeling of the Marysville cohort, including all individuals who participated in the health examination in 1980 (Lockey et al., 1984) and 2002−2005 (Rohs et al., 2008) and who were not exposed to asbestos from a source outside of the Marysville facility (see Section 5.2.4 and Appendix E). The modeling of this full cohort

(*n* = 434 individuals) was performed using an alternative critical effect of "any pleural thickening" (APT), a slightly different definition of LPT (diagnostic criteria changed slightly over time) and with "any radiographic change" (ARC). These analyses yielded five other RfC values. A summary table of the primary and alternative derivation of the RfC is provided in Table 5-11 in Section 5.2.5; all eight alternative derivations of the RfC were within threefold of the primary RfC, ranging from 3×10^{-5} fiber/cc up to 2×10^{-4} fiber/cc. This series of derivations further substantiates the primary RfC derived from the Marysville workers evaluated in 2002−2005, and hired in 1972 or later.

Confidence in the principal study is considered medium. The data used are human epidemiological data which are preferred to animal bioassays, and the principal study (Rohs et al., 2008) is conducted in a population of occupationally exposed workers with long-term, relatively low intensity, exposures. While deriving the primary analysis from the group of workers evaluated in 2002−2005 and hired after 1972 resulted in a smaller data set with fewer cases to model, alternative RfC derivations based on the larger group of workers without restriction on the date of hire (and many more cases) yielded similar values of the RfC. The exposure assessment in the principal study is based on measured data. The main source of uncertainty in the exposure estimates is incomplete exposure measurements for some of the occupations/tasks before industrial hygiene improvements that started about 1973 or 1974 and continued throughout the 1970s (see Appendix F, Figure F-1). The principal study assessed the health outcome cross sectionally and this may underrepresent the true health burden as individuals with more severe disease could have left employment or may have died and not been included in the follow up study, resulting in an underestimation of overall toxicity. However, for health outcomes not considered to be frank effects, such as LPT, this underestimation should be minimal. Further, Rohs et al. (2008) compared the study participants with the complete study population and found no evidence of major differences in the two group's exposure distributions. Thus, the potential for selection bias is considered to be low. In terms of the sensitivity of the principal study to detect the critical effect (LPT) by radiograph, it is known that HRCT can identify asbestos-related lesions in the respiratory tract that cannot be identified by standard radiographs [e.g., Janković et al. (2002), Lebedova et al. (2003), and Šimundić et al. (2002)]. Thus, the technology employed for determining the prevalence of radiographic changes in the Marysville cohort will likely underestimate the prevalence of pleural lesions that could be detected using HRCT.

Confidence in the completeness of the overall database is medium. The database consists of long-term mortality and morbidity studies in humans exposed via inhalation to LAA. The mortality studies do not provide appropriate data for RfC derivation for pleural abnormalities, although the two other morbidity studies (Alexander et al., 2012; Larson et al., 2012a) do support the conclusion that low levels of exposure to LAA is associated with increased prevalence of LPT. It is known that inhaled asbestos fibers migrate out of the lung and into other tissues (see

Section 3.1), which leads to uncertainty regarding the assumption that other health effects would not be expected. While a potential for autoimmune effects and cardiovascular disease is noted in exposed individuals, data are insufficient to provide a quantitative exposure response relationship for these endpoints. It is unknown whether an RfC based on these other health would result in a higher or lower estimate for the RfC. Nor is there evidence as to whether any of these other effects would occur earlier following exposure to LAA than LPT occurs. No data exist on general systemic effects in laboratory animals or humans. Therefore, overall confidence in the RfC is medium, reflecting medium confidence in the principal study and medium confidence in the completeness of the overall database.

6.2.1.1. *Uncertainty and Sensitivity Analyses for Reference Concentration (RfC) Derivation*

It is important to consider the sources of uncertainties in the derivation of the RfC for LAA. These include the following:

Measurement error in exposure assessment and assignment. The estimated exposure for each individual relied on self-reported employment history, which may be subject to recall error. Only data from 1972 and later were used for an RfC derivation based on lack of fiber measurements prior to this date, but some uncertainty remains due to the limited amount of industrial hygiene data collected in 1972−1973. There is also uncertainty in the post-1972 data regarding asbestos content and potency of fibers originating from other ore sources (Virginia, South Carolina, and South Africa). Although LAA was not used in the facility after 1980, industrial hygiene measurements collected after 1980 showed low levels of fibers. Regarding nonoccupational exposure, any exposure to LAA outside of the workplace is not likely to contribute significantly to cumulative exposure; ~10% of workers reported bringing raw vermiculite home, and the majority showered and changed clothes before leaving the workplace. As a sensitivity analysis, EPA evaluated the change in the POD when setting all exposure measurements after 1980 to zero, and when using the geometric mean rather than the arithmetic mean to summarize multiple fiber measurements for a given task/location/time period. These analyses showed a difference of −65 to +50% in the POD.

Radiographic assessment of localized pleural thickening. Conventional radiographs—rather than more sensitive and specific high-resolution computed tomography—were used to determine the health outcome. Localized pleural thickening may be difficult to detect on these radiographs, leading to the potential for outcome misclassification. However, uncertainty in the reading of x-rays in each individual is considered minimal because determinations of pleural outcomes detectable on x-rays were based on agreement among independent classifications of each radiograph done by multiple qualified chest radiologists.

Use of an alternative critical effect. In addition to the primary analysis using a critical effect of LPT, EPA also derived an RfC based on the alternative endpoint of any pleural thickening (APT), and based on any radiographic change (ARC). In the primary analytic group of workers evaluated in 2002−2005 and hired in 1972 or later, the two alternative endpoints are identical to the critical effect of LPT, because the one individual with DPT

also had LPT, and none had interstitial changes. In the larger group of workers used to estimate the effect of TSFE (all evaluated in 2002−2005), there were 69 cases of APT and 71 with ARC, of which the majority (n = 66) were LPT. Consequently, the RfC derived using these two alternative endpoints of APT or ARC were identical (to one significant digit) to that derived for LPT, 9×10^{-5} fiber/cc.

Length of follow-up. Time from first exposure to x-ray was 23.2−32.7 years in the primary analytic group of workers evaluated in 2002−2005, and hired in 1972 or later (mean of 28.2 years). The literature shows that the prevalence of LPT may increase with time, beyond this observed range of time from first exposure. The lack of observed data beyond ~30 years after first exposure (on average) is a source of uncertainty when characterizing the exposure-response relationship for a full lifetime of exposure (e.g., 70 years).

Model Form. A number of model forms were explored in the initial stages of analysis, and generally showed reasonably close fits as measured by the AIC. The Dichotomous Hill model with a plateau fixed at 85% was selected for RfC derivation due to its greater flexibility and ability to evaluate sensitivity to model assumptions. EPA also evaluated the sensitivity of the fixed plateau parameter and found that the POD changed very little (<16%) when fixing the plateau at different values (70, 100%) or when estimating the plateau from the Marysville data.

Effect of covariates. Information on a number of covariates was available for the Marysville workers, including demographic characteristics (gender, smoking status, BMI) as well as potentially exposure-related factors (hire year, job tenure, exposure duration, and age at x-ray). The potential for these factors to confound the association between LAA exposure and LPT was investigated in two ways. First, each was evaluated for association with the exposure, association with the outcome, and whether it was an intermediate in the pathway between exposure and outcome (i.e., did they meet the theoretical definition for a confounder). By these standards, none of the covariates was a confounder. Second, each covariate was included in the final model to evaluate the impact on the estimated effects of LAA exposure and TSFE; the differences were quite small, and none of the covariates were significantly associated with risk of LPT in these models.

6.2.2. Cancer/Inhalation

6.2.2.1. *Background and Methods*

The most appropriate data set for deriving quantitative cancer risk estimates based on LAA exposure in humans is the cohort of workers employed at the vermiculite mining and milling operation near Libby, MT (see Section 4.1.1.1). The Libby, MT worker cohort has been the focus of two epidemiologic investigations by the NIOSH scientists. A database created by NIOSH in the 1980s contains demographic data, work history, and vital status at the end of May of 1982 for 1,881 workers at the vermiculite mine, mill, and processing plant in Libby, MT (see Section 4.1.1.1). Vital status follow-up was completed by NIOSH through 2006 using the National Death Index (Bilgrad, 1997). Nearly 54% of workers in the cohort (n = 1,009) had died

by December 31, 2006. The data from this update (provided by NIOSH) is the basis of EPA exposure-response modeling.

EPA does not have sufficient information to select models for the epidemiology data on the basis of the biological mechanism of action for lung cancer or mesothelioma (see Section 3). In this situation, EPA's 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 LAA, possible exposure metrics were explored for model fit to the chosen models forms. The exposure metric options were selected to provide a range of shapes that was sufficiently flexible to allow for a variety of ways that time and duration might relate to cancer risk in the data being modeled. EPA then evaluated how well the models and exposure metric combinations fit the data being modeled. Then EPA calculated a reasonable upper bound on risk using selected exposure metrics. This is explained in more detail below and in Section 5.4.5. However, there are uncertainties in the modeling of the epidemiological data that may impact the IUR and these are described in Section 6.2.8 below and in greater detail in Section 5.4.6.

In the Libby, MT worker cohort data developed by NIOSH and used by EPA in this assessment, detailed work histories, together with job-specific exposure estimates, allowed for the reconstruction of each individual's occupational exposure experience over time to define multiple exposure metrics. From this information-rich, individual-level data set from NIOSH, EPA constructed a suite of the different metrics of occupational exposure which had been proposed in the asbestos literature or used in EPA health assessment on general asbestos exposures (U.S. EPA, 1988a) as well as modifications proposed (Berry et al., 2012). This suite of models was defined a priori to encompass a reasonable set of proposed exposure metrics to allow sufficient flexibility in model fit to these data. These exposure metrics were evaluated in analytic-regression models to test which exposure metrics were the best empirical predictors of observed cancer mortality, and the better fitting models were advanced for consideration as the basis of the exposure-response relationship for the IUR. The types of exposure metrics evaluated were intended to allow for variations of the classic metric of cumulative exposure, allowing for more or less weight to be placed on earlier or later exposures. These simulated exposure metrics were derived mathematically to approximate underlying processes that are not well understood. Thus, the empirical fit of various exposure metrics to the observed epidemiologic data is evaluated statistically, and the exposure metrics have epidemiological interpretation but do not necessarily have direct biological interpretations.

Exposure estimates for all exposure metrics were adjusted to account for the time period between the onset of cancer and mortality. The lag period defines an interval before death, or end of follow-up, during which any exposure is excluded from the calculation of the exposure metric. There was one important limitation of the NIOSH JEM. Of the 991 workers hired before 1960, 706 workers with unknown department code and unknown exposure assignments

hired between 1935 and 1959 had the same average estimated exposure intensity. The lack of information on specific job assignments for such a large portion of these early workers when exposures were higher resulted in the misclassification of the exposure and effectively yielded exposure metrics that were differentiated only by the duration of each worker's employment. For this reason and because there was little measured fiber exposure data during the earlier period, identifying an adequate exposure-response model fit was unsuccessful. The two biggest problems were that the duration of employment was the best-fitting metric for modeling mesothelioma and that the Cox model assumptions were violated in modeling lung cancer mortality (see Section 5.4.3.4). As a result, this assessment developed a subcohort analysis by dividing the whole cohort into two groups: those hired before 1960 and those hired after 1959. This removed all but nine cohort members with missing department code and job category information and lessened the effect of estimates of early exposures where no air sampling data were available. For the subcohort of those hired after 1959, those two biggest problems were resolved: the assumptions of the Cox model were satisfied, and a lagged cumulative exposure with a decay (rather than duration of exposure, as for the full cohort) was the best-fitting metric for mesothelioma.

Of the 880 workers hired after 1959, 230 (26%) had died by December 31, 2006. The number of mesothelioma deaths in the subcohort is relatively small (n = 7, two deaths coded in ICD-10 and five deaths coded in ICD-9), but the rate of mesothelioma mortality was very similar in the subcohort (24.7 per 100,000 person-years versus 26.8 per 100,000 person-years for the full cohort [18 mesothelioma deaths], a difference of less than 10%).

6.2.3. Modeling of Mesothelioma Exposure Response

A Poisson model is employed for estimating the absolute risk of mesothelioma following exposure to LAA, as the Poisson distribution is an appropriate model to use with data that are counts of a relatively rare outcome, such as observed mesothelioma deaths in the Libby, MT worker cohort. Estimation of the exposure-response relationship for mesothelioma using the Poisson model was performed in WinBUGS software by a MCMC Bayesian approach with an uninformative or diffuse (almost flat) prior. The model was run to fit the mortality data to exposure data for various exposure metrics described above. To comparatively evaluate how much better one model fits than another, the DIC was used. DIC is used in Bayesian analysis and is an analogue of AIC (Burnham and Anderson, 2002). Use of the DIC and AIC is standard practice in comparing the fit of nonnested models to the same data set with the same dependent outcome variable but different independent covariates.

Modeling of mesothelioma mortality included an exposure metric with a cubic function of time (see eq 5-9), originally proposed in Peto et al. (1982) and employed in derivation of the IUR for asbestos (U.S. EPA, 1988a, 1986a), as well as modifications of Peto model (Peto model

with clearance) proposed in the asbestos literature (Berry et al., 2012). See Section 5.4.3 for further details.

For the subcohort hired after 1959, two cumulative exposure metrics with decay provided the best model fits. Both metrics had a common 5-year half-life, with lag times of either 10 or 15 years. The Peto model and Peto model with clearance did not fit as well. As it is less likely that exposure during the last few years before death were contributory to the development of the cancer and cancer mortality, the zero-lag metrics were dropped from further consideration. The selected metric as well as the Peto model and Peto model with clearance were retained for derivation of the IUR (see Section 6.2.7 below and for additional detail see Section 5.4.5). The selected exposure metric was cumulative exposure with a 5-year half-life and a 10-year lag time with a central estimate for the slope (KM) of 3.11×10^{-4} per fiber/cc-yr with a 95% upper confidence limit (UCL) of 5.08×10^{-4} per fiber/cc-yr.

6.2.4. Unit Risk Estimates for 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 LAA toxicity to a structured representation of the general U.S. population in such a manner as to yield age-specific risk estimates for cancer mortality in the presence or absence of exposure to LAA (see Section 5.4.5; Appendix G).

A default linear low-dose extrapolation was used because the mode of action by which LAA causes mesothelioma was not established. The lower limit on the effective concentration (LEC_{01}) yielded a unit risk for mesothelioma mortality of 0.053 per fiber/cc (POD of 1% divided by the LEC_{01}).

The value of the effective concentration (EC) that would correspond to the measure of central tendency is the EC_{01}. This value is used in the derivation of a combined risk of mesothelioma and of lung cancer. The EC_{01} yielded a lifetime central estimate value of 0.032 per fiber/cc.

For mesothelioma, the undercounting of cases (underascertainment) is a particular concern given the limitations of the ICD classification systems used before 1999. In practical terms, this means that some true occurrences of mortality due to mesothelioma are missed on death certificates and in almost all administrative databases such as the National Death Index. Even after introduction of special ICD code for mesothelioma with introduction of ICD-10 in 1999, detection rates are still imperfect (Camidge et al., 2006; Pinheiro et al., 2004), and the reported numbers of cases typically reflect an undercount of the true number. Kopylev et al. (2011) reviewed the literature on this underascertainment and developed methods to account for the likely numbers of undocumented mesothelioma deaths.

To compensate for mesothelioma underascertainment attributable to ICD coding, the mesothelioma mortality unit risk was further adjusted following the analysis of Kopylev et al.

(2011). The adjusted mesothelioma central (i.e., maximum likelihood estimate) risk, corresponding to the best-fit metric, was 0.044 per fiber/cc, and the adjusted mesothelioma mortality unit risk was 0.074 per fiber/cc.

The adjusted mesothelioma risks for the Peto model and Peto model with clearance ranged from 2-fold lower (0.035 per fiber/cc) to 3.6-fold higher (0.265 per fiber/cc). Thus, there is uncertainty in mesothelioma risks generated from similar-fitting models from different exposure metrics (see details in Section 5.4.5.3).

6.2.5. Modeling of Lung Cancer Exposure Response

All multivariate extended Cox models were fit to the subcohort hired after 1959 with covariates for gender, race, date of birth, and exposure. Exposure for each of the 40 exposure parameterizations was calculated independently, and the fit of these exposure metrics was evaluated one at a time. Of the 40 exposure-response metrics, 14 demonstrated an adequate fit to the data as measured by the overall model fit with the likelihood ratio test ($p < 0.05$) as well as having statistically significant exposure metrics ($p < 0.05$). However, only the nine models that demonstrated adequate model and exposure metric fit and incorporated a lag period to account for cancer latency were considered further in the development of the IUR (see Tables 5-43 and 5-50).

Lagging exposure by 10 years was a better predictor of lung cancer mortality compared to other lags. As it is less likely that exposure during the last few years before death were contributory to the development of the cancer and cancer mortality, the zero lag metrics were dropped from further consideration. The residence time-weighted cumulative exposure, both with and without decay of the exposure metric, did not fit these lung cancer mortality data well compared to the other models (see Table 5-44); this form of exposure metric does not demonstrate evidence of an empirical fit to these epidemiologic data.

The model with the smallest AIC was for cumulative exposure with a 10-year half-life for decay and a 10-year lag for cancer latency. The extended Cox model estimated a beta (the lung cancer slope factor: KL) of 1.26×10^{-2} per fiber/cc-yr based on a 365-day year, and the 95th percentile upper bound was 1.88×10^{-2} per fiber/cc-yr. The *p*-value for the LAA regression coefficient beta (slope) was <0.001. The slopes and confidence interval for the other exposure metrics, which had similar fits to these data are reported in Table 5-45. Uncertainty in the choice of the exposure metric is considered in the derivation of the unit risk (see details in Section 5.4.5.2), representing the range of unit risks that are derived from these similarly fitting metrics. The model results that were ultimately selected to reflect the upper bound among the range of results were based on the cumulative exposure with a 10-year lag exposure metric (CE10). The extended Cox model estimated a beta (slope) of 5.28×10^{-3} per fiber/cc-yr based on a 365-day year, and the 95th percentile upper bound was 1.00×10^{-2} per fiber/cc-yr.

6.2.5.1. *Analysis of Potential Confounding of Lung Cancer Results by Smoking in the Subcohort*

EPA used two approaches to address the confounding issue, including restriction of the cohort and an analytic evaluation of the potential for confounding by smoking including the method described by Richardson (2010). Richardson (2010) describes a method to determine whether an identified exposure relationship with lung cancer is confounded by unmeasured smoking in an occupational cohort study. EPA implemented this methodology to model the potential effects of LAA on the risk of COPD mortality on the subcohort of workers hired after 1959 (see Section 5.4.3.8). Summarizing these findings, EPA used the method described by Richardson (2010) to evaluate whether exposures to LAA predicted mortality from COPD as an indication of potential confounding by smoking and found a nonsignificant negative relationship, which was inconsistent with confounding by smoking.

6.2.6. Unit Risk Estimates for Lung Cancer Mortality

The increased risk of lung cancer 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 applying the estimated LAA-specific toxicity to a structured representation of the general U.S. population in such a manner as to yield age-specific risk estimated for cancer mortality in the presence or absence of exposure to LAA (see Section 5.4.5; Appendix G). A default linear low-dose extrapolation was used because the mode of action by which LAA causes lung cancer was not established.

The nine exposure-response models retained in Table 5-45 all had reasonably similar goodness of fit. No single model stands out as clearly statistically superior; however, there is a range of quality of fit within the set that could be considered to have adequate fit. The lung cancer mortality unit risks are shown in Table 5-52.

Using the results of the exposure model based on cumulative exposure with a 10-year lag for cancer latency, the LEC_{01} yielded a lifetime unit risk of 0.0679 per fiber/cc. The value of the risk that would correspond to the measure of central tendency involves the EC_{01} rather than the LEC_{01}. The EC_{01} yielded a lifetime central estimate of 0.0399 per fiber/cc.

The resulting unit risks in Table 5-52 ranged from 0.0260 to 0.0679 per fiber/cc, for a lifetime continuous exposure. This shows that the unit risk based on the exposure metric with the lowest AIC value (i.e., cumulative exposure with a 10-year half-life for decay and a 10-year lag for cancer latency) is in the center of this range (i.e., 0.0389 per fiber/cc). This estimate is in the middle of the range of possible unit risks and does not capture the uncertainty across metrics with similar goodness of fit (see details in Section 5.4.6).

The model results selected to represent the upper-bound risk among the range of reasonable results are based on a CE10 metric with a 10-year lag. The model results selected to

reflect the upper bound among the range of results are based on the CE10 exposure metric with a 10-year lag, providing a unit risk of 0.0679 per fiber/cc.

6.2.7. Inhalation Unit Risk (IUR) Derivation Based on Combined Mesothelioma and Lung Cancer Mortality from Exposure to Libby Amphibole Asbestos

Once the cancer-specific lifetime unit risks are selected, the two are then combined. It is important to note that this estimate of overall potency describes the risk of mortality from cancer at either of the considered sites and is not just the risk of both cancers simultaneously. Because each of the unit risks is itself an upper-bound estimate, summing such upper-bound estimates across mesothelioma and lung cancer mortality is likely to overpredict the overall risk. Therefore, following the recommendations of the *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a), a statistically appropriate upper bound on combined risk was derived to gain an understanding of the overall risk of mortality resulting from mesothelioma and from lung cancer. For mesothelioma, the exposure-response models developed by EPA using personal exposure data on the subcohort (see Table 5-50) provided better fit to the subcohort data than the Peto model and the Peto model with clearance that have been proposed in the asbestos literature. For lung cancer, this assessment selected the upper bound among the lung cancer lifetime unit risks from the plausible exposure metrics (regardless of the small residual differences in quality of fit). Because there were few metrics with unit risks higher than the best fitting metric's unit risk for lung cancer mortality endpoint, this method effectively selects the highest lifetime unit risk among those considered for the lung cancer mortality endpoint.

Table 6-1 shows cancer-specific unit risks as well as combined risk of mesothelioma and lung cancer. The IUR value of 0.17 per fiber/cc, continuous lifetime exposure, accounts for important quantitative uncertainties in the selection of the specific exposure metric that may have remained in an IUR that might have been based on the best-fitting exposure models alone. Additional uncertainties are discussed in detail in Section 5.4.6.

Table 6-1. Estimates of the combined central estimate of the unit risk for mesothelioma and lung cancer and the combined upper-bound lifetime unit risks for mesothelioma and lung cancer risks (the Inhalation Unit Risk) for different combination of mesothelioma and lung cancer models.[a,b] Primary IUR value in bold.

Lung cancer	Mesothelioma	Combined central estimate per fiber/cc	Combined upper bound per fiber/cc
Selected IUR based directly on the Libby data			
CE10	CE10 5-yr half-life	0.115	**0.169**
Best models from the epidemiologic literature (Peto model with clearance)			
CE10	Peto with clearance Decay rate of 6.8%/yr Power of time = 3.9	0.089	0.135
CE10	Peto with clearance Decay rate of 15%/yr Power of time = 5.4	0.061	0.092
Alternative model from the epidemiologic literature (Peto model)			
CE10	Peto No decay Power of time = 3	0.203	0.308

[a]Note that for all the IUR values presented in this table, the fiber concentration is presented here as continuous lifetime exposure in fibers/cc, where exposure measurements are based on analysis of air filters by PCM. Current analytical instruments used for PCM analysis have resulted in a standardization of minimum fiber width considered visible by PCM between 0.2 and 0.25 µm. Historical PCM analysis (1960s and early 1970s) generally had less resolution, and fibers with minimum widths of 0.4 or 0.44 µm were considered visible by PCM (Amandus et al., 1987b; Rendall and Skikne, 1980). Methods are available to translate exposure concentrations measured in other units into PCM units for comparison.

[b]While this assessment is informed by studies of other types of asbestos, it is not a complete toxicity review of other amphiboles or of chrysotile asbestos.

Age-dependent adjustment factor

As discussed in Section 4.7.1.1, there is no chemical-specific information for LAA, or general asbestos that would allow for the computation of a chemical-specific age-dependent adjustment factor for assessing the risk of exposure that includes early-life exposures.

The review of mode-of-action information in this assessment (see Section 4.6.2.4 and 4.6.2.5) concluded that the available information on the mode of action by which LAA causes lung cancer or mesothelioma is complex and a mode of action is not established at this time. Thus, in accordance with 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 for substances that act through a mutagenic mode of action is not recommended.

6.2.7.1. *Comparison with Other Published Studies of Libby, MT Workers Cohort*

Several published studies have previously evaluated risk of mesothelioma and lung cancer [i.e., Sullivan (2007), Berman and Crump (2008), Larson et al. (2010b), and Moolgavkar et al. (2010)] in the Libby, MT workers cohort. For mesothelioma, only Moolgavkar et al. (2010) provided an exposure-response relationship for absolute risk of mesothelioma mortality that would be comparable with this current assessment. Based on the full cohort, with mortality data through 2001 and a modification of the Peto/Nicholson exposure metric, life-table analysis would provide an upper-bound unit risk of approximately 0.13 per fiber/cc continuous lifetime exposure. Therefore, use of the exposure response modeling of Moolgavkar et al. (2010), would provide an IUR for excess mesothelioma mortality in close agreement with the IUR derived in this assessment (see Section 5.4.5.3.1 for more details).

For lung cancer, all of the studies provide exposure-response relationships in terms of relative risk of lung cancer mortality, and thus, may provide risk estimates comparable to this assessment. However, inclusion criteria, length of mortality follow-up, and analytic methods differ among the analyses—thus, the results are not necessarily interchangeable. For comparison purposes, the lung cancer unit risks from these studies are computed from life-table analyses (see Table 5-54). The lung cancer unit risks calculated based on the published literature, ranged from 0.010 to 0.079 per fiber/cc (based on the upper confidence limit). This is in close agreement with this current assessment where an upper-bound estimate of 0.068 per fiber/cc, continuous lifetime exposure is derived (see Section 5.4.5.3.1 for more details).

6.2.8. Uncertainty in the Cancer Risk Values

It is important to consider the uncertainties in the derivation of the mesothelioma and lung cancer mortality risks in this assessment in the context of uncertainties in animal-based health assessments. This assessment does not involve extrapolation from high doses in animals to low doses in humans. The current assessment is based on a well-documented and well-studied cohort of workers with adequate years of follow-up to evaluate mesothelioma and lung cancer mortality risks with PODs within the range of the data. The discussions in Section 5.4.6 explore uncertainty in the derivation of the IUR in order to provide a comprehensive and transparent context for the resulting cancer mortality risk estimates.

Section 5.4.6.1 details the several sources of uncertainty in the assessment of the cancer exposure-response relationships and the use of those data to derive the inhalation unit risk. The text that follows summarizes the primary sources of uncertainty and, where possible, the expected direction of effect on the exposure-response risk estimates and the inhalation units risk.

1) *Uncertainty in low-dose extrapolation (see Section 5.4.6.1.1)*

- Some uncertainty remains in the extrapolation of risks based on occupational exposure to environmental exposure levels, but this uncertainty is considered to be low as the lower range of occupational exposure overlaps with expected environmental exposure levels.

2) *Uncertainty in exposure assessment, including analytical measurements uncertainty (see Section 5.4.6.1.2)*

- The JEM was based on the "high" exposure estimate for each job according to Amandus et al. (1987b), and to some extent this could be an overestimate of exposure. The associated cancer risk would be somewhat underestimated resulting in a somewhat underestimated IUR.

- The JEM was largely based on estimated fiber concentration using PCM measurement (with some extrapolations in time), and because PCM may count all long and thin objects as fibers, these measurement could overestimate the true LAA fiber concentrations, leading to an overestimate of exposure and a somewhat underestimated cancer risk resulting in a somewhat underestimated IUR.

- PCM measurements in the era of NIOSH measurements in Libby used a lower resolution, and therefore, included only somewhat thicker fibers, thereby counting fewer fibers than would have been counted by later PCM standards. These earlier measurements could underestimate the true LAA fiber concentrations, leading to an underestimate of exposure and an overestimate of cancer risk resulting in a somewhat overestimated IUR.

- The PCM measurement is the available exposure metric for analysis of the Libby worker cohort at the time of this assessment. Currently, there is no optimal choice of the best dose metric for asbestos, in general and in particular, for LAA. Uncertainties related to PCM analytical method are discussed in Section 2, and such uncertainties cannot be related to the IUR at the time of this assessment.

- Random measurement error in the assignment of exposures could have the effect of underestimating the risk of lung cancer mortality because that measure of risk is based on a relative measure. The effect would be to somewhat underestimate the risk of lung cancer, resulting in a somewhat underestimated unit risk for lung cancer. It is unclear what the impact of such measurement error would be on the absolute risk of mesothelioma.

- Exposure to other kinds of asbestos and residential exposure to LAA may have caused workers' actual personal exposures (as the sum of occupational and nonoccupational exposures) to have been underestimated by the use of estimated Libby occupational exposure information alone. This could underestimate the true LAA fiber exposures leading to an overestimate of the associated cancer risk resulting in a somewhat overestimated IUR.

3) *Uncertainty in model form (see Section 5.6.4.1.3)*

- For mesothelioma, the Poisson model is the standard epidemiologic form and considered to be the most appropriate model form for rare health outcomes; therefore, uncertainty is considered to be low. For lung cancer mortality, the Cox proportional hazards model is the standard epidemiologic form. It is considered to be the most appropriate model form for health outcomes with time-varying exposure data and thus uncertainty is considered to be low.

4) *Uncertainty in selection of exposure metric (see Section 5.6.4.1.4)*

- There is uncertainty about what metric should be used for modeling exposures to LAA. Table 5-53 illustrates the uncertainty in the IUR due to exposure metric selection. The quantitative uncertainty is about threefold.

5) *Uncertainty in assessing mortality corresponding to other cancer endpoints (see Section 5.6.4.1.5)*

- The lack of sufficient numbers of workers to estimate the risk of other cancers potentially related to LAA exposure is an uncertainty of unclear direction but is considered to be low due to the rarity of those cancers.

6) *Uncertainty in control of potential confounding in modeling lung cancer mortality (see Section 5.4.6.1.6)*

- The uncertainty in control of potential confounding by smoking is considered to be low as the described sensitivity analysis did not show evidence of potential confounding.

7) *Uncertainty due to potential effect modification (see Section 5.4.6.1.7)*

- Smoking was not considered to be related to LAA exposure, and therefore, smoking is not considered to be a likely effect modifier of cancer risk. Age has been shown to be a potential effect modifier of lung cancer risk but there was no evidence of this relationship in the subcohort.

8) *Uncertainty due to length of follow-up (see Section 5.4.6.1.8)*

- There is uncertainty related to the limited follow-up for cancer mortality, and it is possible that with subsequent mortality follow-up, the IUR could change in a direction that is unknown.

9) *Uncertainty in the use of life-tables to calculate cancer mortality IUR (see Section 5.4.6.1.9)*

- The life-table procedure computes the extra risk of death from birth to 85 years of age. If the life-tables were extended from 85 to 90 years to account for longer life spans, the selected lung cancer mortality unit risk (Table 5-53 shows this as 0.068) would be somewhat larger, about 5−10%, and the selected mesothelioma unit risk (Table 5-53 shows this as 0.122) would be slightly less (about 3%).

Taking both effects into consideration, the uncertainty in the IUR is considered to be low.

10) Uncertainty in combining mortality risks to derive a composite cancer mortality IUR (see Section 5.4.6.1.10)

- EPA assumed that the cancer risks were independent, conducted a bounding analysis, and showed the related uncertainty to be very low.

11) Uncertainty due to extrapolation of findings in adults to children (see Section 5.4.6.1.11)

- There is uncertainty in the assumption that risks are independent of age and that children are at the same exposure-related risk as adults. The lack of published information on cancer risks associated with exposures during childhood remains an uncertainty of unclear magnitude.

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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 their review of EPA's draft assessment entitled *Toxicological Review of Libby Amphibole Asbestos* (August 2011) (SAB, 2013).

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. LPT was introduced as a term in the 2000 ILO guidance. LPT includes plaques on the chest wall and at other sites (e.g. diaphragm). Plaques on the chest wall can be viewed either face-on or in profile. A minimum width of about 3 mm is required for an in-profile plaque to be recorded as present according to the 2000 ILO guidance. 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 and 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 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); 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* (U.S. EPA, 2012)."

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* (U.S. EPA, 2012).

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* (U.S. EPA, 2012) 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 the adjustment from subchronic data to chronic data, EPA reconsidered and concluded that a data-informed increase to the uncertainty factor (UF_S) value from 1 to 10 was appropriate. Although chronic exposure has been generally defined as more than approximately 10% of lifetime, the EPA's RfC guidance (U.S. EPA, 1994) states that for human data"[t]he best data to use for calculating an RfC would be a population study of humans that includes sensitive individuals exposed for lifetime or chronic duration, and that evaluates the critical endpoint or an appropriate early marker for the disease….However, the amount of exposure in a human study that constitutes subchronic

is not defined, and could depend on the nature of the effect and the likelihood of increased severity or greater percent response with duration." This was EPA's conclusion, despite the fact that the average duration of worker exposure in the key study was more than 7 years.

Also, the External Review Draft had not modeled the impact of time since first exposure (TSFE) in the primary modeling analysis that was restricted to workers on whom there was better exposure data (those hired in 1972 or later), in part because there was less variation in TSFE in that subcohort. The SAB also recommended that EPA utilize the full cohort to investigate the impact of TSFE while also using the subcohort hired in 1972 or later to relate exposure to effect. Thus, EPA followed a modeling approach that provided information on the joint effect of TSFE and exposure concentration and considered how to use those model results to evaluate the likely impact of additional follow-up, or TSFE, beyond that observed in the principal study.

EPA concluded that an uncertainty factor of 10 is appropriate because the exposure-response modeling demonstrated that the range of TSFE in the Marysville workers may not be of sufficient length 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 a data-informed uncertainty factor of 10 is appropriate to reflect lifetime exposure.

In the External Review Draft, EPA had noted the uncertainty in not having lifetime data in the database uncertainty factor as one factor that contributed to the rationale for a database uncertainty factor (UF_D) of 10. However, the SAB recommended that EPA consider increasing the uncertainty factor for the duration of study (i.e., the UF_S) while reducing the UF_D. EPA concluded that while some database 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 provided 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.

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.

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 External Review Draft.

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.

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 assessment, 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 Sections 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., 1991c)], 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; EPA 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, EPA 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, EPA 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:** EPA 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., 1991c). 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, 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., 1991c)]. 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 5-6. 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, EPA has 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). EPA agrees 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 (fibers/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 intraspecies 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 human variability, neither the SAB nor EPA concluded there was a basis for changing the uncertainty factor (UF_H) 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 (UF_D), EPA concluded that, while some database 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 and thus support a reduction in the UF_D. However, some database 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) pages 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)].

A.8. PUBLIC COMMENTS

Section A.8 responds to public comments with each subsection addressing a different general topic.

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):** Jay Flynn 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 (Elizabeth Anderson, John DeSesso, David Hoel, Jay Flynn, and Lawrence Mohr) 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 and 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 LPT, is an appropriate health endpoint for the derivation of the RfC.

***Noncancer Health Effects Public Comment #2* (Paraphrased):** Several commenters (including Lawrence Mohr) 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) and pleural plaques. 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 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., 2014) (note: citation updated from original comment to include publication information) 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. (2014) was published after the cut-off date of December 31, 2013 for the systematic review and meta-analysis, EPA evaluated the Clark et al. (2014) study as it relates to the meta-analysis. EPA found that inclusion of Clark et al. (2014) 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. (2014) 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) (note: citation updated from original comment to include publication information) 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

not a comprehensive review of the 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 publication 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 final assessment and/or elsewhere in Appendix A.

Noncancer Health Effects Public Comment #5: Beveridge & Diamond (on behalf of W.R. Grace) commented (Section III.A1.a) that "The Draft Assessment Does Not Satisfy EPA's Own Definition of Adverse Effect and, as a Result, Fails to Meet the Agency's IQA Commitment to Apply Its IRIS Policies and Procedures to Ensure and Maximize Quality."

EPA Response: Please see response to the **Major SAB Recommendation *Letter #1*** and ***Noncancer Health Effects Public Comment #1*** above.

Noncancer Health Effects Public Comment #6: Beveridge & Diamond (on behalf of W.R. Grace) commented (Section III.A1.b) that EPA "failed to demonstrate a 'causal' association between LPT and functional impairment."

The comment goes on to say that the "Draft Assessment fails to explain how LPT could plausibly cause, or be on a pathway to, impairment. Indeed, no mode of action has been established. If the exposure to asbestos causes lung decrements, and if the exposure to asbestos causes LPT, hypothetically one might find a correlation between LPT and lung decrements. But this is insufficient to show that LPT itself causes lung decrements. The SAB Report does not cure this deficiency."

EPA Response: EPA defines an "adverse effect" as a "biochemical change, functional impairment, or pathologic lesion that *affects* the performance of the whole organism, or reduces an organism's ability to respond to an additional environmental challenge" (italics added) (U.S. EPA, 2002b).

In this assessment, the critical noncancer effect, localized pleural thickening, is a persistent structural alteration of the pleura, which the EPA Science Advisory Board noted they would consider a pathological change.

The revised LAA Toxicological Review has an extensive discussion of how LPT affects lung function in Appendix I. While Appendix I does not use a summary descriptor of the extent to which the evidence from EPA's systematic review of the literature on this subject supports a decision on causality, it follows the same approach used in frameworks for assessing causality and reaches the conclusion that there is an observed association between the presence of LPT and decreased lung function, and that the association is "unlikely to be explained by other causes of pulmonary function loss." It evaluates the available studies (positive and null or negative) regarding the association between LPT and lung function. It assesses the evidence for an association, consistency, and the strength of association using a meta-analysis and its statistical significance. It examines

whether confounders could explain the observed association and concludes that they are unlikely to explain the observed association.

Appendix I does address several hypotheses that LPT might not affect lung function but simply be a marker of exposure where the exposure affects lung function. Appendix I also notes that there is otherwise not much information as to how LPT might affect lung function. It is, however, recognized in EPA frameworks for evaluating causality that often the mode of action for an effect is unknown, and that knowing a mode of action is not a requirement for judging that there is, or not, a causal relationship.

***Noncancer Health Effects Public Comment #7*:** Beveridge & Diamond (on behalf of W.R. Grace) commented (Section III.A1.c) that "The Draft Assessment's LPT findings relied on irrelevant and non-probative DPT and visceral pleura data, and the Draft Assessment was inaccurate in how it applied an ILO classification. Because of the merging of the analysis of DPT (with known adverse effects) with LPT (which has not been shown to cause adverse effects), the Draft Assessment's analysis is unreliable, inaccurate, and biased."

EPA Response: EPA carefully reviewed its understanding of terminology in the ILO guidelines that define "LPT" and "DPT." The discussions of LPT and the scientific literature in this final assessment uses consistent and accurate terminology. EPA carefully applied ILO classification and avoided blurring the distinctions between different radiological findings on the visceral pleura, such as DPT or other general or unclassified pleural thickening**.**

In the meta-analysis presented in Appendix I where EPA further reviewed additional literature on the association of LPT with decrements in lung function, EPA only considered studies of workers with pleural plaques who did not have DPT or parenchymal abnormalities in order to avoid confusion between LPT and DPT.

Please see response to the ***Noncancer Health Effects Public Comment #2*** above.

***Noncancer Health Effects Public Comment #8*:** Beveridge & Diamond (on behalf of W.R. Grace) commented (Section III.A1.d) that "the Draft Assessment fails to identify and consider all of the relevant literature, including authoritative papers and studies that contradict the Draft Assessment's position, and studies that use the most sensitive radiographic diagnostic tool."

EPA Response: EPA performed a systematic identification and analysis of the relevant literature and transparently reported the analysis and findings (see Appendix I). In Appendix I, EPA specifically identified relevant HRCT studies and conducted meta-analyses of x-ray and HRCT studies and of HRCT studies separately. EPA also thoroughly evaluated consensus statements from ATS and ACCP.

Please see response to the **Major SAB Recommendation *Letter #1*** and ***Noncancer Health Effects Public Comment #1*** above.

***Noncancer Health Effects Public Comment #9* (Paraphrased):** Beveridge & Diamond (on behalf of W.R. Grace) commented (Section III.A1.e) that there are concerns arising from potential confounding. One concern stated was that the draft assessment fails to consider and account for important confounders and specifically that subpleural fat deposits can be mistaken for pleural plaques (LPT) on lung x-rays. A second concern was that studies could be complicated by risk factors for pulmonary decrements such as smoking and BMI.

EPA Response: Each of these potential limitations has been addressed by EPA.

In its systematic literature review, EPA evaluated whether each study compared participants with reference populations and in its meta-analyses of FVC and FEV1, EPA only used studies with appropriate internal controls (see Appendix I).

EPA identified and accounted for potential confounders, effect modifiers and study limitations such as: smoking and BMI. Additional analyses in Appendix I indicated that the decrements associated with the presence of LPT are not likely to be due to limitations in the study designs, undetected subclinical fibrosis or misidentification of pleural plaques due to subpleural fat pads.

Please see response to the **Major SAB Recommendation *Letter #1*** and ***Noncancer Health Effects Public Comment #1*** above.

***Noncancer Health Effects Public Comment #10* (Paraphrased):** Beveridge & Diamond (on behalf of W.R. Grace) commented (Section III.A1.f) that there is no support for conjecture that LPT is associated with pain and/or dyspnea.

EPA Response: A direct association between localized pleural thickening and chest pain or dyspnea (defined as "difficult or labored breathing; shortness of breath") was discussed in the draft assessment, but is not cited in the final assessment as the basis for concluding that LPT is an adverse or deleterious effect. Instead, this final assessment systematically reviewed the literature as to whether LPT affects lung function and discusses that even a 5% change in mean lung function would be expected to functionally impair some individuals with otherwise low lung function and would be expected to reduce their ability to respond to additional environmental challenge. That analysis is described in Appendix I.

Noncancer Health Effects Public Comment #11: Beveridge & Diamond (on behalf of W.R. Grace) commented (Section III.B1) that "the Draft Assessment has not demonstrated that LPT is an adverse effect as defined by EPA, because LPT has not been demonstrated to cause, or itself to present, a functional impairment."

EPA Response: Please see response to the **Major SAB Recommendation *Letter #1*** and ***Noncancer Health Effects Public Comment #1*** above.

***Noncancer Health Effects Public Comment #12* (Paraphrased):** Beveridge & Diamond (on behalf of W.R. Grace) commented (Section IV.A) that EPA fails to identify relevant studies for selection of critical effect.

EPA Response: EPA performed systematic identification and analysis of the relevant literature and transparently reported the analysis and findings (see Appendix I). In Appendix I, EPA identified relevant HRCT studies and conducted meta-analysis of x-ray and HRCT studies and HRCT studies separately. EPA also thoroughly evaluated consensus statements from ATS and ACCP.

Please see response to the **Major SAB Recommendation *Letter #1*** and ***Noncancer Health Effects Public Comment #1*** above.

Noncancer Health Effects Public Comment #13 **(Paraphrased):** Beveridge & Diamond (on behalf of W.R. Grace) commented (Section IV.B) that EPA does not conduct a rigorous weight-of-evidence evaluation.

> **EPA Response:** EPA did conduct a rigorous "weight-of-evidence" evaluation of the evidence regarding the relationship between LPT and lung function.
>
> The revised LAA Toxicological Review has an extensive discussion of how LPT affects lung function in Appendix I. While Appendix I does not use a summary descriptor of the extent to which the evidence from EPA's systematic review of the literature on this subject supports a decision on causality, it follows the same approach used in frameworks for assessing causality and reaches the conclusion that there is an observed association between the presence of LPT and decreased lung function, and that the association is "unlikely to be explained by other causes of pulmonary function loss." It evaluates the available studies (positive and null or negative) regarding the association between LPT and lung function. It assesses the evidence for an association, consistency, and the strength of association using a meta-analysis and its statistical significance. It examines whether confounders could explain the observed association and concludes that they are unlikely to explain the observed association.
>
> Appendix I does address several hypotheses that LPT might not affect lung function but simply be a marker of exposure where the exposure affects lung function. Appendix I also notes that there is otherwise not much information as to how LPT might affect lung function. It is, however, recognized in EPA frameworks for evaluating causality that often the mode of action for an effect is unknown, and that knowing a mode of action is not a requirement for judging that there is, or may be, a causal relationship.

Inhalation Reference Concentration (RfC) Public Comment #14 **(Paraphrased):** Beveridge & Diamond (on behalf of W.R. Grace) commented (Section IV.C.2) that EPA does not follow its own guidance, particularly on RfC critical effect.

> **EPA Response:** Please see response to ***Noncancer Health Effects Public Comment #1*** above.

Noncancer Health Effects Public Comment #15 **(Paraphrased):** Beveridge & Diamond (on behalf of W.R. Grace) commented (Section IV.D) that certain methods and data (i.e., additional follow-up by Dr. James Lockey and data collected by ATSDR) underlying the assessment are not publicly available for public review, analysis and comment and stated that such data is needed for a sound assessment. (The comment recommended EPA postpone completing its assessment until those studies become publicly available and EPA receives public comment on those data and their implications.)

> **EPA Response:** During the peer review of the draft IRIS assessment of LAA, Dr. Lockey publicly informed the EPA's Science Advisory Board (SAB) of his on-going research (as noted by the public commenter). These data mostly consist of additional follow-up regarding some of the workers in Marysville, Ohio and include studies of lung volume and diffusion in about 154 of the 231 workers studied in 2004.
>
> These data remain unpublished and therefore are not included in the IRIS assessment of LAA. Additionally, at this time, after the drafting of the assessment, its peer review, and

further review of supporting literature as recommended by the SAB, EPA does not consider these studies necessary to evaluate the relationship between exposure to LAA and the prevalence of localized pleural thickening in workers evaluated in prior studies of Marysville workers. Nor does EPA now consider these studies needed to further support the conclusion that LPT is adverse. Appendix I summarizes a range of studies that relate the presence of LPT with decrements in lung function.

With respect to the data collected by the ATSDR in Libby, Montana, in 2000 and 2001, this information is available in the published, peer-reviewed, literature. These publicly available studies conducted by ATSDR were summarized in the external review draft assessment and remain in the final IRIS assessment. The assessment provides a rationale to explain why the ATSDR data were not relied upon and why EPA considered the Marysville, Ohio data to provide a better dataset for derivation of the RfC for noncancer effects and the NIOSH Libby worker dataset an appropriate dataset for derivation of the cancer inhalation unit risk.

Although on-going analysis of those exposed to LAA will increase understanding of the toxicity of this material, the data referenced by the public commenter do not serve as the basis of the assessment and postponing completion of the IRIS LAA assessment is not warranted.

Further discussion of EPA's selection of critical studies and endpoints is above in the response to the **Major SAB Recommendation *Letter #1*** and ***Noncancer Health Effects Public Comment #1*** above.

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

***Carcinogenicity Public Comment #1* (Paraphrased):** Elizabeth Anderson 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 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)). Please also see the response to **Major SAB Recommendation *Letter #5*** comment.

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 better 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 better 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 set of 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*** comment. 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):** Beveridge & Diamond (on behalf of W.R. Grace) 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 (including Beveridge & Diamond and David Hoel) 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):** The American Chemistry Council noted that the justification of the uncertainty factors was inadequate.

EPA Response: EPA has reconsidered the choice of UFs in light of the SAB recommendations, 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 (including the American Chemistry Council, Elizabeth Anderson, Terry Trent and Karen Ethier) 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 United States. 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 9×10^{-5} fibers/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.

***Inhalation Reference Concentration (RfC) Public Comment #10* (Paraphrased):** Beveridge & Diamond (on behalf of W.R. Grace) commented (Section III.A2.a) that noncancer toxicity value is based on unduly restricted and confounded data set.

EPA Response: Please see response to ***SAB Inhalation Reference Concentration (RfC) #13*.**

***Inhalation Reference Concentration (RfC) Public Comment #10* (Paraphrased):** Beveridge & Diamond (on behalf of W.R. Grace) commented (Section III.B.2) that the noncancer Draft Assessment selected a statistical model that is not justified and not scientific.

EPA Response: Please see response to the **Major SAB Recommendation *Letter #3*.*Inhalation Reference Concentration (RfC) Public Comment #11:*** Beveridge & Diamond (on behalf of W.R. Grace) commented (Section IV.F and IV.G) that "The Draft Assessment Does Not Address the Expected 'Central Tendency' Risks to Affected Populations and Fails to Set Forth Upper and Lower Bound Estimates of Expected LAA Hazards to Affected Populations."

EPA Response: The assessment does provide central estimates of the point of departures for noncancer effects, along with lower bounds on the point-of-departure concentrations. These values provide information on the degree of uncertainty with respect to the points of departure.

EPA also does not at this time have a methodology for reflecting central or upper-bound estimates of the noncancer point of departure in statements about concentration unlikely to be without significant deleterious effects such as the RfC.

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 sixfold, 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.

Inhalation Unit Risk (IUR) Public Comment #10 **(Paraphrased):** Beveridge & Diamond (on behalf of W.R. Grace) commented (Section III.A2.b) that cancer toxicity value is based on unduly restricted and confounded data set.

EPA Response: Please see response to the **Major SAB Recommendation** ***Letter #6*** and ***SAB Inhalation Unit Risk (IUR) #19.***

Inhalation Unit Risk (IUR) Public Comment #11 **(Paraphrased):** Beveridge & Diamond (on behalf of W.R. Grace) commented (Section III.B3) that the cancer Draft Assessment selected a statistical models that are scientifically unsound.

EPA Response: Please see response to ***Inhalation Unit Risk (IUR) Public Comment #6***.

Inhalation Unit Risk (IUR) Public Comment #12: Beveridge & Diamond (on behalf of W.R. Grace) commented (Section IV.F and IV.G) that "The Draft Assessment Does Not Address the Expected 'Central Tendency' Risks to Affected Populations and Fails to Set Forth Upper and Lower Bound Estimates of Expected LAA Hazards to Affected Populations."

EPA Response: The assessment does provide central estimates of the point of departures for cancer effects, along with lower bounds on the point-of-departure concentrations. These values provide information on the degree of uncertainty with respect to the points of departure. In addition Table 5-53 provides estimate of central risk of mesothelioma or lung cancer along with the upper bound on risk.

EPA does not, however, at the current time have a methodology for low-dose extrapolation of cancer risk that yields a lower bound inhalation unit risk at lower doses. A linear extrapolation from the confidence limits on the cancer points of departure might not reflect the uncertainty at those lower concentrations.

A.9. OTHER GENERAL PUBLIC COMMENTS WITH EPA RESPONSES:

General Public Comment #1**:** Beveridge & Diamond (on behalf of W.R. Grace) commented (Section III.A.3) that "The Assessment Fails to Address Information Presented by Commenters Identifying Fundamental Flaws in the Draft Assessment's Analysis."

EPA Response: EPA has considered all the public and peer-reviewed comments in developing this final revised assessment. This appendix describes how EPA responded to the most significant peer review and public comments.

***General Public Comment #2* (Paraphrased):** Beveridge & Diamond (on behalf of W.R. Grace) commented (Section III.C) that draft assessment is incomplete and lacks transparency.

> **EPA Response:** EPA considers the assessment complete and transparent in presentation of selection of critical effect and in presentation of models and modeling results. Specific points raised in that section are responded elsewhere as they repeat previous comments made on RfC or IUR.

General Public Comment #3: Beveridge & Diamond (on behalf of W.R. Grace) commented (Section IV.C.1) that EPA should "Implement the April 2011 Formaldehyde Peer Review Report 'Chapter 7' IRIS recommendations as 'best available science' and 'sound and objective scientific practices'." The comment continued that EPA should "For those IRIS reforms that EPA has instituted for other ongoing draft IRIS assessments, either implement these reforms for this IRIS assessment or explain why the reforms do not represent 'best available science' or 'sound and objective scientific practices'."

> **EPA Response:** In April 2011, the National Research Council (NRC) released its *Review of the Environmental Protection Agency's Draft IRIS Assessment of Formaldehyde*. In addition to offering comments specifically about EPA's draft formaldehyde assessment, the NRC made several recommendations to EPA for improving the development of IRIS assessments. EPA agreed with the recommendations and is implementing them following a phased approach that is consistent with the NRC's "Roadmap for Revision," which viewed the full implementation of their recommendations by the IRIS Program as a multi-year process.
>
> The IRIS LAA assessment is in Phase 1 and has focused on a subset of the short-term recommendations, such as editing and streamlining, increasing transparency and clarity, and using more tables, figures, and appendices to present information and data. For example, the assessment includes clear explanations of the methods used to develop the LAA assessment, and descriptions of the decisions made in developing the hazard identification and dose-response analyses. As recommended, supplementary information and analyses are presented in appendices and standardized tables were incorporated for clarity in evidence presentation. Additionally, detailed discussions of mechanistic studies on the biological response to LAA were included and the weight-of-evidence discussion was expanded to include a formal mode-of-action analysis. All critical studies and the candidate studies for the derivation of the noncancer critical effect were thoroughly evaluated using standard protocols for evidence evaluation that are provided in existing EPA guidance with the evaluation criteria and study findings presented in tables in Section 5. Furthermore, text has been expanded to include more description of the considerations made in selecting the study that formed the basis for the quantitative reference concentration and cancer risk estimates and selection considerations are also summarized in a table. A detailed discussion of model selection for the epidemiological data sets is included.

***General Public Comment #4* (Paraphrased):** Beveridge & Diamond (on behalf of W.R. Grace) commented (Section IV.E) that the assessment lacks a meaningful discussion of the population likely to be affected by the assessment.

> **EPA Response:** The commenter states that the assessment should discuss whether this assessment, especially its RfC for noncancer effects, will be applied to populations

exposed to forms of asbestos not originating in the Rainy Creek complex near Libby, MT and that the assessment should discuss population exposure to such other forms of asbestos whose toxicity is likely to be compared to that of LAA.

This assessment is clearly identified as an assessment of the risks of exposure to asbestos originating in the Rainy Creek complex near Libby, Montana. Populations exposed to that material include populations in Libby and populations in locations at which people have been exposed to asbestos originating near Libby.

While this assessment included data on the toxicity of other types of asbestos to inform the mechanistic relationship between LAA and health effects, it did not include a full literature review of other amphiboles and therefore cannot reach conclusions as to other types of asbestos. That was beyond the scope of this assessment and does not affect to quality, transparency, or utility of this assessment for characterizing the risks of exposure to LAA.

General Public Comment #5 **(Paraphrased):** Beveridge & Diamond (on behalf of W.R. Grace) commented (Section IV.H) that the assessment fails to identify significant uncertainties.

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

General Public Comment #6 **(Paraphrased):** Beveridge & Diamond (on behalf of W.R. Grace) commented (Section V) that the RfC may be below background.

EPA Response: Please see response to ***Inhalation Reference Concentration (RfC) Public Comment #9***.

A.10. OTHER GENERAL PUBLIC COMMENTS TO THE SAB WITH EPA RESPONSES:

Other Public Comment #1 **(Paraphrased):** Some commenters (including the American Chemistry Council) 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 (including from the American Chemistry Council) 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 (of this report).

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

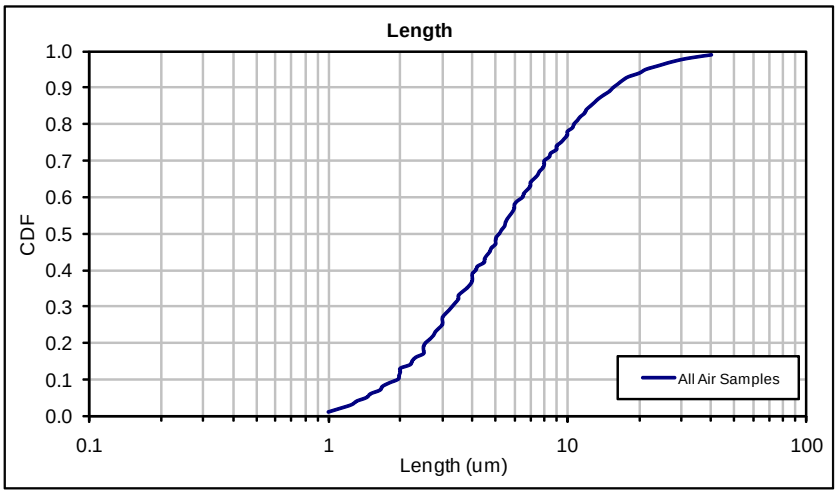
Program	Program Description	Program Date Range	Sampling and Analysis Plan (s)	Number of LA Structures [a]
Phase 1	Initial investigation sampling to assess nature and extent of potential contamination. Includes source areas (e.g., screening plant, export plant), commercial buildings, and residential properties.	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 (2002a)	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 (2005c)	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 (2008c)	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

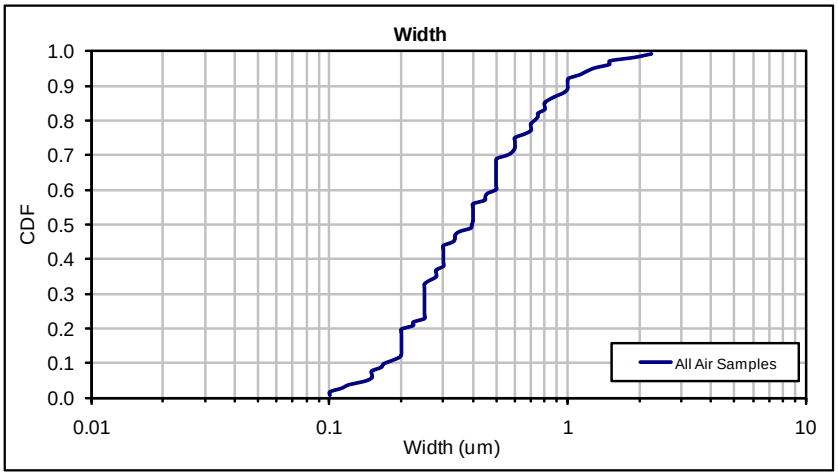
(a) Restricted to LA structures recorded in accordance with a 5:1 aspect ratio rule.

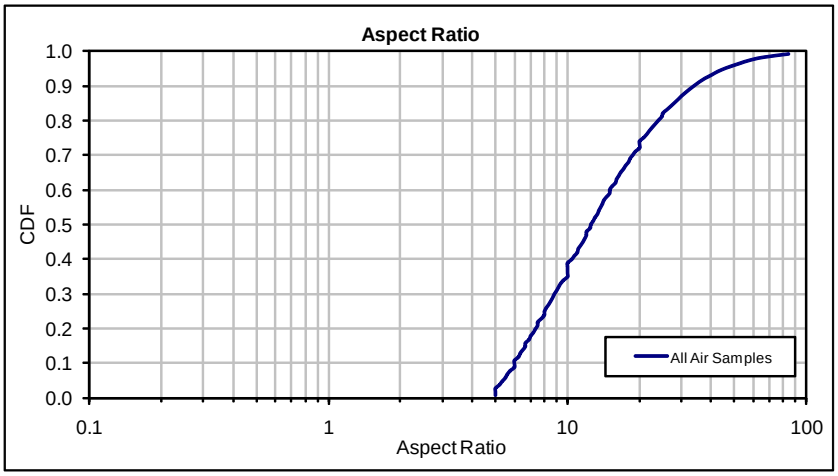
LA structure counts are based on a download of Libby 2DB performed on 12-8-09 and the Libby OU3 DB on 2-9-10.

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





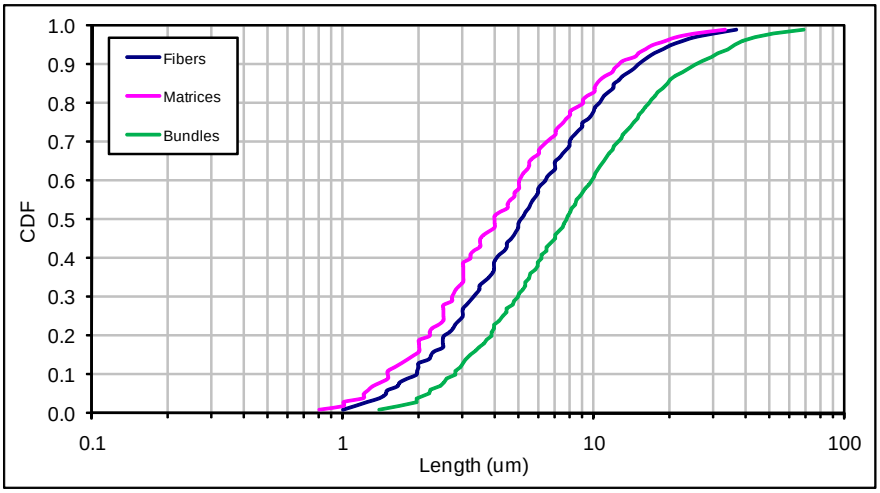


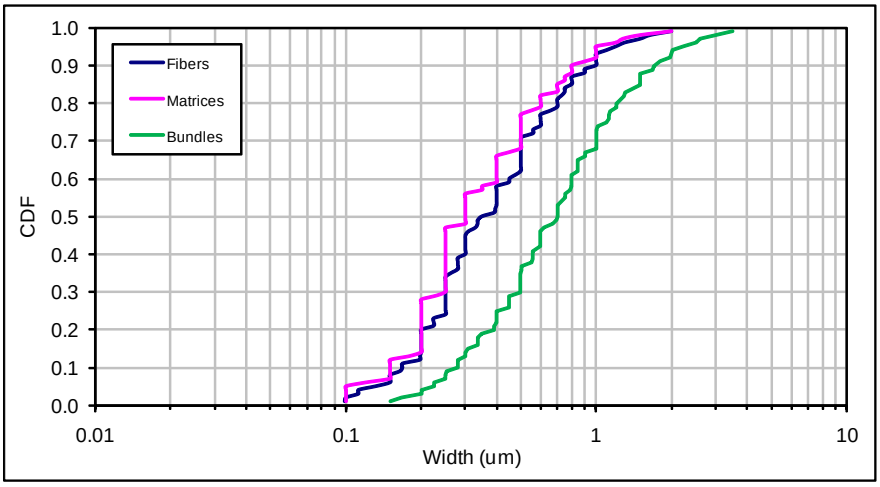
Data are based on a download of Libby 2DB performed on 12-8-09 and the Libby OU3 DB on 2-9-10.

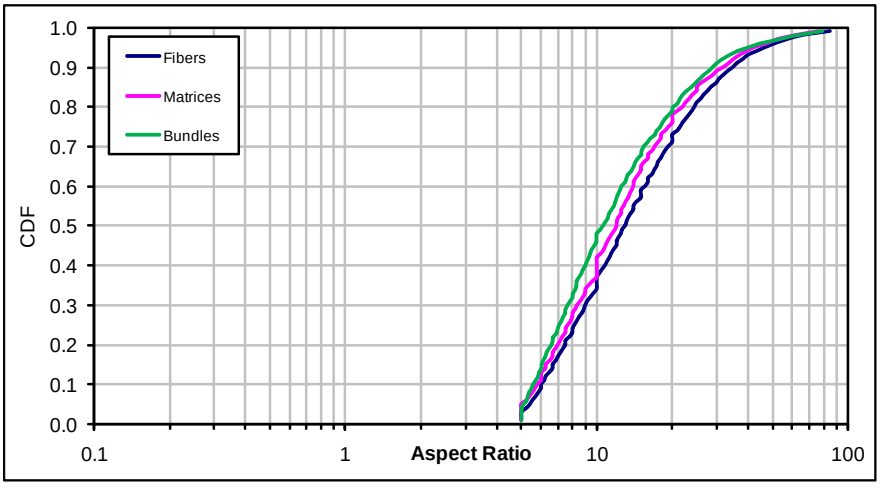
All Air Samples

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





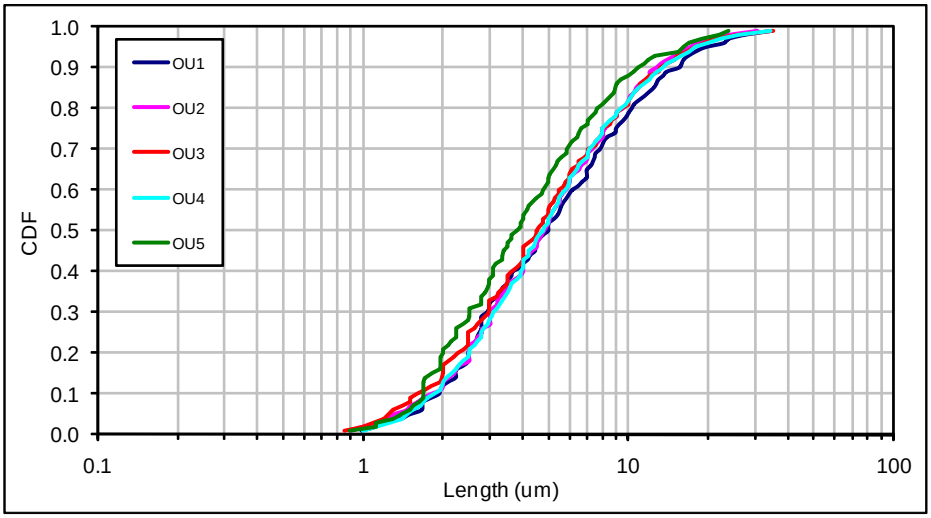


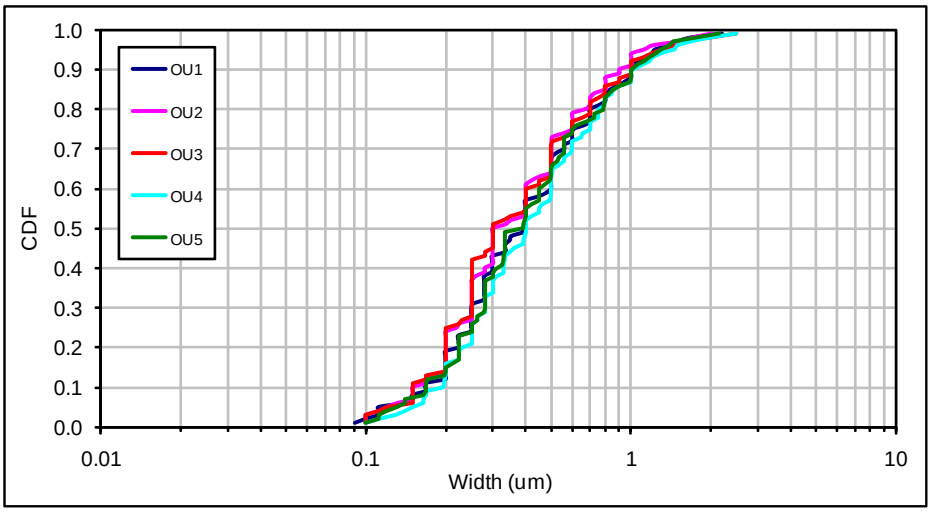
Data are based on a download of Libby 2DB performed on 12-8-09 and the Libby OU3 DB on 2-9-10.

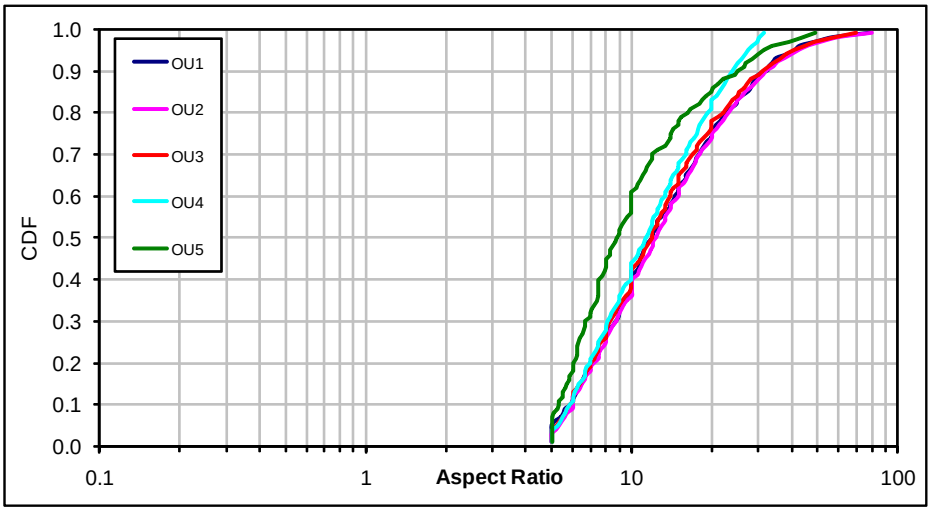
Structure Type	N Structures
F	23,933
B	2,366
M	3,150

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

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



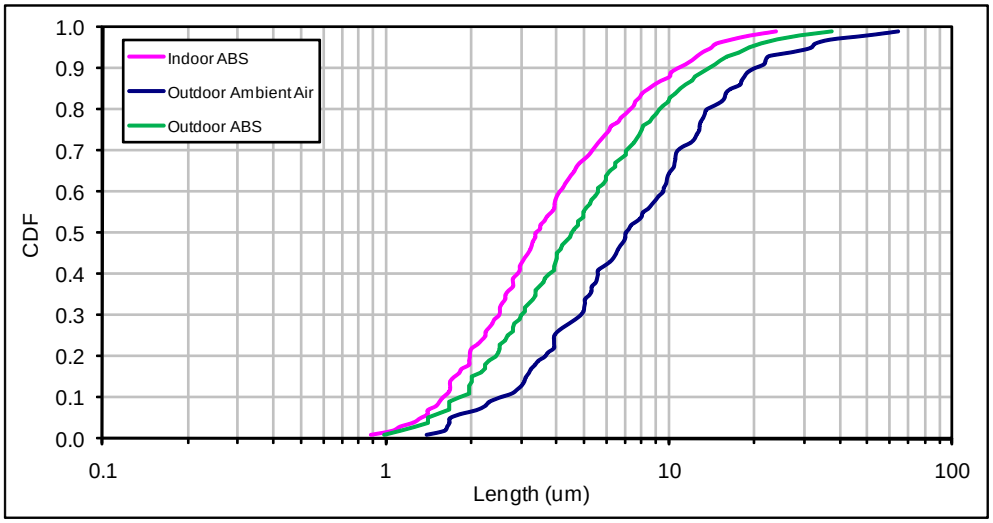


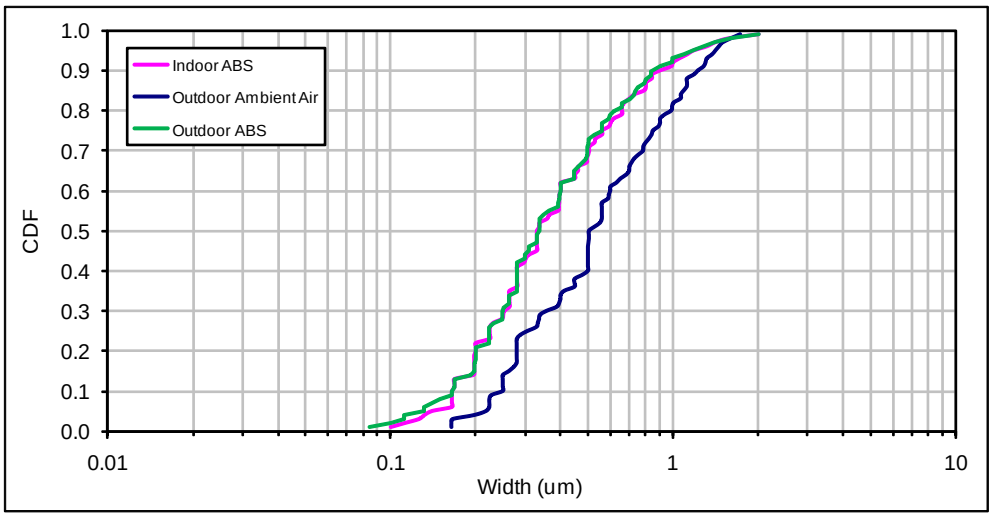


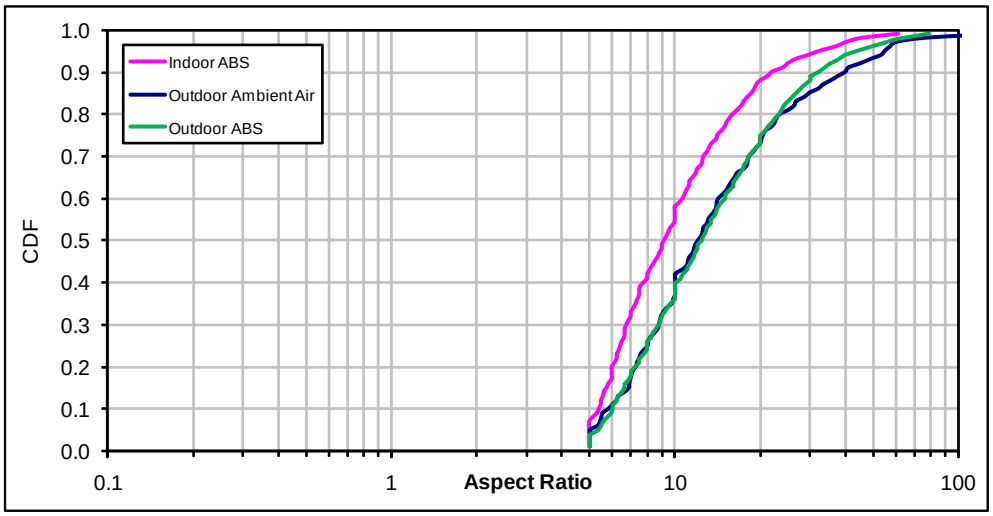
Data are based on a download of Libby 2DB performed on 12-8-09 and the Libby OU3 DB on 2-9-10.

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



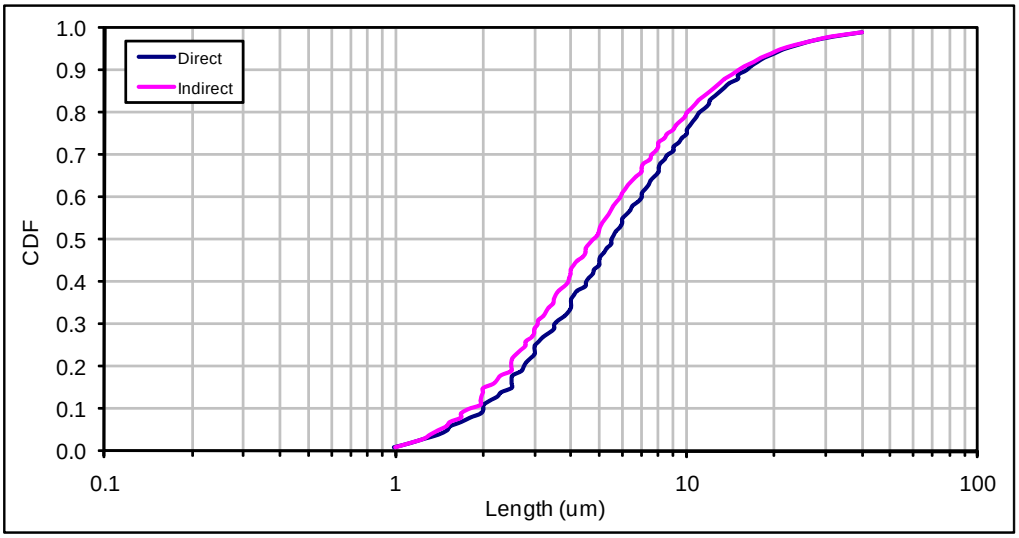


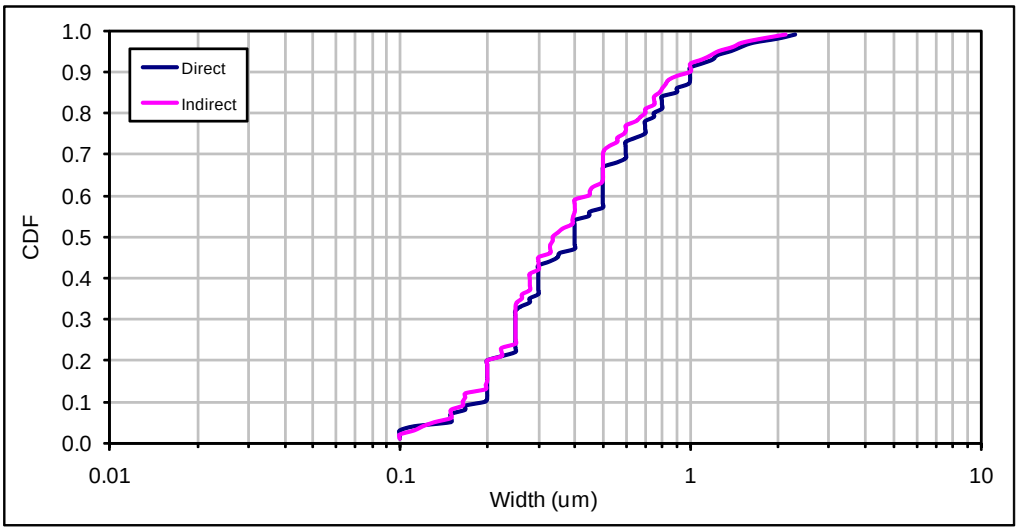


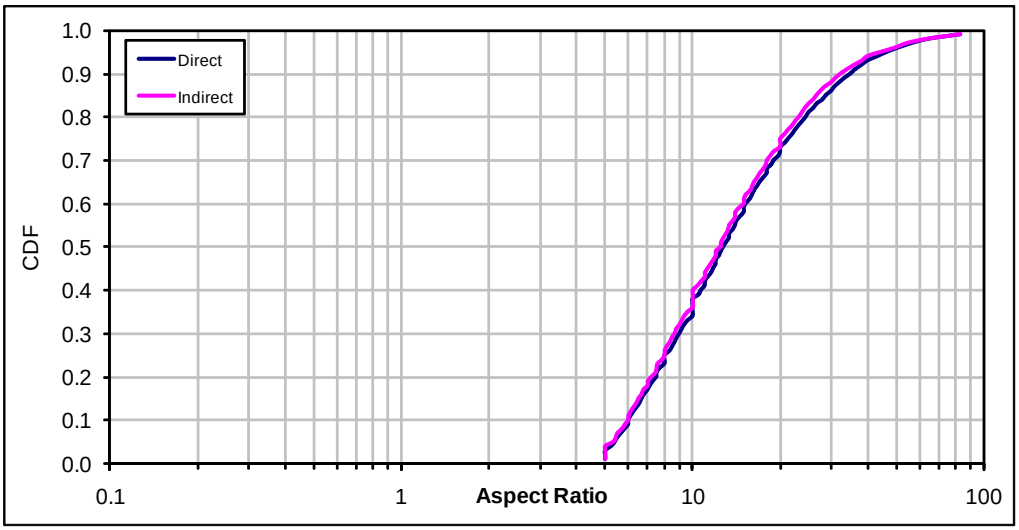
Data are based on a download of Libby 2DB performed on 12-8-09 and the Libby OU3 DB on 2-9-10.

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



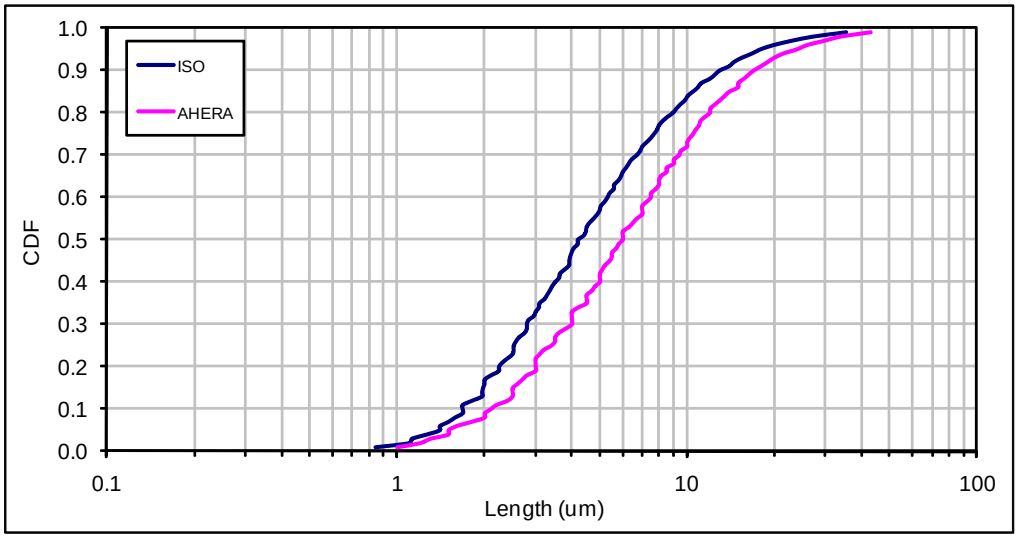


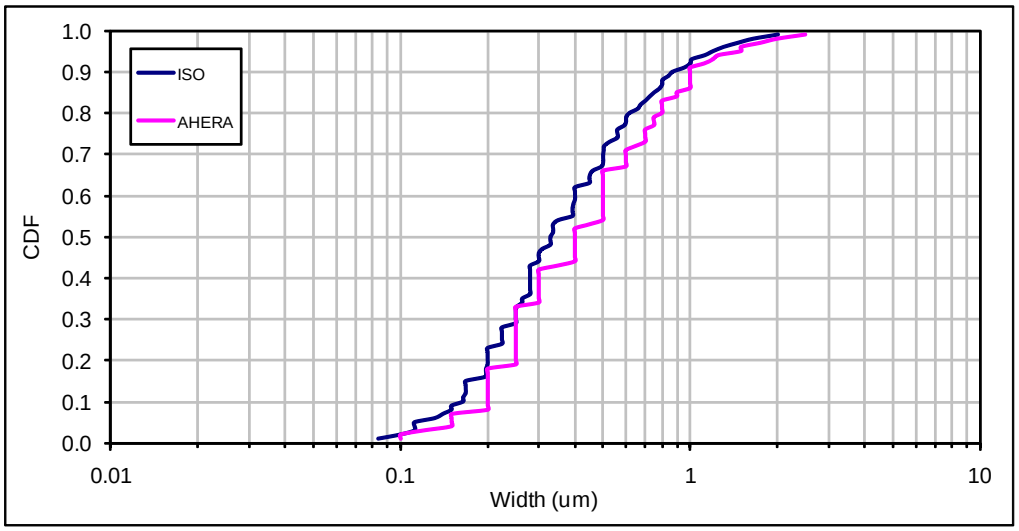


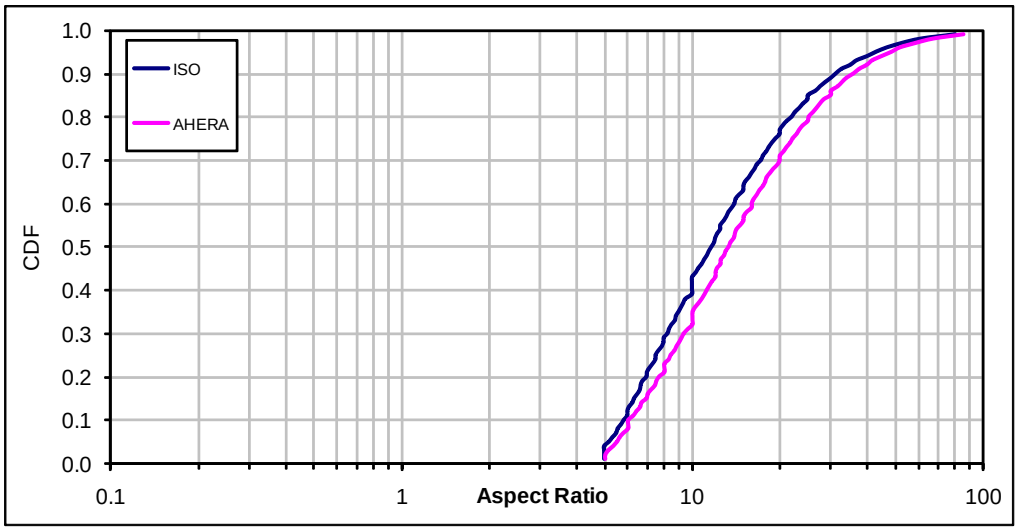
Data are based on a download of Libby 2DB performed on 12-8-09 and the Libby OU3 DB on 2-9-10.

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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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 Phalaborwa, 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 and pyroxenite, and biotitite, a rock composed almost completely of biotite Meeker et al. (2003). 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 vermiculite 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, Palabora, 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 g were mixed with 18 g of analytical silica sand and placed in a fluidized bed asbestos segregator vessel to load 25 mm MCE air sampling filters (0.8-µm 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 atoms per formula unit [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.

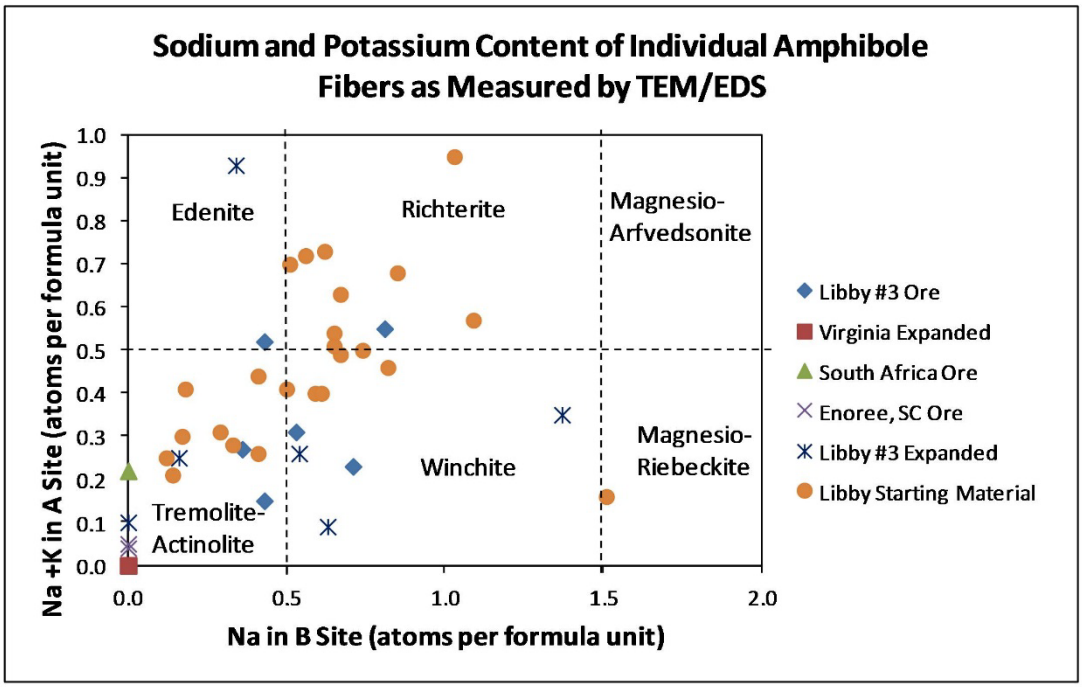

Figure C-1. Cation values for Na in the B site and the Na + K in the A site from individual amphibole fibers.

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.

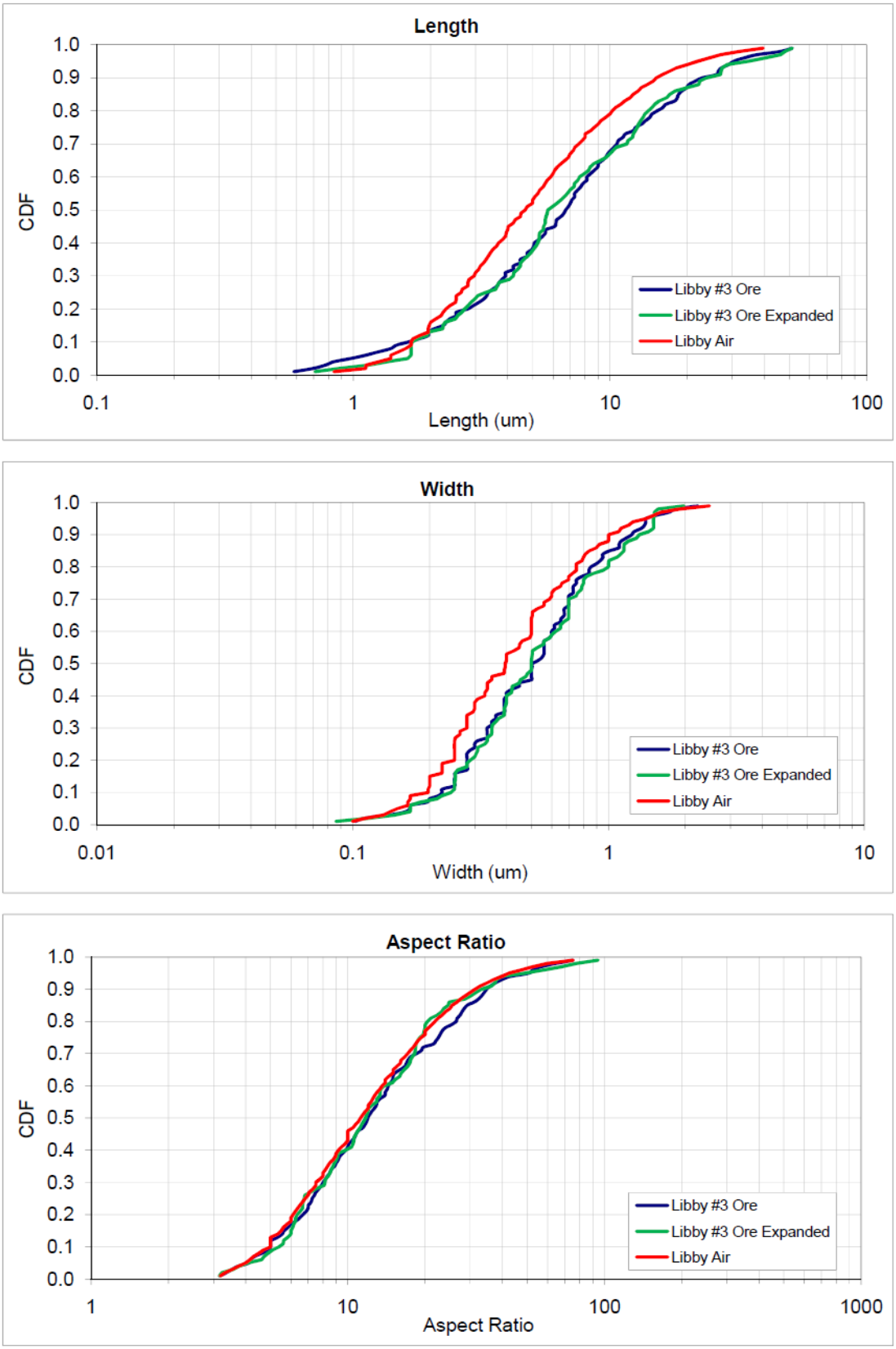

Figure C-2. Particle size distribution of LA amphiboles.

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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
Urogenital	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. (2005b), 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 exogenous 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 wollastonite 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), Smith et al. (1979), or 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 µg/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 µg/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 µg/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 appeared to activate NLRP3, chrysotile led to a greater effect as measured by cell death,

[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.

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 wollastonite. System x^-_c was increased in LAA-treated cells but not in silica or wollastonite 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., 2005b).

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 (µg/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 µg/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 µg/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).

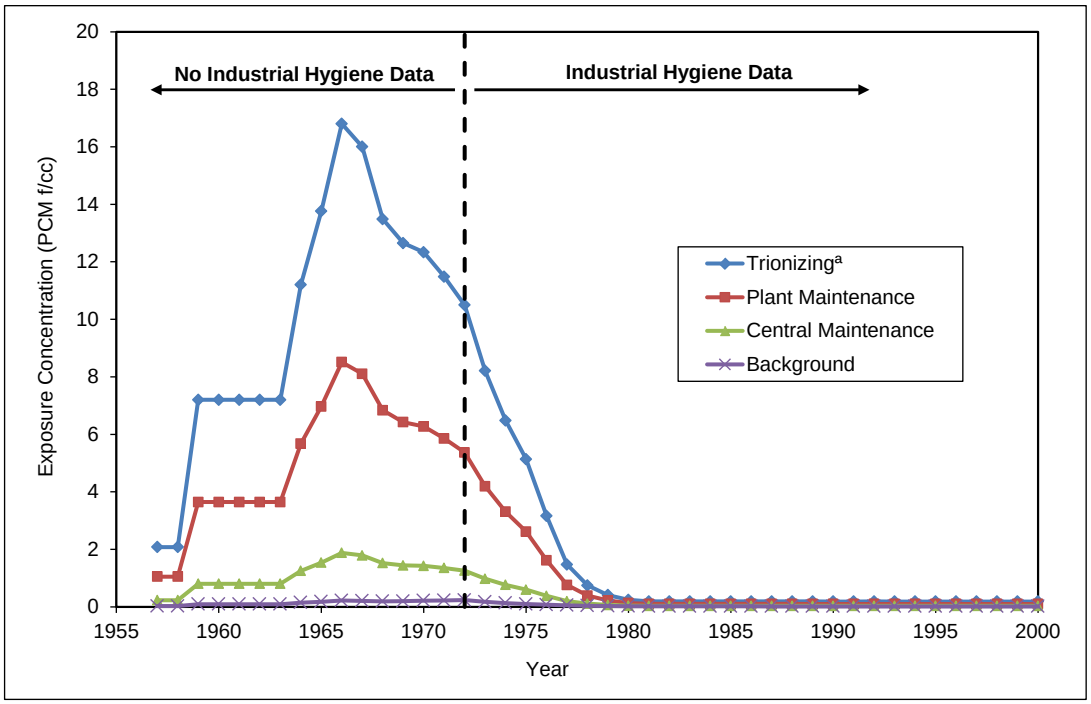


Figure E-1. Exposure concentrations in Marysville, OH facility.

[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), one 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. 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 modified 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., 1991c). 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	$p(x,T) = bkg + \frac{Plateau(T) - bkg}{1 + \exp[-a - \ln(x)]}$ $Plateau(T) = bkg + (1 - bkg) \times \Phi(T\|m,s)$

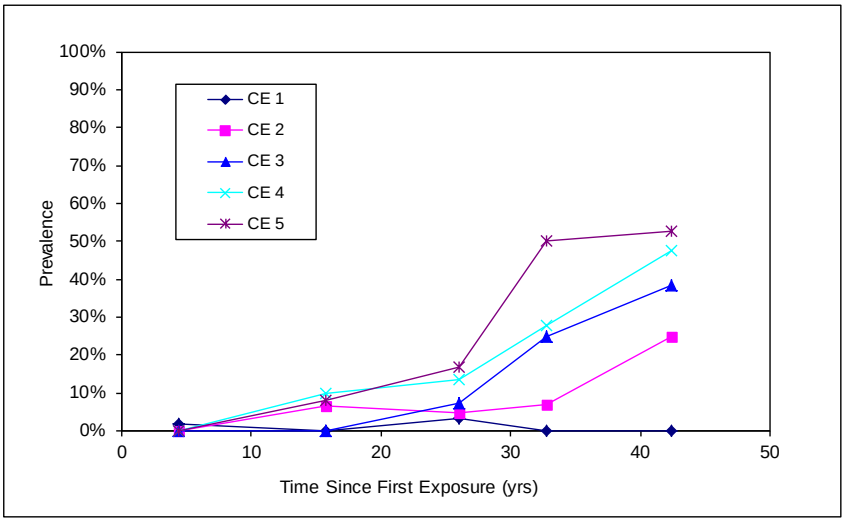
The background prevalence (*bkg*) of the health effect of interest was treated as an estimated parameter for all models. The exposure metrics tested included mean exposure concentration, CE, and RTW exposure. Univariate models that were tested included log-logistic (UV LL) and Dichotomous Hill with estimated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

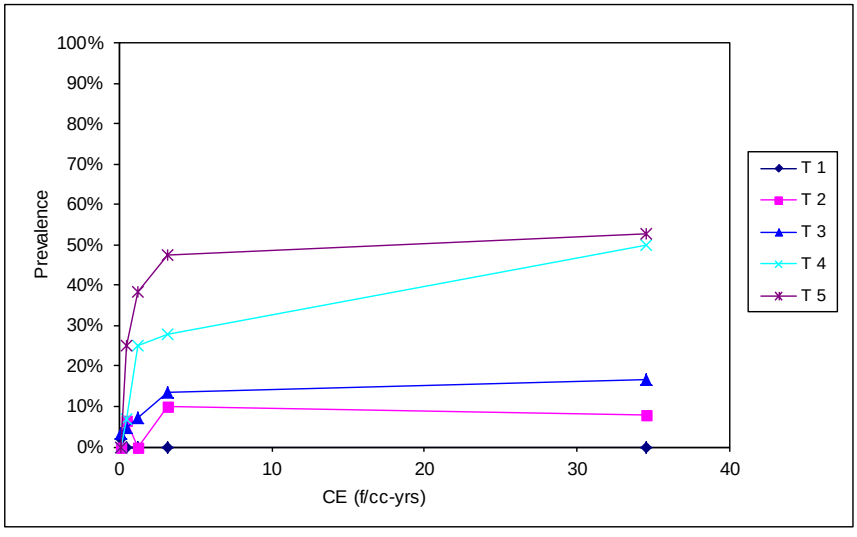
Panel A: Prevalence vs. time since first exposure stratified by cumulative exposure.



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., 1991c).

- 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 statistically significant association between duration of exposure and prevalence of APT in the

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

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

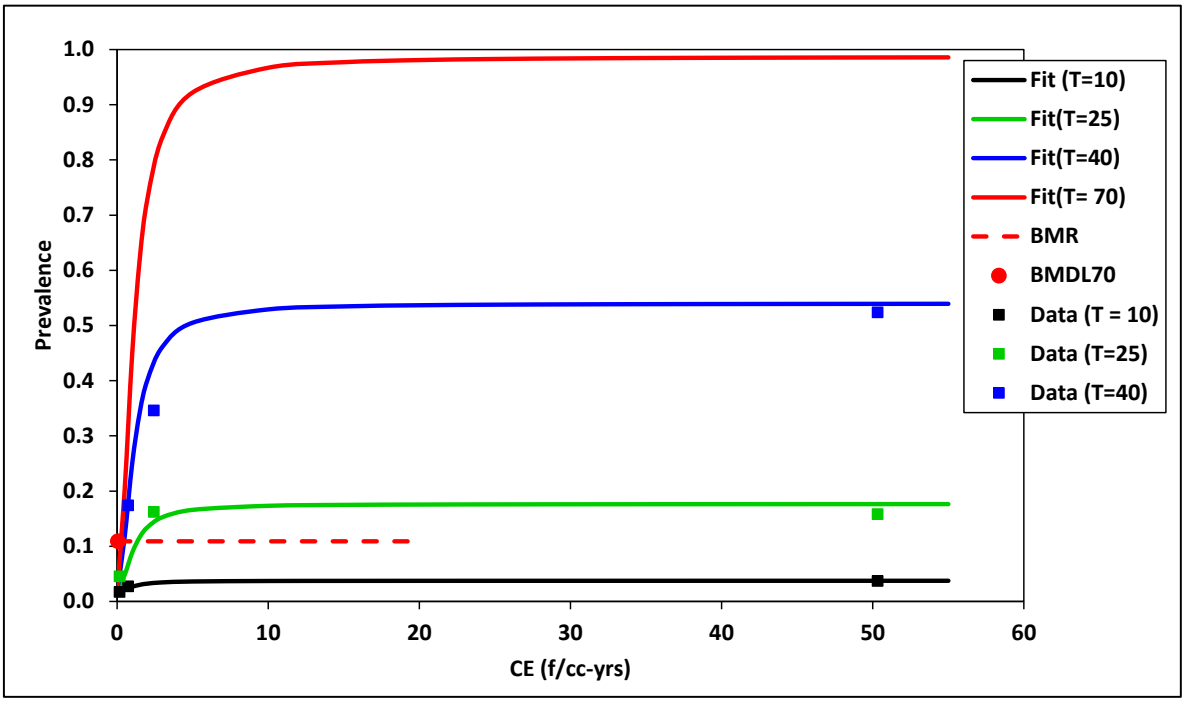
Using these binning rules yielded the prevalence of APT for each bin is shown in Table E-8.

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)

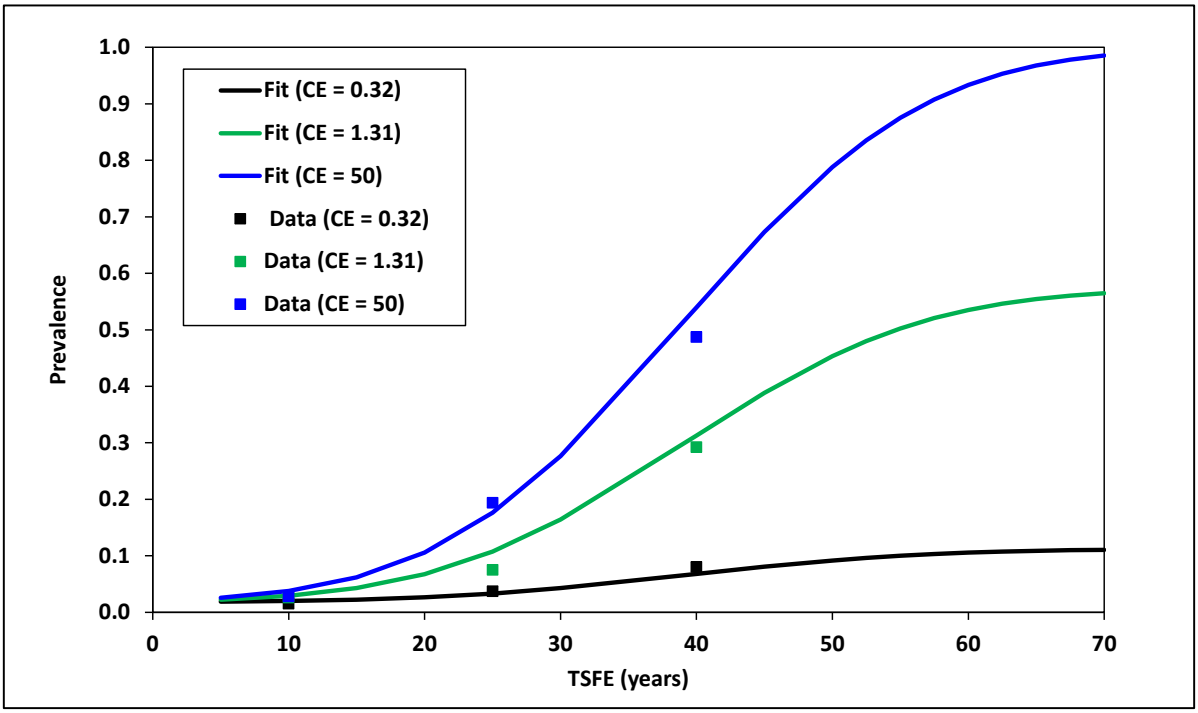
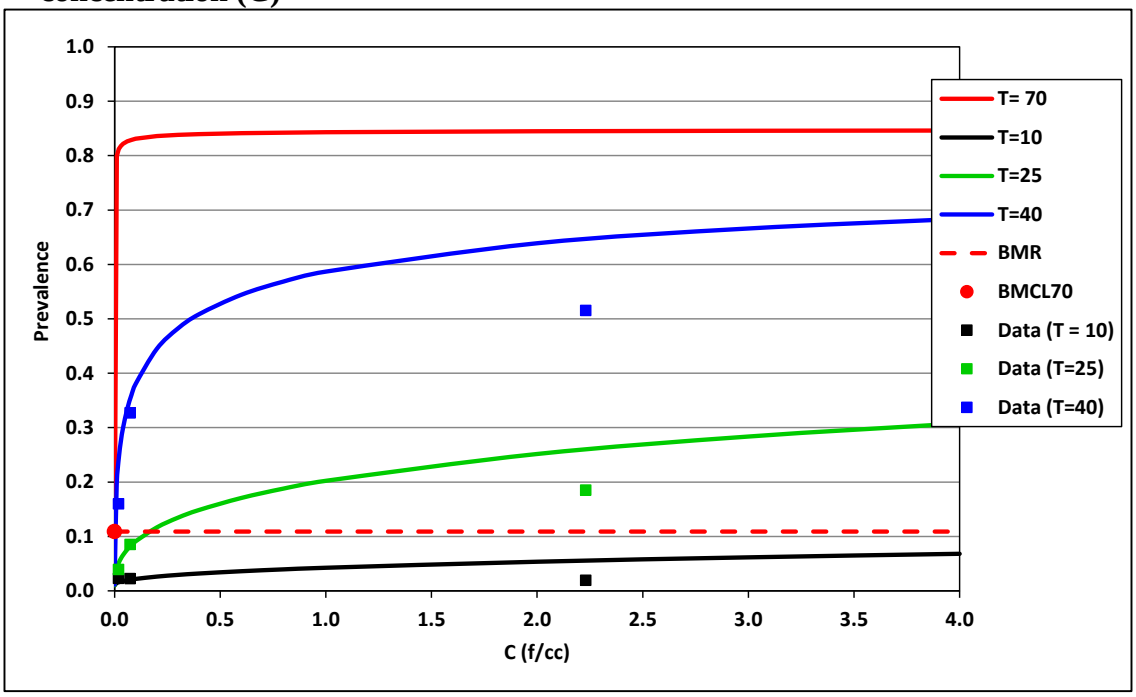


Figure E-3. Graphical display of predicted vs. observed any pleural thickening (APT) prevalence for cumulative normal Dichotomous Hill (CN DH) model fit to the combined cohort.

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)

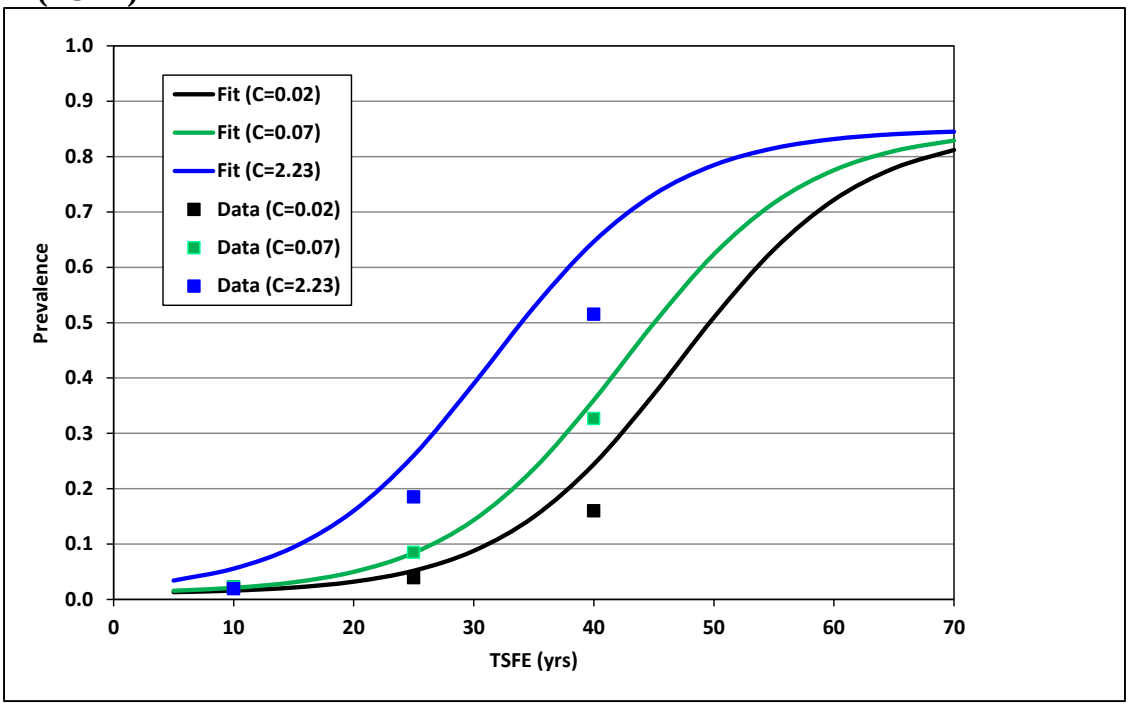


Figure E-4. Graphical display of predicted vs. observed any pleural thickening (APT) prevalence for the Bivariate Dichotomous Hill model with fixed plateau (BV DH FP) with exposure parameters of mean exposure concentration (C) and time since first exposure (TSFE) fit to the combined cohort.

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.

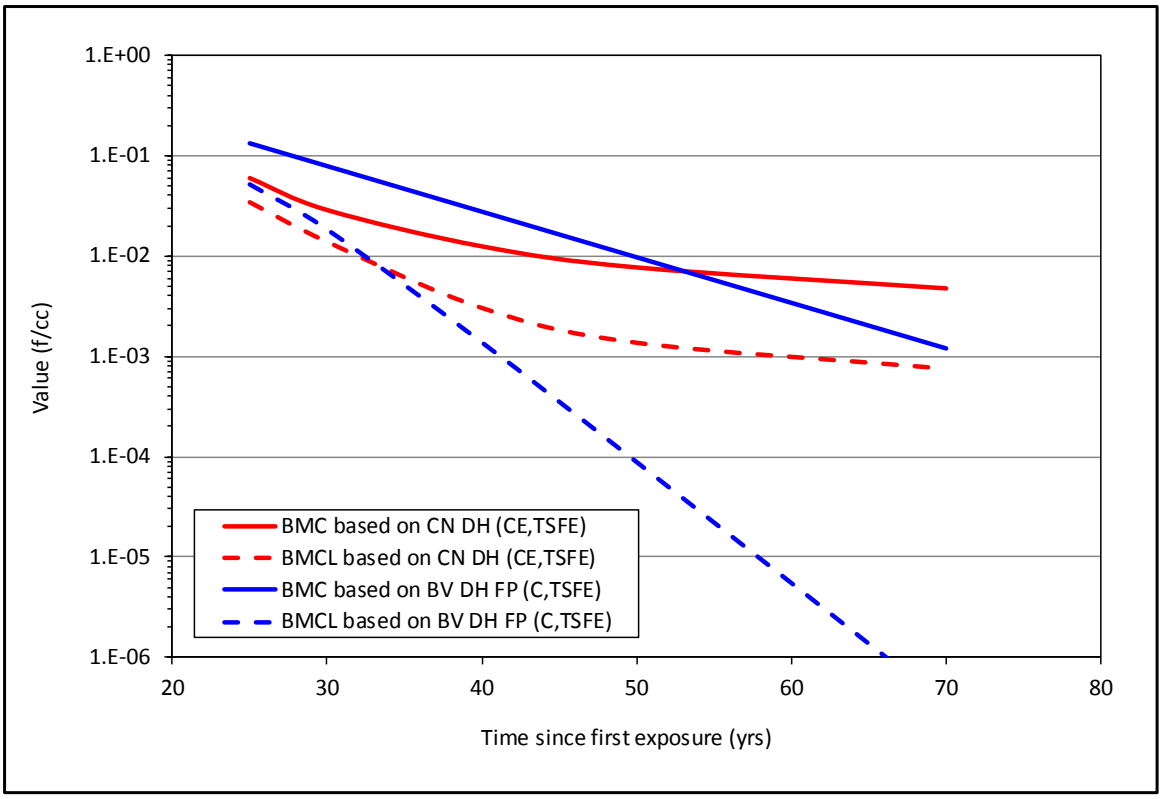


Figure E-5. Benchmark concentration (BMC) and lower limit of benchmark concentration (BMCL) values as a function of time since first exposure (TSFE) for two models: the cumulative normal Dichotomous Hill (CN DH) model using cumulative exposure and TSFE fit to the combined cohort, and the Bivariate Dichotomous 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, 2002b, 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 (fibers/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

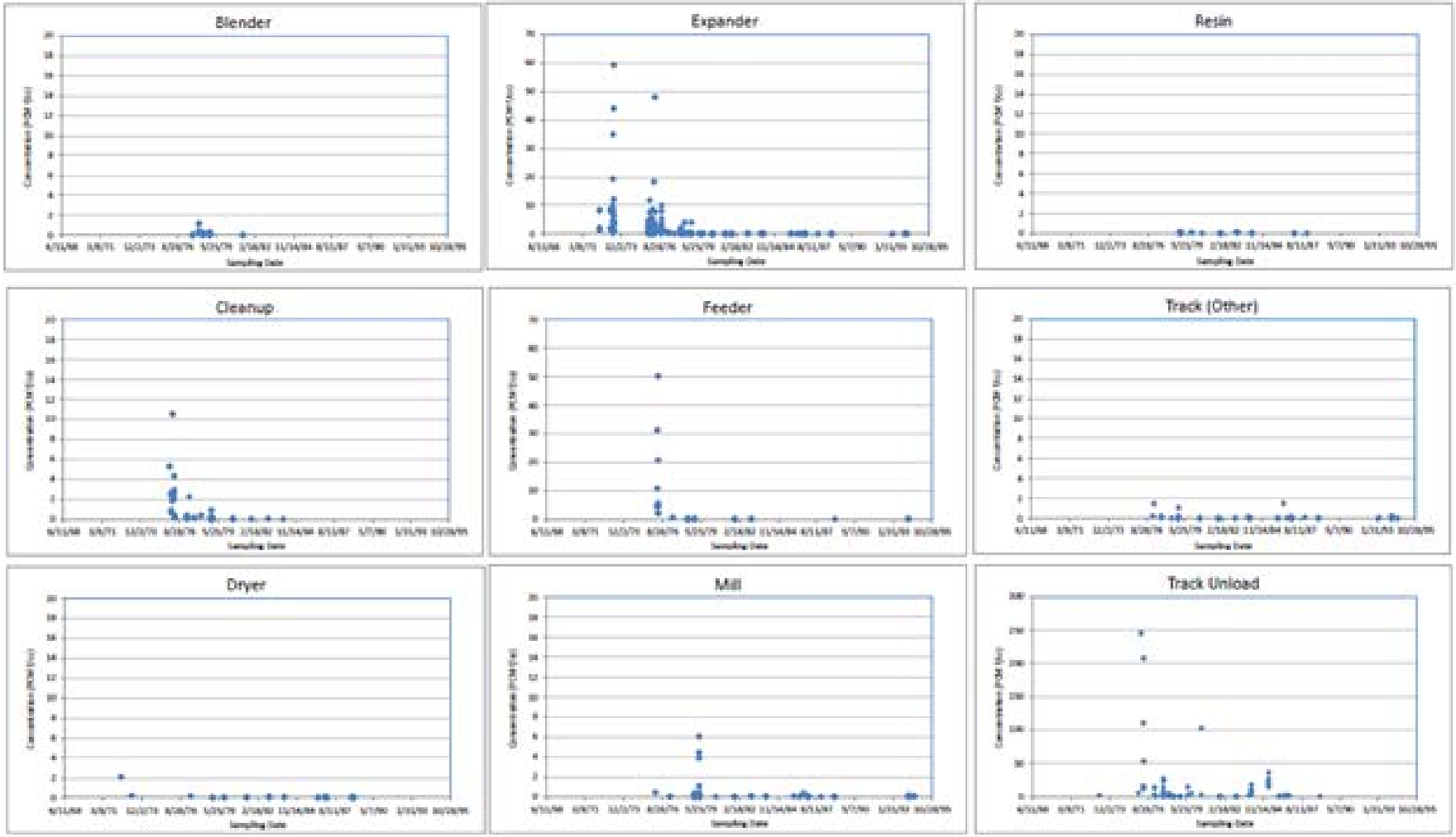


Figure F-1. Trionizing department data by year and job.

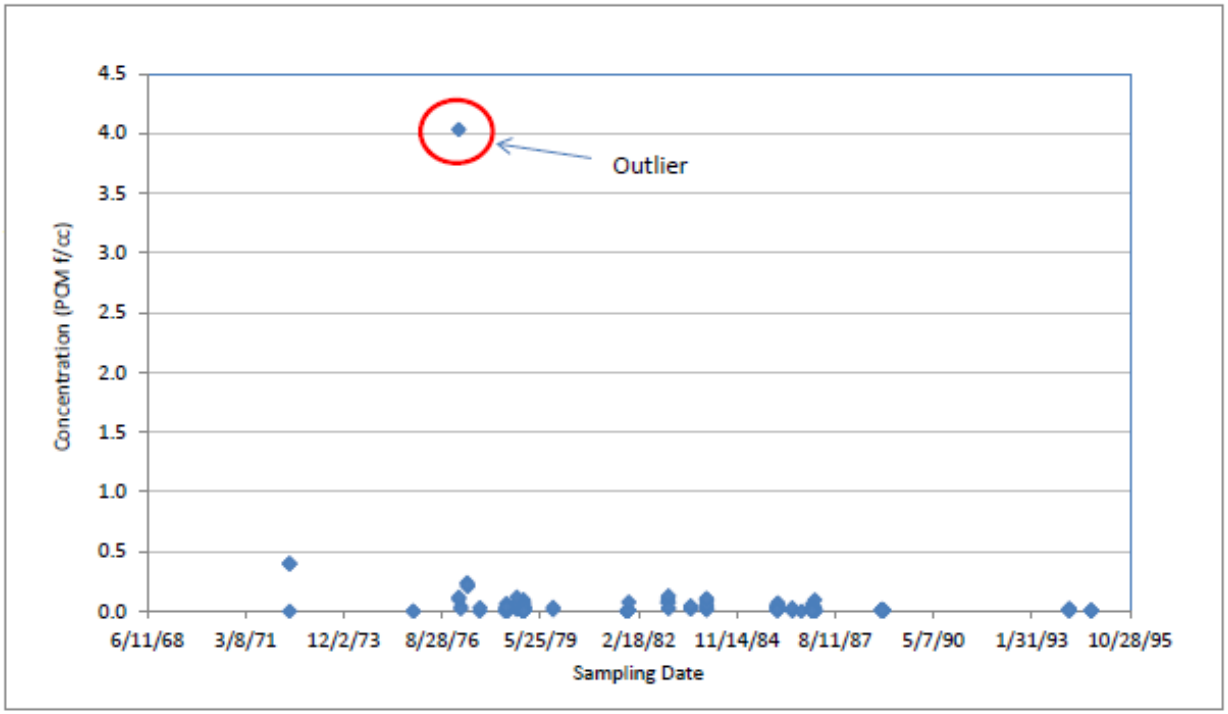


Figure F-2. Background data by year.

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."

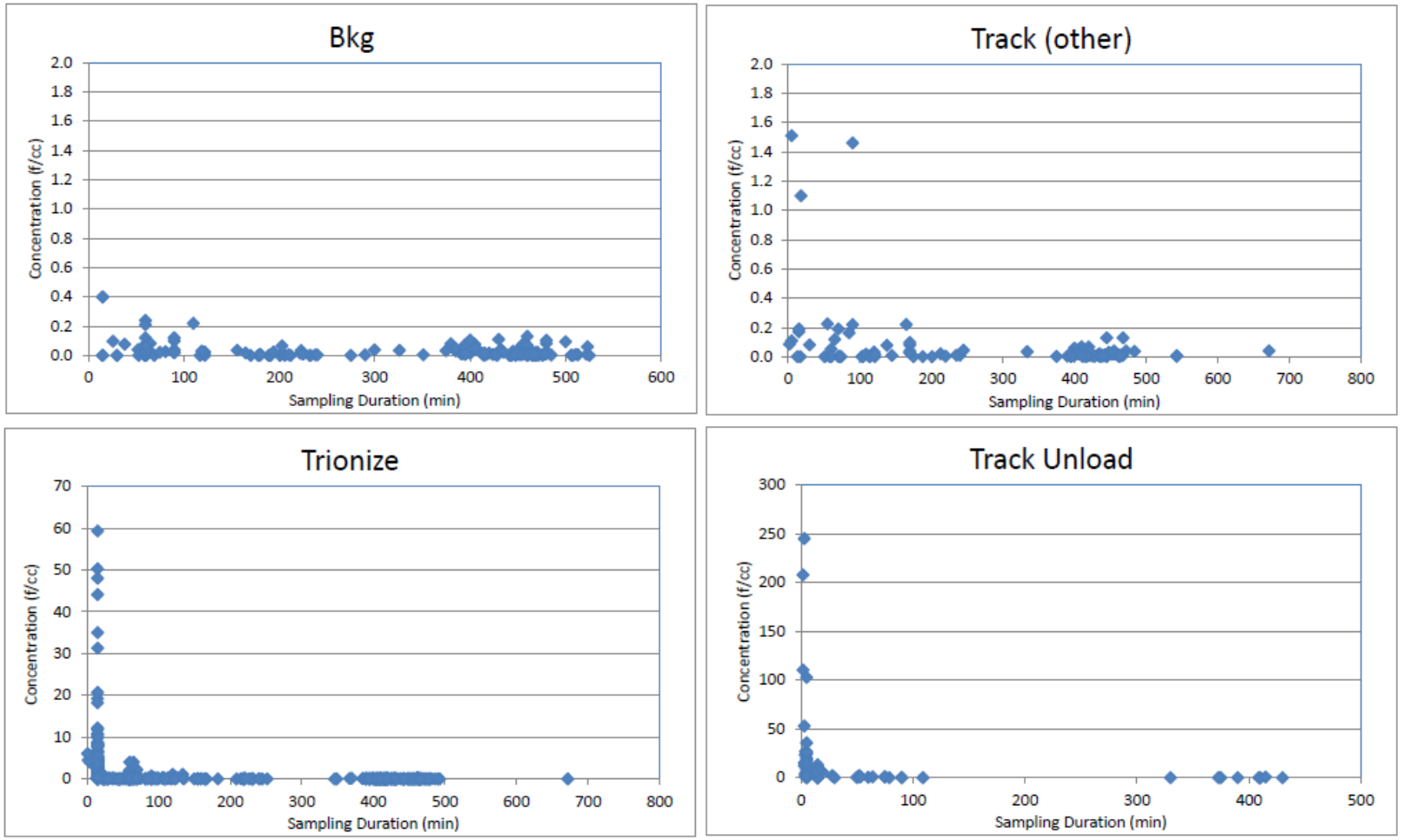


Figure F-3. Relation between sampling duration and measured concentration.

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 (fibers/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).

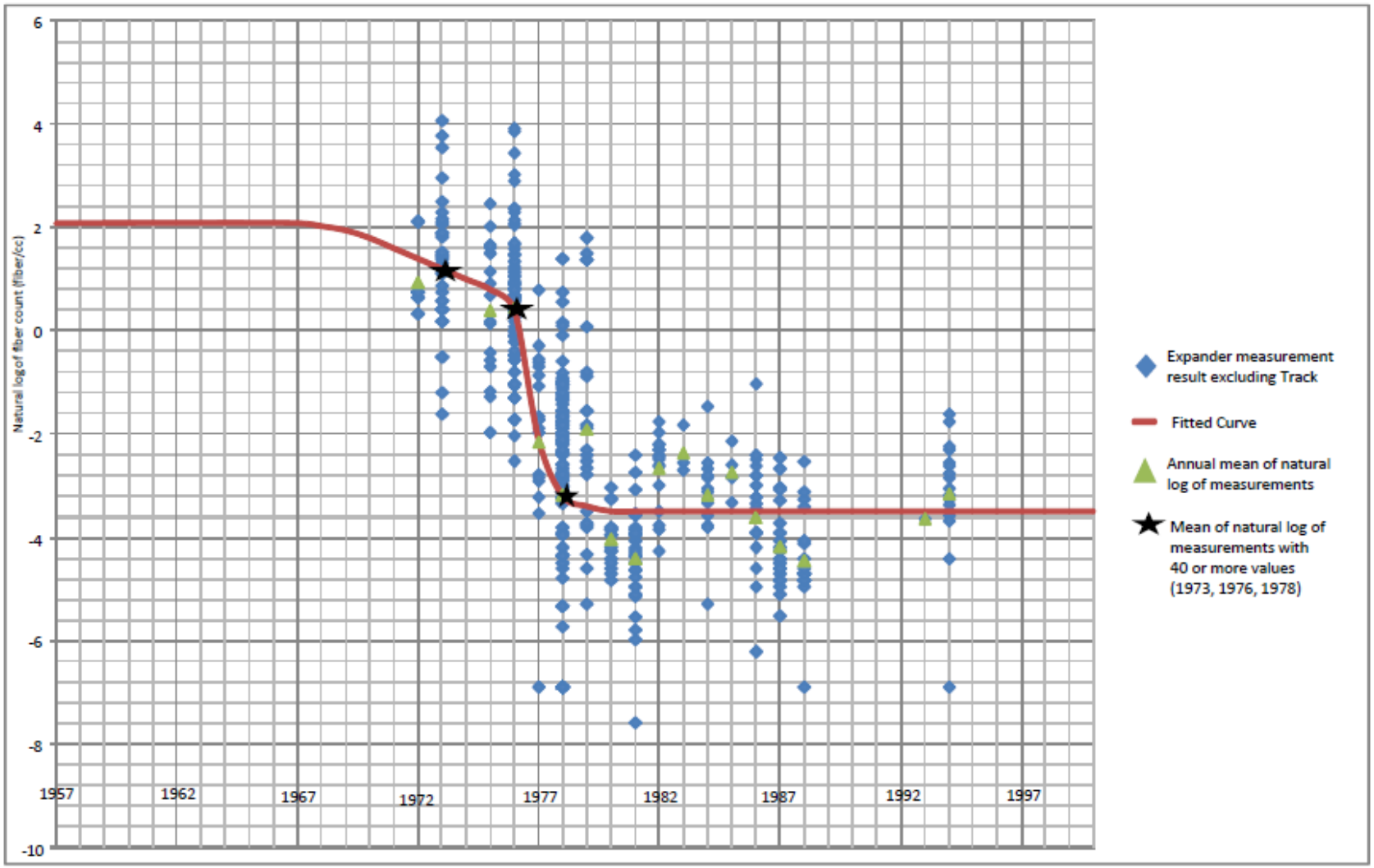


Figure F-4. Natural logarithm of all usable industrial hygiene measurements across all indoor jobs within the trionizing department, and the fitted line (red) used to represent the geometric mean.

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, 2008b; 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 fibers/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.

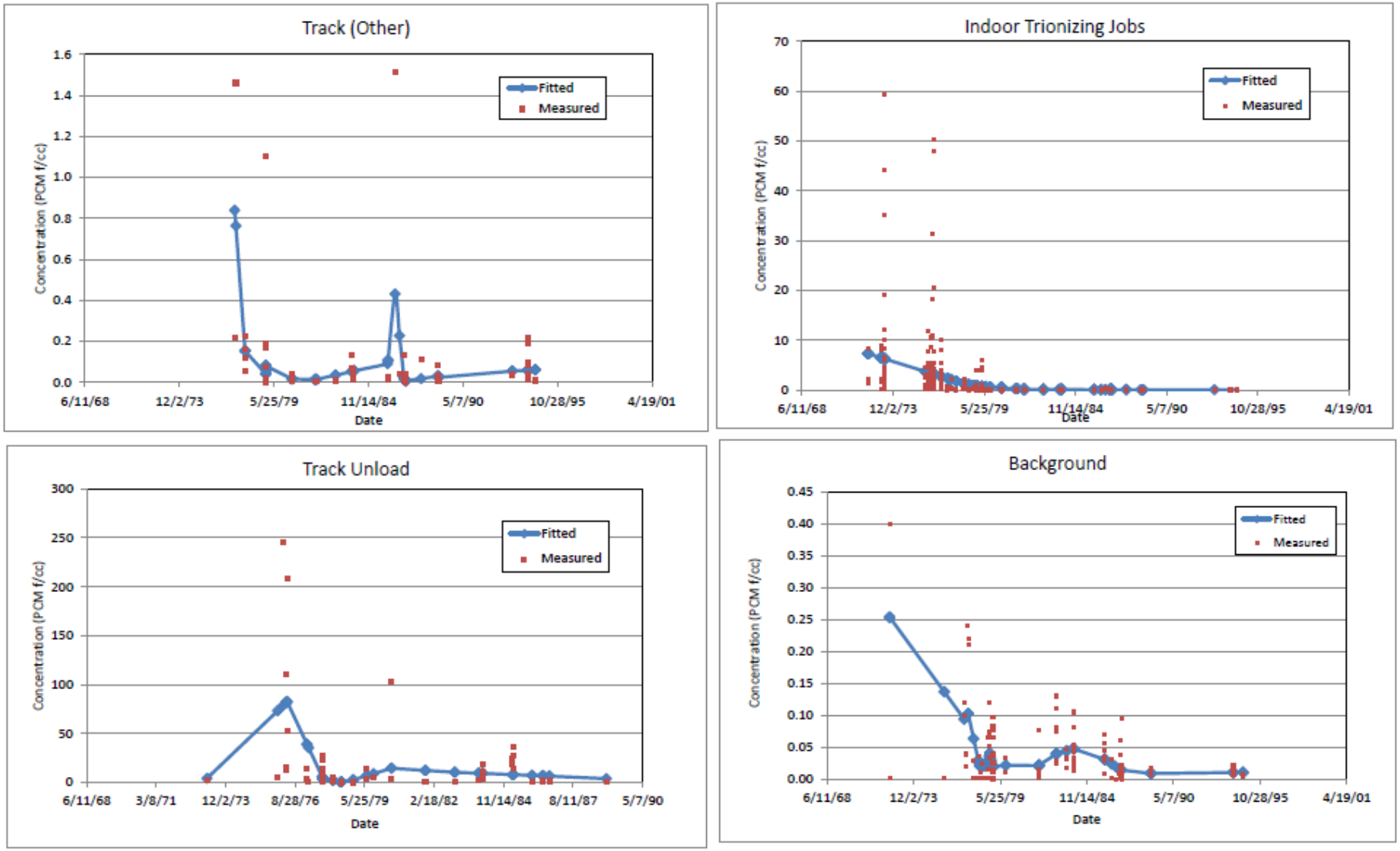


Figure F-5. Local regression (LOESS) fitting results.

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

$$C(t) = \mu(t) + e_t \qquad \text{(F-1)}$$

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*:

$$\mu(t) = a \times \exp(-b \times t) \qquad \text{(F-2)}$$

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):

$$\text{Var}\{C(t)\} = \sigma^2 \times \mu(t)^{\theta} \qquad \text{(F-3)}$$

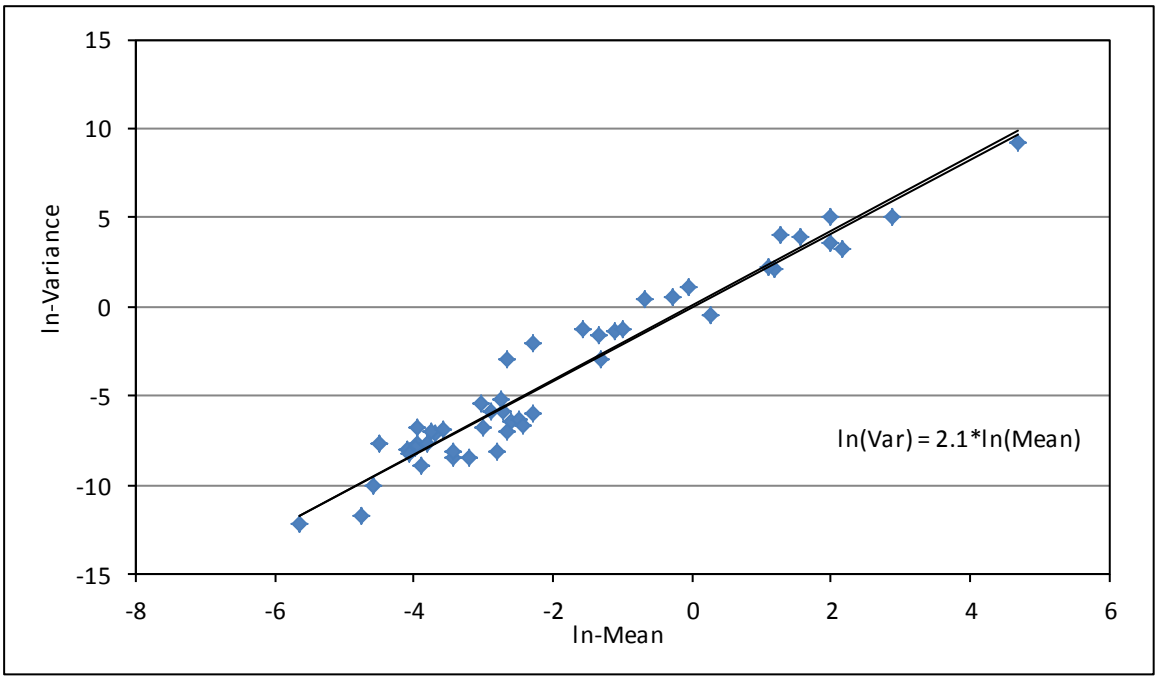


Figure F-6. Variance in industrial hygiene (IH) data as a function of the mean.

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 $\theta - \sim 1$ 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.

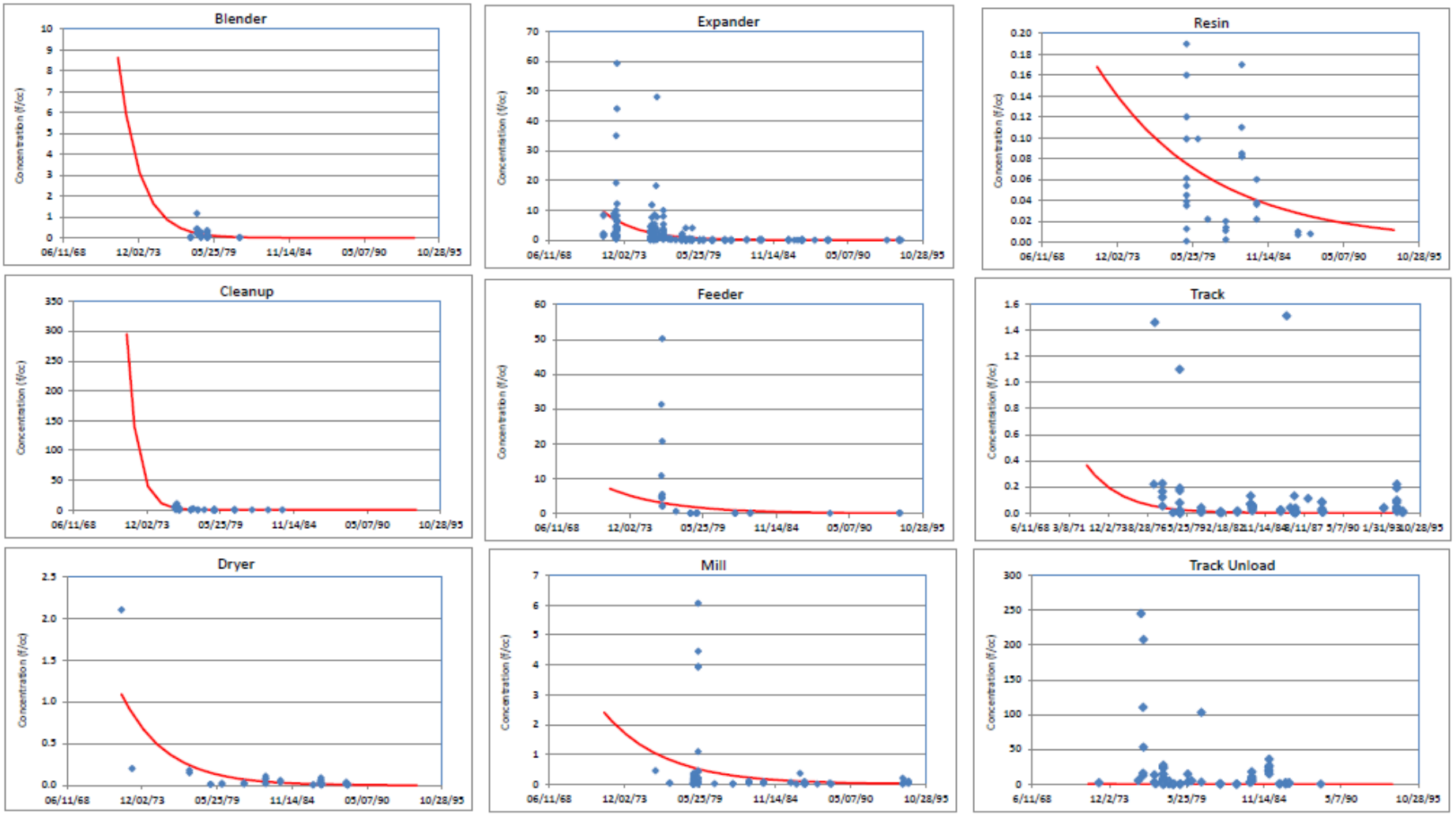


Figure F-7. Trionizing department data stratified by job. Variance-weight fitting with independent *b* terms.

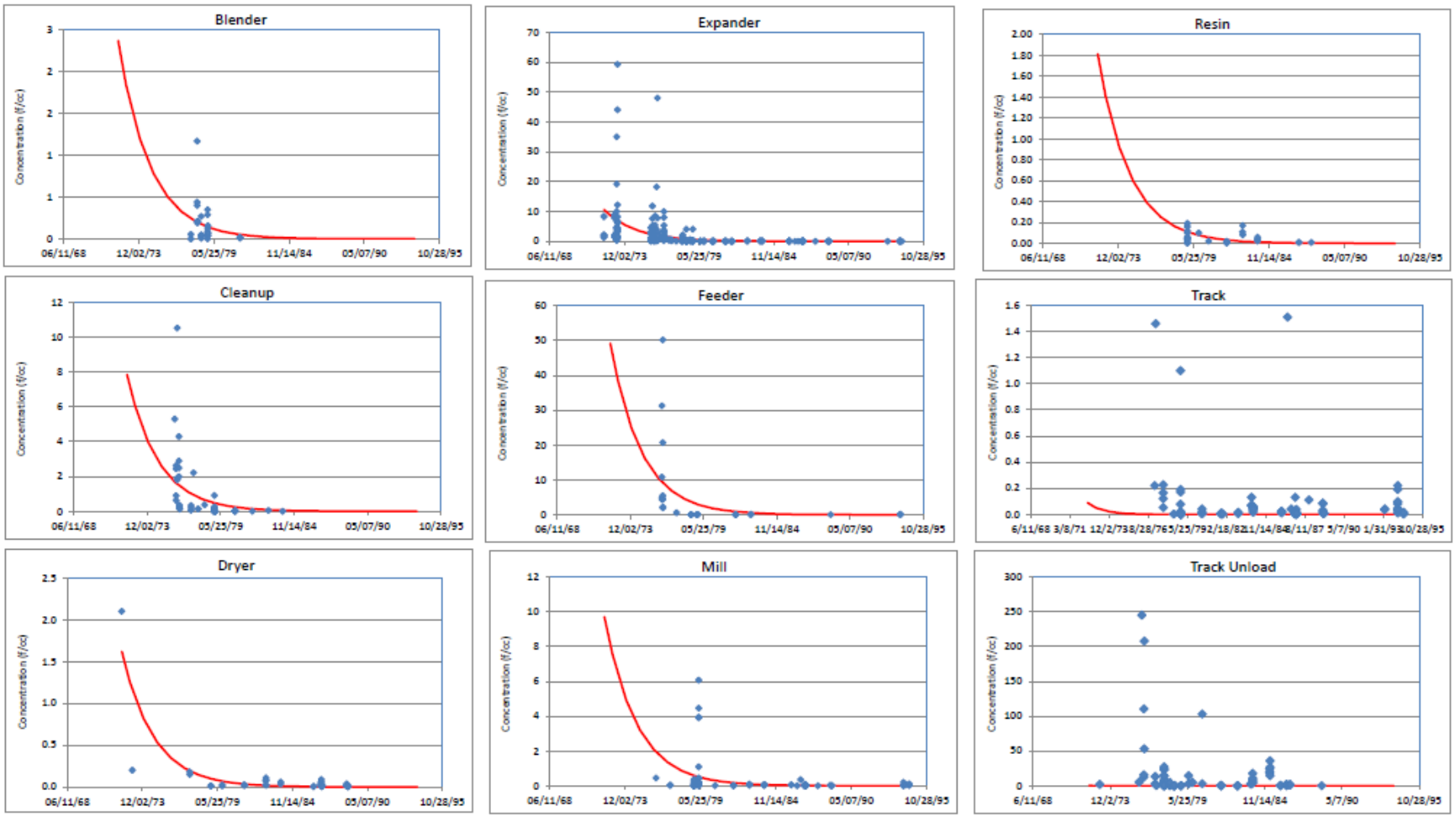


Figure F-8. Trionizing department data stratified by job. Variance-weight fitting with common *b* terms for indoor and outdoor jobs.

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.

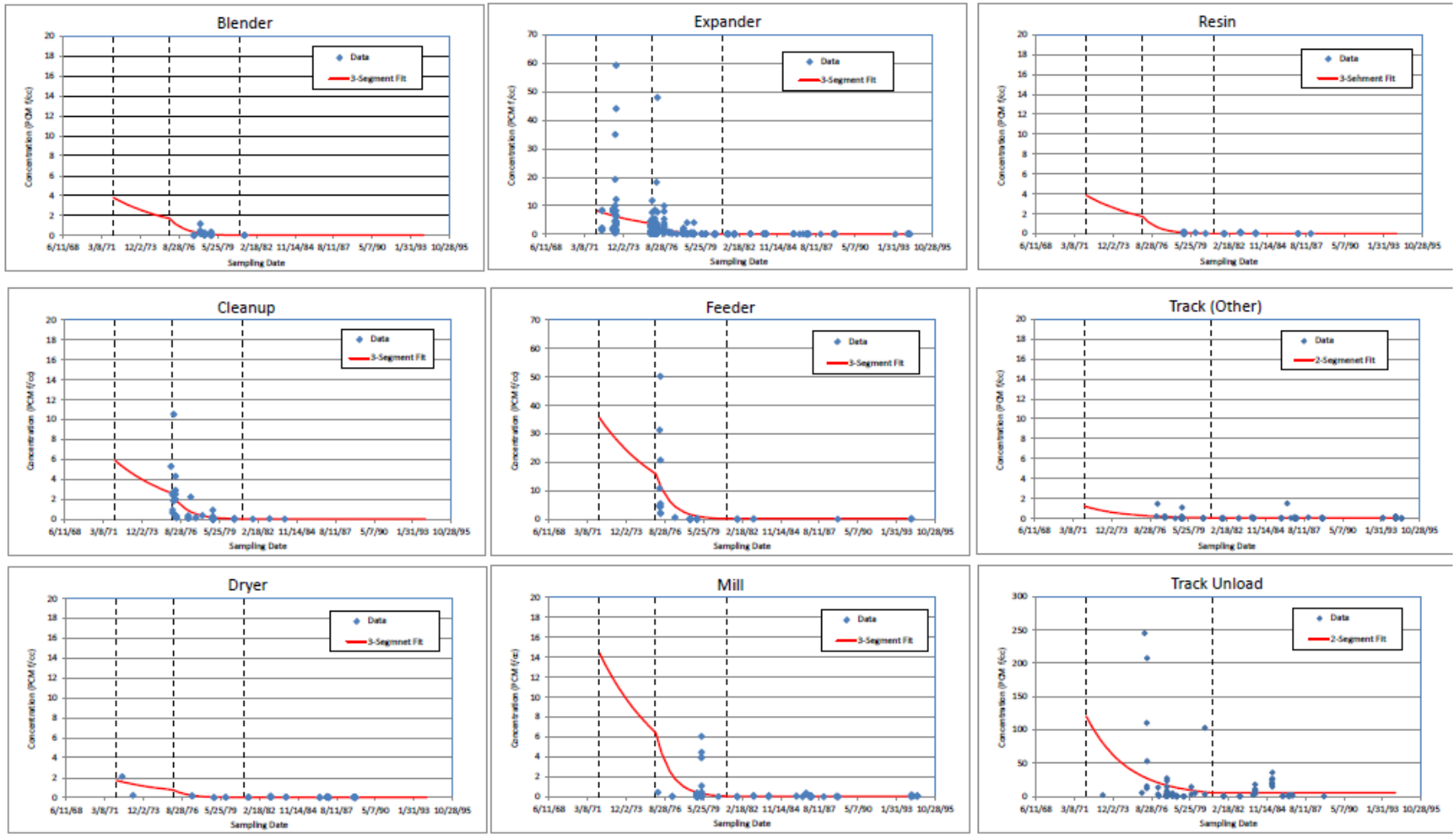


Figure F-9. Weighted exponential fits to indoor (3-segment) and outdoor (2-segment) trionizing jobs.

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."

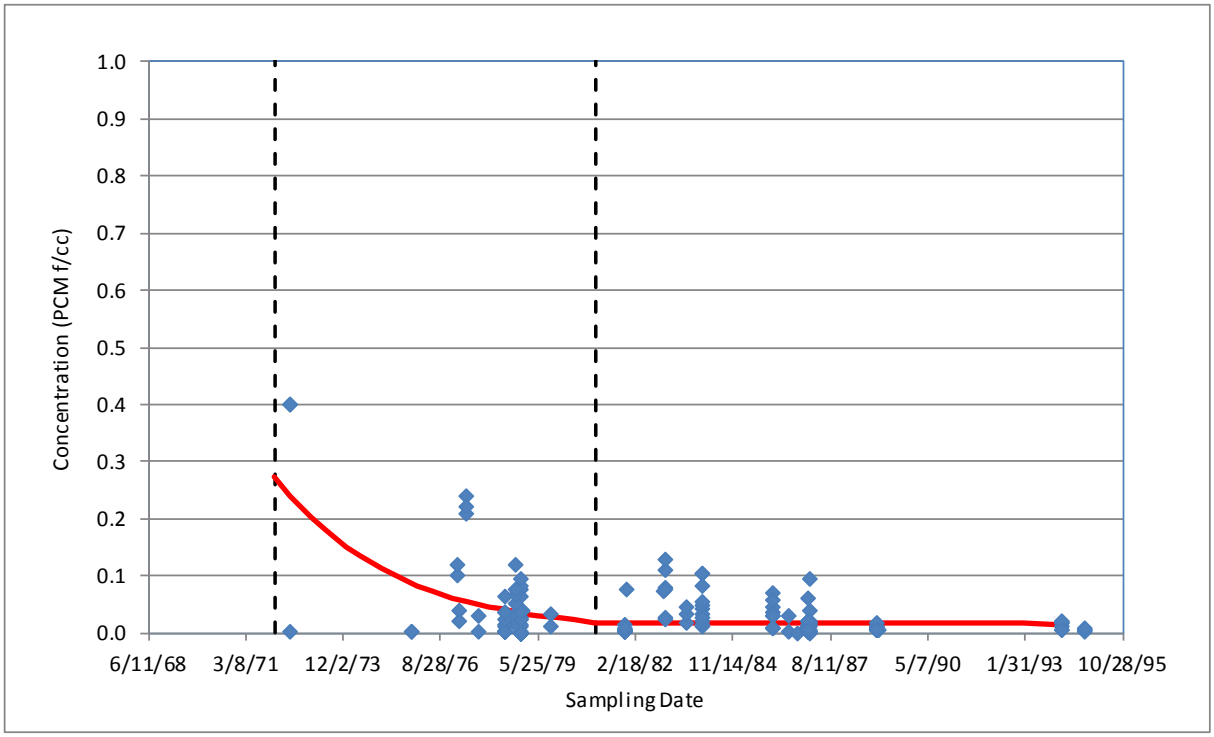
F.5.3.1.1.7. ***Data for other departments ("background").*** As discussed previously, industrial hygiene measurements in locations where only expanded vermiculite or no vermiculite was used were defined as having "plant background" exposure. These included measurements in polyform, office, research, 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 fibers/cc-years, which is calculated as the product of average exposure concentration at work ($\bar{C}$, fibers/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:

$$\text{CHEEC (f/cc-year)} = \sum\left(\bar{C}_{d,i} \times \text{Seasonal Adj. factor}_{d,i} \times N_{\text{i}}/365.25\right) \qquad \text{(F-11)}$$

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.

F.7. REFERENCES

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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, 2005a), 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 (rate $\times 10^5$) (Xu et al., 2010).

Column C: All-cause hazard rate for interval i (h^*x_i) (= all-cause mortality rate × number of years in age interval).

Column D: Probability of surviving interval i (q_i) [= $\exp(-h^*x_i)$].

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 (h_i). 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^*x_i) [= $h^*x_i + (hx_i - h_i)$].

Column I: Probability of surviving interval i without dying from mesothelioma for exposed people (qx_i) [= $\exp(-h^*x_i)$].

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 [= $(hx \div h^*x_i) \times Sx_i \times (1 - qx_i)$] ($R_x$, 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 fiber/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 ($\times 10^5$)**	**All-cause hazard rate (h^*)**	**Prob. of surviving interval (q)**	**Prob. of surviving up to interval (S)**	**Lagged exp. mid. int. (Xdose)**	**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 (R_x)**
<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 fiber/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
Age int.	All-cause mortality ($\times 10^5$)	All-cause hazard rate (h^*)	Prob. of surviving interval (q)	Prob. of surviving up to interval (S)	Lagged exp. mid. int. (Xdose)	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 (R_x)
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

Table G-1. Mesothelioma extra risk calculation for environmental exposure to 0.1479 fiber/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
Age int.	**All-cause mortality ($\times 10^5$)**	**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 (R_x)**
70–74	2,491.3	0.1246	0.8829	0.7710	2.131	0.0011	0.1256	0.8819	0.7642	0.0008
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 R_x = 0.0100										

exp. = exposure, haz. = hazard, int. = interval, meso. = mesothelioma, mid. = mid-interval, 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^*x_i) (= all-cause mortality rate × number of years in age interval).

Column E: Probability of surviving interval i (q_i) [= $\exp(-h^*x_i)$].

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 [= $(h_i \div h^*_i) \times S_i \times (1 - q_i)$], 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^*x_i) [= $h^*x_i + (hx_i - h_i)$].

Column L: Probability of surviving interval *i* without dying from lung cancer for exposed people (qx_i) [= $\exp(-h^*x_i)$].

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 [= $(hx_i \div h^*x_i) \times Sx_i \times (1 - qx_i)$] ($R_x$, 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 fiber/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 ($\times 10^5$)	Lung CA mortality ($\times 10^5$)	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 (R_o)	Lagged exp. mid. int. (Xdose)	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 (R_x)
<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 fiber/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 ($\times 10^5$)	Lung CA mortality ($\times 10^5$)	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 (R_o)	Lagged exp. mid. int. (Xdose)	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 (R_x)
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 fiber/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 ($\times 10^5$)**	**Lung CA mortality ($\times 10^5$)**	**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 (R_o)**	**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 (R_x)**
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
$R_o = 0.0531$								$R_x = 0.0625$					

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), NIOSH (2011), and NRC (1984). Risk assessment terminology for the IRIS program can be found in the IRIS Glossary.

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 length greater than or equal to 5 µm and an aspect ratio greater than or equal to 3:1 (by PCM) or 5:1 (by transmission electron microscopy [TEM]).

Fibril*:* A single fiber which cannot be separated into smaller components without losing its fibrous properties or appearance. 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 nonasbestiform, 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.

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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 circumscribed pleural thickening (plaques) and diffuse pleural thickening (DPT), either with or without costophrenic angle obliteration. LPT was introduced as a term in the 2000 ILO guidance. LPT includes plaques on the chest wall and at other sites (e.g. diaphragm). Plaques on the chest wall can be viewed either face-on or in profile. A minimum width of about 3 mm is required for an in-profile plaque to be recorded as present according to the 2000 ILO guidance. Neither classification for pleural thickening (LPT or DPT) in the 2000 ILO guidelines exactly corresponds with the previous ILO classification systems for pleural thickening; LPT is defined differently than the previous category of pleural plaques, and DPT is defined more narrowly due to the requirement for continuity with costophrenic angle obliteration and a 3 mm minimum width for DPT extending up the lateral chest wall.

Different researchers have used different terminology for circumscribed pleural thickening or plaques when implementing the 1980 ILO guidelines, most often using the term "pleural plaques." "Some studies clearly included in reported plaques sites other than the chest wall, while other studies did not explicitly describe inclusion of plaques in other sites.

Because the "LPT" designation is fairly recent, few studies provide data for this specific outcome. Therefore, EPA also considered studies examining the relationship between circumscribed pleural thickening (plaques) as defined in the 1980 ILO guidelines and pulmonary function.

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

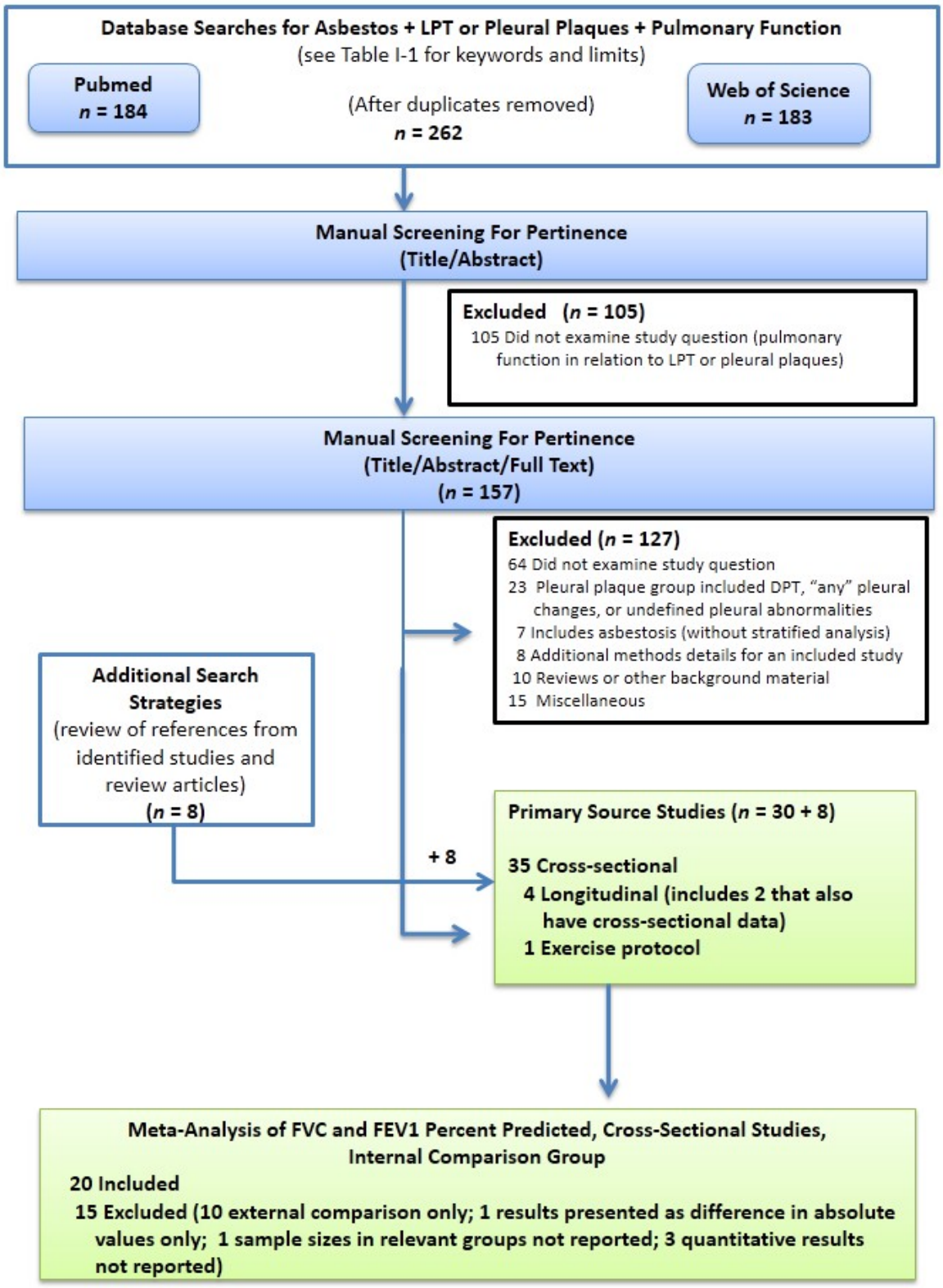

Figure I-1. Summary of literature search for studies of relation between localized pleural thickening (LPT) or pleural plaques and pulmonary function.

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 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); no information about reading protocol also considered a limitation. 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; Chow et al., 2009; Sandrini et al., 2006; Ameille et al., 2004; Kilburn and Warshaw, 1991; Hillerdal, 1990; Kilburn and Warshaw, 1990; Hjortsberg et al., 1988; McLoud et al., 1985; 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, percentage predicted; excluded profusion scores ≥1/0 Fiber type: unknown	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 Fiber type: mixed	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 Fiber type: mixed	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="8">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
Fiber type: unknown</td><td>From Tables III, IV, and V.
Mean (SD) percentage predicted, by group
<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>Prevalence, by group<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>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.
[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="4">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)
Fiber type: unknown</td><td>From Table IV.
Percentage predicted, by group[a]
<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>[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 (limited to nonsmokers) 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; did not discuss details of profusion scores Fiber type: mostly chrysotile	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 Fiber type: unknown	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) Fiber type: mixed	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.			

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			
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) Fiber type: unknown	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).			
(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 Fiber type: mostly chrysotile	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 Fiber type: unknown **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.			

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			
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 Fiber type: unknown **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*; internal comparison, percentage predicted; potentially inadequate consideration of smoking; did not discuss details of profusion scores Fiber type: unknown	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.			
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 Fiber type: LAA	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.			

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			
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 Fiber type: unknown	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 Fiber type: unknown **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.			
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 Fiber type: unknown	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

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			
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 Fiber type: unknown	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 Fiber type: mixed	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
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 Fiber type: mixed	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

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
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, percentage predicted; 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; for these two studies, the smoking-adjusted results are used in the meta-analysis (for Weill et al. (2011) results on males are used). 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. 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). That article 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 (Oldenburg et al., 2001; 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 (Rui et al., 2004; 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 over selection of symptomatic individuals (Miller et al., 2013; Rui et al., 2004; Singh et al., 1999; García-Closas and Christiani, 1995)

- Only one x-ray reader or different readers in different locations (without validation sample), or lack of details about x-ray or HRCT reading protocol) (Miller et al., 2013; Rui et al., 2004; Oldenburg et al., 2001; Singh et al., 1999; Soulat 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; Rui et al., 2004; Oldenburg et al., 2001; 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)

Inadequate consideration of smoking as a potential confounder (Miller et al., 2013; van Cleemput et al., 2001; Singh et al., 1999; Soulat 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).

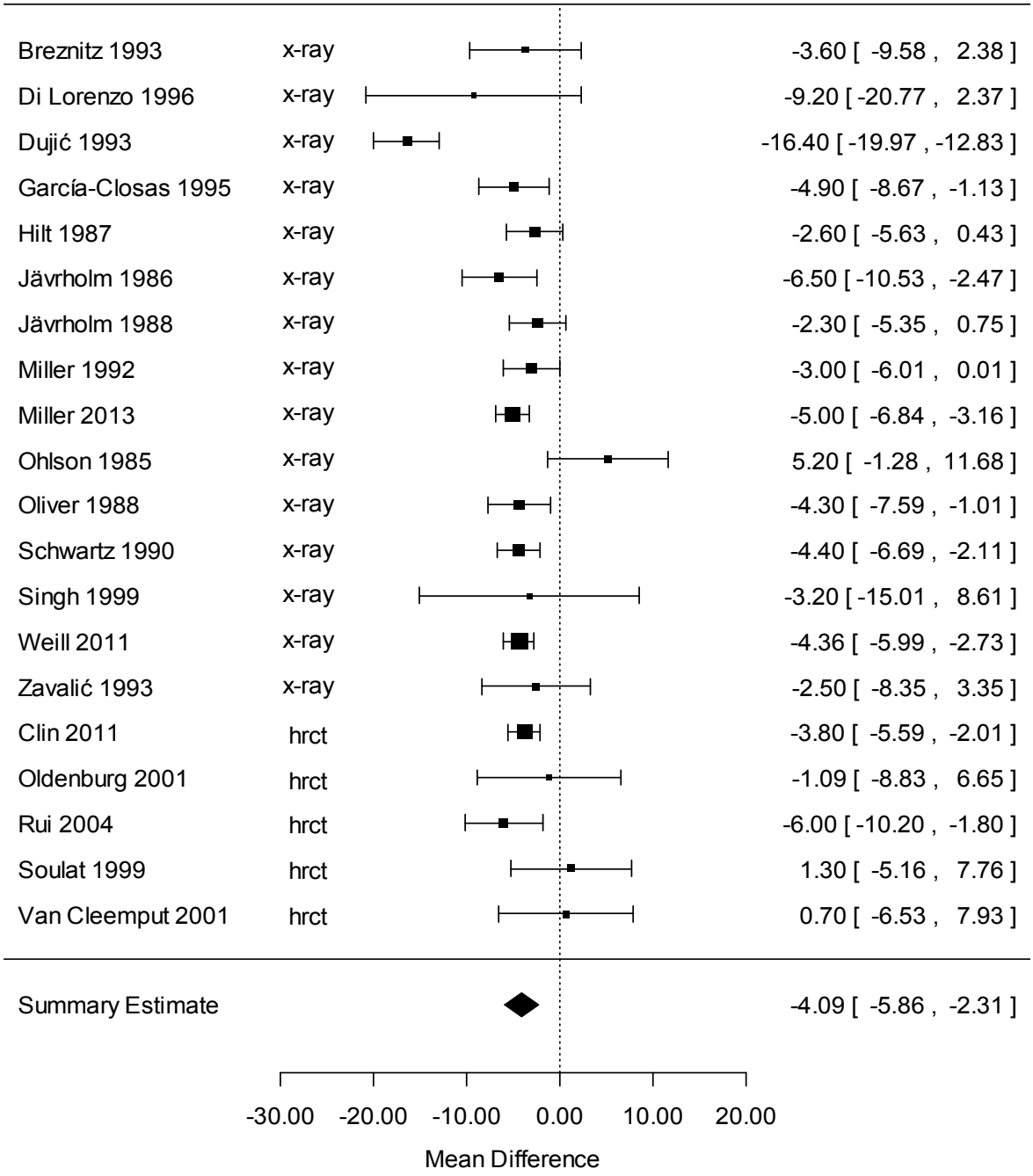

Figure I-2. Study-specific and summary effect estimates for change in percentage predicted forced vital capacity (FVC) comparing asbestos-exposed groups with and without localized pleural thickening (LPT) or pleural plaques, x-ray and high resolution computed tomography (HRCT) cross-sectional studies. Data are mean values; bars and values in brackets are 95% CI, size of data point is proportional to study weight.

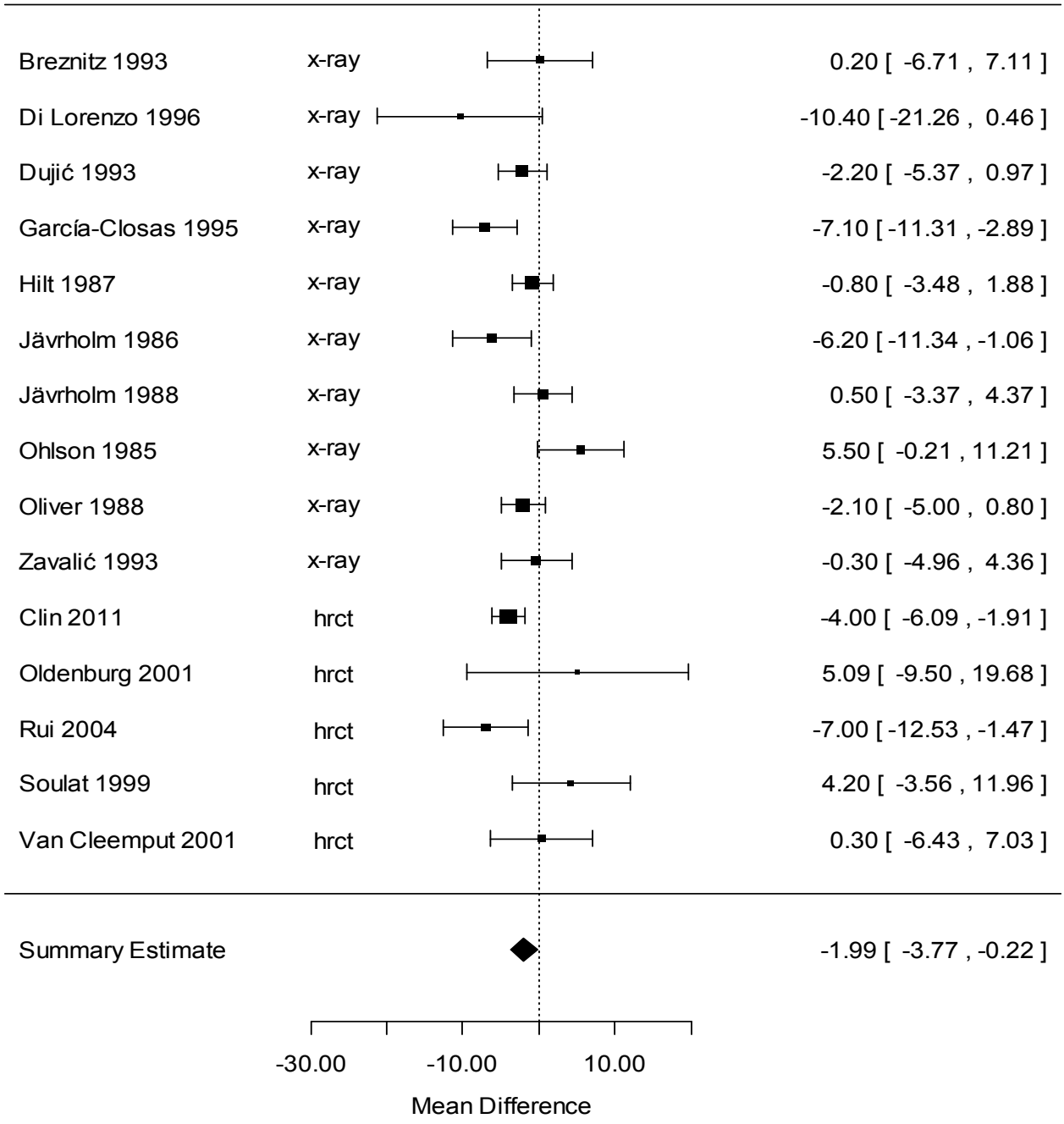

Figure I-3. Study-specific and summary effect estimates for change in percentage predicted forced expiratory volume (FEV_1) comparing asbestos-exposed groups with and without localized pleural thickening (LPT) or pleural plaques, x-ray and high resolution computed tomography (HRCT) cross-sectional studies. Data are mean values; bars and values in brackets are 95% CI, size of data point is proportional to study weight.

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.

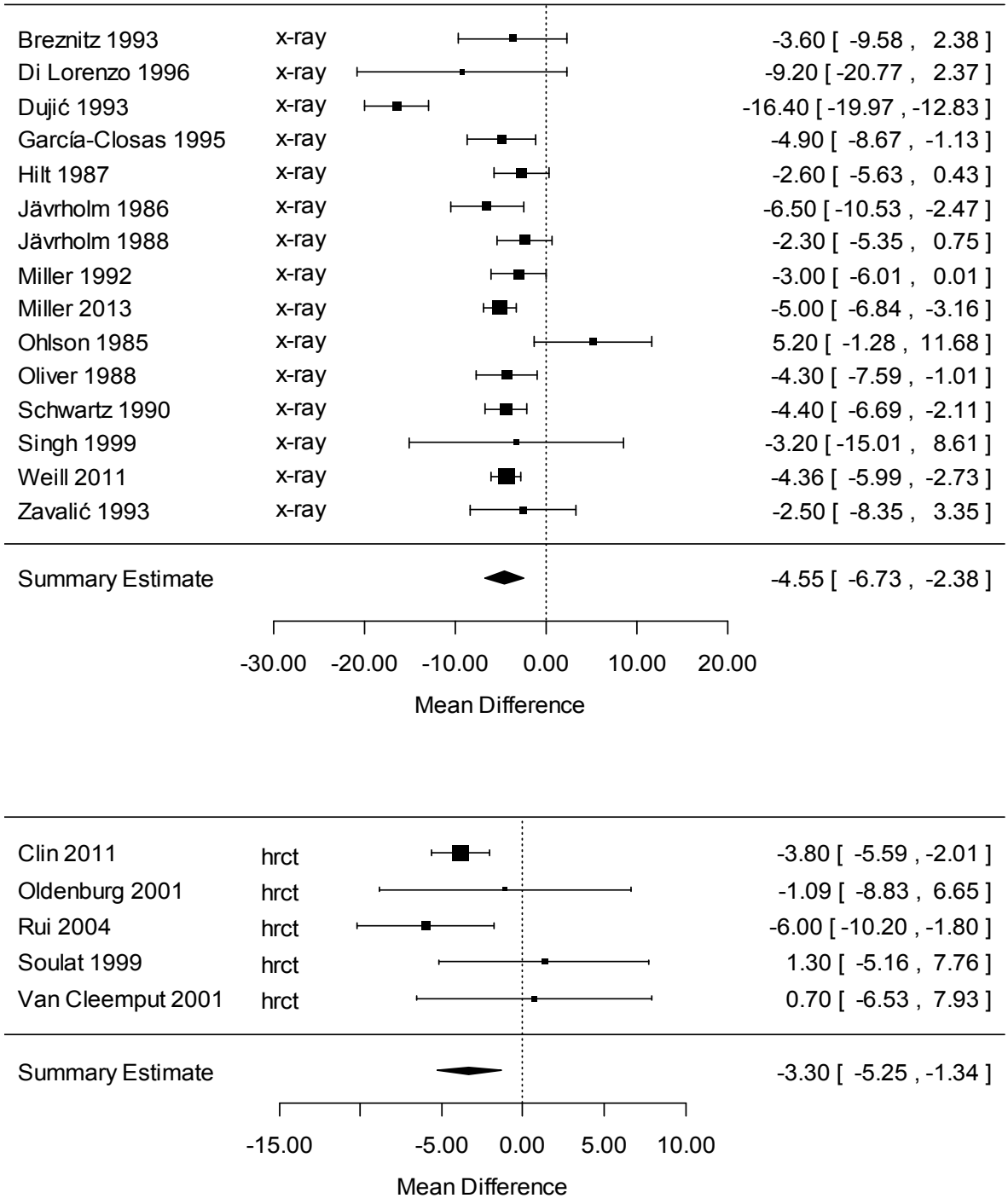

Figure I-4. Study-specific and summary effect estimates for change in percentage predicted forced vital capacity (FVC) comparing asbestos-exposed groups with and without localized pleural thickening (LPT) or pleural plaques, for x-ray (top panel) and high resolution computed tomography (HRCT) (bottom panel) cross-sectional studies. Data are mean values; bars and values in brackets are 95% CI, size of data point is proportional to study weight.

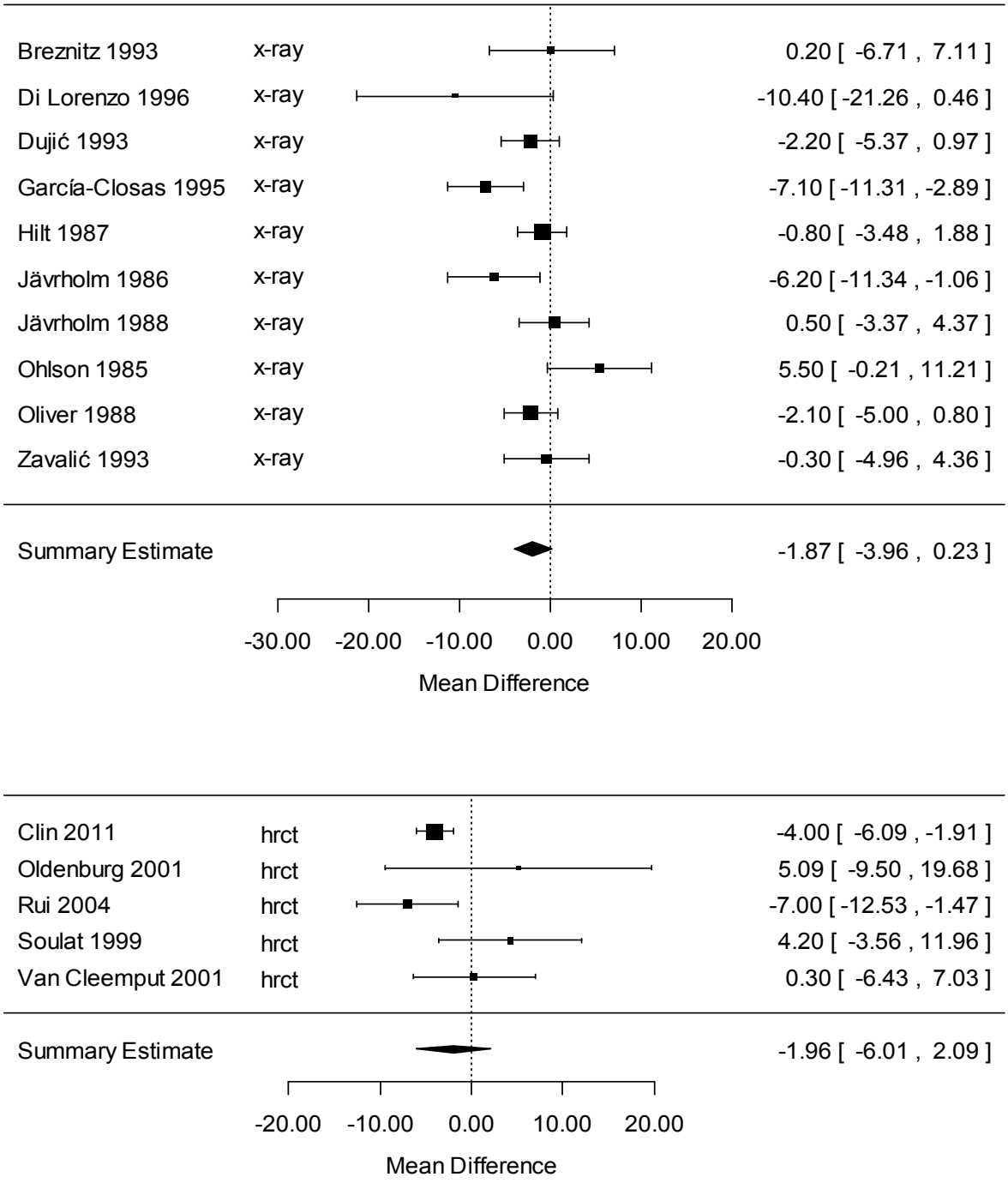

Figure I-5. Study-specific and summary effect estimates for change in percentage predicted forced expiratory volume (FEV_1) comparing asbestos-exposed groups with and without localized pleural thickening (LPT) or pleural plaques, for x-ray (top panel) and high resolution computed tomography (HRCT) (bottom panel) cross-sectional studies. Data are mean values; bars and values in brackets are 95% CI, size of data point is proportional to study weight.

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. Zavalić 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. *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. 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)

Reference, methods details	Results
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)	From Table 6. **Adjusted percent decline (compared with baseline assessment)** **Pleural plaques (n = 24)** / **No pleural plaques (n = 50)** / **Mean difference in amount of loss** FVC: 6.34 / 6.74 / 0.40 FEV_1: 6.43 / 7.39 / 0.96 Adjusted for height, age, tracheal area, cumulative exposure, and smoking.
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	From Table 2. **Mean (SD) percentage predicted, by group** **First examination** / **Last examination** / **Mean reduction (95% CI) for those with plaques[a]** **Plaques (n = 36)** / **No plaques (n = 67)** / **Plaques (n = 36)** / **No plaques (n = 67)** VC: 91 (10) / 97 (10) / 90 (10) / 96 (11) / −3.4 (−7.9, 1.0) FEV_1: 97 (13) / 103 (12) / 95 (14) / 102 (13) / −1.5 (−7.1, 4.0) [a]Adjusted for smoking habit and seniority.
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	From Table 7. **Mean SEM annual loss (mL/yr)** **Pleural plaques (n = 51)** / **No pleural plaques (n = 211)** / **Mean difference in rate of loss** FVC: 31 (12) / 15 (6) / 16 mL/yr
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)	From Table II. **Mean (SD) among people with pleural plaques (n = 18)** **1988** / **2003** / **Difference, 2003 minus 1988** FVC %predicted: 94.74 (17.98) / 80.12 (13.76) / −14.62 FEV_1 %predicted: 93.43 (13.56) / 89.1 (10.84) / −4.33

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. This analysis compared exposed persons with and without pleural plaques, so that while the total decrement in either group could be due in part to asbestos exposure alone, the estimated difference between the groups should primarily reflect the decrement due to pleural plaques. In the meta-analysis by Wilken et al. (2011), asbestos-exposed workers without radiologic abnormalities showed decrements in lung function (i.e., values below 100% of predicted: %pred FVC 95.7 and %pred FEV_1 93.6). Thus, the lung function decrements associated with pleural plaques in this analysis are even more pronounced when compared to 100%pred, or normal lung function.

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; Rui et al., 2004; 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.

LPT was introduced as a term in the 2000 ILO guidance. LPT includes plaques on the chest wall and at other sites (e.g. diaphragm). Plaques on the chest wall can be viewed either face-on or in profile. A minimum width of about 3 mm is required for an in-profile plaque to be recorded as present according to the 2000 ILO guidance. Although no studies reported results for plaques with width of at least 3 mm (i.e., LPT), one large study Clin et al. (2011) (reported results for plaques less than 2 mm and found that those with such plaques had at least 100%pred FVC and FEV_1. Thus, results of analysis for pleural plaques in this Appendix can be seen to apply to LPT.

EPA considered the potential for BMI to affect the observed associations between pleural plaques and lung function. Directionally consistent with this potential bias, a tendency for greater FVC decrements in the x-ray studies (4.55%) relative to the HRCT studies (3.30%) was seen. Given that the FVC loss is still observed in the HRCT studies; however, the associations cannot be fully explained by the effects of BMI. Of the two studies that included BMI in their analyses, one study, using x-rays, observed a slightly higher BMI in people with plaques (mean

30.3 and 28.5 kg/m^2, respectively for with and without plaques), and higher BMI and age were significantly related to decrements in FVC (Weill et al., 2011); EPA used the BMI- and age-adjusted results in its meta-analysis. The other study used HRCT, and observed similar mean BMI between individuals with and without pleural plaques (27.7 and 27.4 kg/m^2, respectively) (Clin et al., 2011). More generally, the prediction of FEV_1 and FVC is not improved by considering weight after taking into account height, age, race, and sex in cross-section analyses of lung function (Hankinson et al., 1999). EPA does not believe large differences in BMI by radiographic group are likely in the remaining studies examined, and overall, does not believe that the observed associations between pleural plaques and lung function decrements are biased by an effect of BMI.

With regard to fiber type, 13 studies did not report fiber type of asbestos exposure, four reported mixed exposure, two reported mostly chrysotile exposure, and one reported LAA exposure. Thus, EPA could not examine fiber characteristics in this analysis. However, EPA is not aware of any studies of pleural plaques and lung function that indicated potential differences in association by fiber type. Only study of exposure to LAA (Weill et al., 2011) showed decrease in %pred FVC (this study did not report FEV_1) comparable to overall result (4.36 vs. 4.09). Moreover, the results from the studies included in this meta-analysis did not display great variability, although it is likely that study populations were exposed to different fiber types (or mixtures).

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. 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 LPT) represent a persistent structural alteration of the pleura. The statistical association between pleural plaques and LPT and decrements in pulmonary function identified herein is consistent with plaques being an indicator of asbestos exposure and indicate that pleural plaques (as defined by 1980 ILO) and LPT are associated with declines in pulmonary function. Although the decrements in mean pulmonary function measures associated with the presence of 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); predicted values based on sex, age, height, and smoking habits.	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, based on single individuals)	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}	Analysis stratified by smoking status (current and former smokers, nonsmokers)	Table 1. Results stratified by smoking

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; Smoking data by group not reported and not included in analysis.	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 Quanjer 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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APPENDIX J.
DOCUMENTATION OF IMPLEMENTATION OF THE 2011 NATIONAL RESEARCH COUNCIL RECOMMENDATIONS

Background: On December 23, 2011, The Consolidated Appropriations Act, 2012, was signed into law.[1] The report language included direction to EPA for the Integrated Risk Information System (IRIS) Program related to recommendations provided by the National Research Council (NRC) in its review of EPA's draft IRIS assessment of formaldehyde.[2] The report language included the following:

> The Agency shall incorporate, as appropriate, based on chemical-specific data sets and biological effects, the recommendations of Chapter 7 of the National Research Council's Review of the Environmental Protection Agency's Draft IRIS Assessment of Formaldehyde into the IRIS process…For draft assessments released in fiscal year 2012, the Agency shall include documentation describing how the Chapter 7 recommendations of the National Academy of Sciences (NAS) have been implemented or addressed, including an explanation for why certain recommendations were not incorporated.

The NRC's recommendations, provided in Chapter 7 of the review report, offered suggestions to EPA for improving the development of IRIS assessments. Consistent with the direction provided by Congress, documentation of how the recommendations from Chapter 7 of the NRC report have been implemented in this assessment is provided in the tables below. Where necessary, the documentation includes an explanation for why certain recommendations were not incorporated.

The IRIS Program's implementation of the NRC recommendations is following a phased approach that is consistent with the NRC's "Roadmap for Revision" as described in Chapter 7 of the formaldehyde review report. The NRC stated that, "the committee recognizes that the changes suggested would involve a multiyear process and extensive effort by the staff at the National Center for Environmental Assessment and input and review by the EPA Science Advisory Board and others."

The IRIS LAA assessment is in Phase 1 of implementation, which focuses on a subset of the short-term recommendations, such as editing and streamlining documents, increasing transparency and clarity, and using more tables, figures, and appendices to present information

[1]Pub. L. No. 112−74, Consolidated Appropriations Act, 2012.
[2]National Research Council, (2011). Review of the Environmental Protection Agency's Draft IRIS Assessment of Formaldehyde.

and data in assessments. Phase 1 also focuses on assessments near the end of the development process and close to final posting. Chemical assessments in Phase 2 of the implementation will address all of the short-term recommendations from Table J-1. The IRIS Program is implementing all of the recommendations, but recognizes that achieving full and robust implementation of certain recommendations will be an evolving process with input and feedback from the public, stakeholders, and external peer review committees. Chemical assessments in Phase 3 of implementation will incorporate the longer-term recommendations made by the NRC as outlined below in Table J-2, including the development of a standardized approach to describe the strength of evidence for noncancer effects.

In May 2014, the NRC released their report reviewing the IRIS assessment development process. The NRC stated that the changes that EPA has proposed or implemented in the IRIS process represented substantial improvements. As part of this review, the NRC made several recommendations with respect to the systematic review and integration of scientific evidence for chemical hazard and dose-response assessments that will be implemented in future assessments. The NRC also stated that EPA should continue to improve its evidence-integration process incrementally and enhance the transparency of its process. The NRC recommendations will inform the IRIS Program's efforts in this area going forward.

Table J-1. EPA's implementation of the 2011 National Research Council's recommendations in the Libby Amphibole asbestos (LAA) assessment

NRC recommendations that the EPA is implementing in the short term	***Implementation in the LAA assessment***
General recommendations for completing the IRIS formaldehyde assessment that the EPA will adopt for all IRIS assessments (p. 152)	
1. To enhance the clarity of the document, the draft IRIS assessment needs rigorous editing to reduce the volume of text substantially and address redundancies and inconsistencies. Long descriptions of particular studies should be replaced with informative evidence tables. When study details are appropriate, they could be provided in appendices.	**Implemented.** The main body of the LAA assessment has been rigorously edited by disciplinary experts. The longer descriptions of the animal and mechanistic studies are now contained in Appendix D. Overall, the revised assessment contains 29 new tables and seven new figures to improve transparency and increase clarity. In direct response to a recommendation from the external peer review by EPA's Science Advisory Board (SAB), a new appendix has been added to present a systematic literature review of studies related to localized pleural thickening and lung function. This appendix supports the selection of the noncancer critical effect of localized pleural thickening.

Table J-1. EPA's implementation of the 2011 National Research Council's recommendations in the Libby Amphibole asbestos (LAA) assessment

NRC recommendations that the EPA is implementing in the short term	*Implementation in the LAA assessment*
2. Chapter 1 needs to be expanded to describe more fully the methods of the assessment, including a description of search strategies used to identify studies with the exclusion and inclusion criteria articulated and a better description of the outcomes of the searches and clear descriptions of the weight-of-evidence approaches used for the various noncancer outcomes. The committee emphasizes that it is not recommending the addition of long descriptions of the EPA guidelines to the introduction, but rather clear concise statements of criteria used to exclude, include, and advance studies for derivation of the reference concentrations (RfCs) and unit risk estimates.	**Partially Implemented.** Clear and concise statements of criteria used to evaluate and advance studies for the derivation of the RfC are in Section 5.2.1. At the recommendation of the SAB, EPA conducted a systematic literature review of studies related to localized pleural thickening and lung function. A systematic literature search was done covering the time span to December 2013; this search is described in detail in Appendix I. Statements of criteria used to evaluate and advance studies for the literature review of localized pleural thickening and lung functions are in Appendix I.
3. Standardized evidence tables for all health outcomes need to be developed. If there were appropriates tables, long text descriptions of studies could be moved to an appendix or deleted.	**Partially Implemented.** Long text descriptions of laboratory animal and mechanistic studies were moved to an appendix (Appendix D), and the tables were formatted in response to the SAB peer review panel recommendations. Standardized evidence tables of studies related to localized pleural thickening are included in the new Appendix I.
4. All critical studies need to be thoroughly evaluated with standardized approaches that are clearly formulated and based on the type of research: for example, observational epidemiologic or animal bioassays. The findings of the reviews might be presented in tables to ensure transparency.	**Partially Implemented.** All critical studies were thoroughly evaluated in Section 4, with laboratory animal study details presented in Appendix D. The candidate studies for the derivation of the noncancer critical effect were thoroughly reviewed with the evaluation criteria and study findings presented in tables in Section 5.

Table J-1. EPA's implementation of the 2011 National Research Council's recommendations in the Libby Amphibole asbestos (LAA) assessment

NRC recommendations that the EPA is implementing in the short term	***Implementation in the LAA assessment***
5. The rationales for the selection of the studies that are advanced for consideration in calculating the RfCs and unit risks need to be expanded. All candidate RfCs should be evaluated together with the aid of graphic displays that incorporate selected information on attributes relevant to the database.	**Implemented**. Section 5.2.1 is devoted to the selection of the principal study for the derivation of the RfC. This section contains two tables outlining the characteristics of the candidate studies and the rationale for selecting the principal study. As different subcohorts within the principal study were also used to derive candidate RfCs, those findings are presented for comparison in Table 5-11. NIOSH provided data from the largest occupational cohort study of workers exposed to LAA. The NIOSH data set provided information on individuals' exposure data with extended cancer mortality follow-up and these data were used to derive the cancer unit risk. Comparisons of the lung cancer and mesothelioma unit risks from the LAA assessment with alternative derivations from related analyses of the same principal study are shown in Tables 5-54 and 5-55.
6. Strengthened, more integrative and more transparent discussions of weight of evidence are needed. The discussions would benefit from more rigorous and systematic coverage of the various determinants of weight of evidence, such as consistency.	**Partially Implemented.** The weight of evidence discussion in the LAA assessment has been expanded to include a formal mode-of-action analysis (see Section 4.6.2). This analysis includes discussion of the available data supporting the weight of evidence descriptor for cancer, with specific discussion of dose-response concordance, temporal relationship biological plausibility and human relevance. For noncancer, a formal meta-analysis was used for determining the critical effect of localized pleural thickening (critical effect) on lung function measures (Appendix I).
General Guidance for the Overall Process (see p. 164)	
7. Elaborate an overall, documented, and quality-controlled process for IRIS assessments.	**Implemented**. EPA has created discipline-specific workgroups to formalize an internal process to provide additional overall quality control for the development of IRIS assessments. This initiative uses a team approach to making timely, consistent decisions about the development of IRIS assessments across the Program. This team
8. Ensure standardization of review and evaluation approaches among contributors and teams of contributors; for example, include standard approaches for reviews of various types of studies to ensure uniformity.	

Table J-1. EPA's implementation of the 2011 National Research Council's recommendations in the Libby Amphibole asbestos (LAA) assessment

NRC recommendations that the EPA is implementing in the short term	***Implementation in the LAA assessment***
9. Assess disciplinary structure of teams needed to conduct the assessments.	approach has been utilized for the development of the LAA assessment. Additional objectives of the teams are to help ensure that the necessary disciplinary expertise is available for assessment development and review, to provide a forum for addressing peer review recommendations, and to monitor progress in implementing the NRC recommendations.
Evidence Identification: Literature Collection and Collation Phase (see p. 164)	
10. Select outcomes on the basis of available evidence and understanding of mode of action.	**Implemented**. The LAA assessment has detailed discussions of mechanistic studies on the biological response to LAA, including inflammation, genotoxicity and cytotoxicity (see Section 4.4 and Appendix D) and includes a formal mode of action framework analysis for carcinogenicity (see Section 4.6.2).
11. Establish standard protocols for evidence identification.	**Partially Implemented.** To update the LAA assessment in response to the SAB recommendations, a systematic literature search of the critical noncancer health effect (localized pleural thickening) was done covering the time span to December 2013; this search is described in detail in Appendix I. This is being fully implemented by the IRIS program as part of Phase 2.
12. Develop a template for description of the search approach.	This is being fully implemented by the IRIS program as part of Phase 2.
13. Use a database, such as the Health and Environmental Research Online (HERO) database, to capture study information and relevant quantitative data.	**Implemented.** HERO links were incorporated for all citations.
Evidence Evaluation: Hazard Identification and Dose-Response Modeling (see p. 165)	
14. Standardize the presentation of reviewed studies in tabular or graphic form to capture the key dimensions of study characteristics, weight of evidence, and utility as a basis for deriving reference values and unit risks.	**Partially Implemented.** The LAA Assessment includes tables describing the available epidemiological studies of LAA-exposed populations. With respect to the key study, the assessment also presents the characteristics of workers and attributes of exposure in tabular and graphical form.

Table J-1. EPA's implementation of the 2011 National Research Council's recommendations in the Libby Amphibole asbestos (LAA) assessment

NRC recommendations that the EPA is implementing in the short term	***Implementation in the LAA assessment***
15. Develop templates for evidence tables, forest plots, or other displays.	This is being fully implemented by the IRIS program as part of Phase 2.
16. Establish protocols for review of major types of studies, such as epidemiologic and bioassay.	**Partially Implemented.** This assessment was developed using standard protocols for evidence evaluation that are provided in existing EPA guidance.
Selection of Studies for Derivation of Reference Values and Unit Risks (see p. 165)	
17. Establish clear guidelines for study selection. a. Balance strengths and weaknesses. b. Weigh human vs. experimental evidence. c. Determine whether combining estimates among studies is warranted.	**Partially Implemented.** As discussed above, the text has been expanded to include more description of the considerations made in selecting the study that formed the basis for the quantitative cancer risk estimates (see Section 5.2.1). The selection considerations are also summarized in a table (see Table 5-1 and Table 5-2).
Calculation of Reference Values and Unit Risks (see pp. 165−166)	
18. Describe and justify assumptions and models used. This step includes review of dosimetry models and the implications of the models for uncertainty factors; determination of appropriate points of departure (such as benchmark dose, no-observed-adverse-effect level, and lowest observed-adverse-effect level), and assessment of the analyses that underlie the points of departure.	**Implemented**. The LAA assessment has a detailed discussion of model selection for the epidemiological data sets (see Section 5.2.2).
19. Provide explanation of the risk-estimation modeling processes (for example, a statistical or biologic model fit to the data) that are used to develop a unit risk estimate.	**Implemented**. The LAA assessment has a detailed discussion of model selection for the epidemiological data sets (see Section 5.2.2).
20. Provide adequate documentation for conclusions and estimation of reference values and unit risks. As noted by the committee throughout the present report, sufficient support for conclusions in the formaldehyde draft IRIS assessment is often lacking. Given that the development of specific IRIS assessments and their conclusions are of interest to many stakeholders, it is important that they provide sufficient references and supporting documentation for their conclusions. Detailed appendixes, which might be made available only electronically, should be provided, when appropriate.	**Implemented.** The LAA assessment includes documentation of the estimates of the RfC in Section 5.2 and the IUR in Section 5.4.5. This includes clear explanation of the methods used to develop the LAA assessment, and description of the decisions made in developing the hazard identification and dose-response analyses. As recommended, supplementary information and analyses are presented in appendices.

Table J-2. National Research Council (2011) recommendations that the EPA is generally implementing in the long term

NRC recommendations that the EPA is implementing in the long term	Implementation in the LAA Assessment
Weight-of-Evidence Evaluation: Synthesis of Evidence for Hazard Identification (see p. 165) **1.** Review use of existing weight-of-evidence guidelines. **2.** Standardize approach to using weight-of-evidence guidelines. **3.** Conduct agency workshops on approaches to implementing weight-of-evidence guidelines. **4.** Develop uniform language to describe strength of evidence on noncancer effects. **5.** Expand and harmonize the approach for characterizing uncertainty and variability. **6.** To the extent possible, unify consideration of outcomes around common modes of action rather than considering multiple outcomes separately.	**Partially implemented.** As indicated above, Phase 3 of EPA's implementation plan will incorporate the longer-term recommendations made by the NRC (2011). In addition, NRC recently released a report on its review of current methods for weight-of-evidence analyses and EPA will implement revisions to address the recommended approaches for weighing scientific evidence for chemical hazard identification in NRC (2014). In addition, EPA held workshops in August 2013 and October 2014 on issues related to weight-of-evidence to inform future assessments.
Calculation of Reference Values and Unit Risks (see pp. 165−166) **7.** Assess the sensitivity of derived estimates to model assumptions and end points selected. This step should include appropriate tabular and graphic displays to illustrate the range of the estimates and the effect of uncertainty factors on the estimates.	**Implemented.** The LAA assessment presents derivation of multiple alternative RfC estimates for different subcohorts of the principal study, for different health endpoints, and for the application of different uncertainty factors. The LAA assessment also presents multiple derivations of unit risk estimates for different exposure-response models.