



TOXICOLOGICAL REVIEW

OF

LIBBY AMPHIBOLE ASBESTOS

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

August 2011

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

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U.S. Environmental Protection Agency
Washington, DC

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LIST OF ABBREVIATIONS AND ACRONYMS

2-D	two-dimensional
3-D	three-dimensional
AAHAU	Airborne Asbestos Health Assessment Update
AIC	Akaike information criterion
AM	amosite
APC	antigen-presenting cells
ATSDR	Agency for Toxic Substances and Disease Registry
BMC	benchmark concentration
BMCL	lower 95% confidence limit of the benchmark concentration
BMD	benchmark dose
BMDL	lower 95% confidence limit of the benchmark dose
BMI	body mass index
BMR	benchmark response
cc	cubic centimeter
CDF	cumulative distribution frequency
CE	cumulative exposure
CHEEC	cumulative human equivalent exposure for continuous exposure
CI	confidence interval
COPD	chronic obstructive pulmonary disease
COX-2	cyclooxygenase-2
CYP	cytochrome P450
DHE	dehydroergosterol
DIC	deviance information criterion
DLCO	single breath carbon monoxide diffusing capacity
DNA	deoxyribonucleic acid
EC _x	effective concentration
ECSOD	extracellular superoxide dismutase
EDX	energy dispersive x-ray analysis
EPA	U.S. Environmental Protection Agency
EPMA	electron probe microanalysis
FEV1	forced expiratory volume in one second

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LIST OF ABBREVIATIONS AND ACRONYMS (continued)

FVC	forced vital capacity
GSH	glutathione
GST	glutathione S-transferase
HAEC	human airway epithelial cells
HKNM	human pleural mesothelial cells
HO	heme oxygenase
HPRT	hypoxanthine-guanine phosphoribosyltransferase
HRCT	high resolution computed tomography
HTE	hamster tracheal epithelial
IARC	International Agency for the Research on Cancer
ICD	International Classification of Diseases
ICRP	International Commission Radiological Protection
IFN	interferon
IH	industrial hygiene
IL	interleukin
ILO	International Labour Organization
IRIS	Integrated Risk Information System
IUR	inhalation unit risk
JEM	job exposure matrix
LAA	Libby Amphibole asbestos
LEC _x	lowest effective concentration
LDH	lactate dehydrogenase
MCMC	Markov chain Monte Carlo
MESA	Mining Enforcement and Safety Administration
MIP-2	macrophage inflammatory protein-2
MnSOD	manganese superoxide dismutase
MOA	mode of action
mppcf	million particles per cubic foot
MPPD	multipath particle dosimetry
MSHA	Mine Safety and Health Administration
NAT2	N-acetyl-transferase 2
NCHS	National Center for Health Statistics
NDI	National Death Index

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LIST OF ABBREVIATIONS AND ACRONYMS (continued)

Nf2	neurofibromatosis 2
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NMRD	non-malignant respiratory disease
NRC	National Research Council
NTP	National Toxicology Program
NVSR	National Vital Statistics Report
Ogg1	8-oxoguanine-DNA-glycosylase 1
OSHA	Occupational Safety and Health Administration
PARP	poly(ADP-ribose)polymerase
PBS	phosphate buffered saline
PCM	phase contrast microscopy
PCMe	phase contrast microscopy equivalent
PHS	Public Health Service
PM _{2.5}	particulate matter 2.5 µm diameter or less
POD	point of departure
RfC	reference concentration
RfD	reference dose
RNA	ribonucleic acid
ROS	reactive oxygen species
RPM	rat pleural mesothelial
RR	relative risk
RT-PCR	reverse transcription polymerase chain reaction
RTW	residence time-weighted
SE	Standard Error
SEER	Surveillance, Epidemiology, and End Results
SEM	scanning electron microscopy
SH	spontaneously hypertensive
SHE	Syrian hamster embryo
SHHF	spontaneously hypertensive-heart failure
SIR	standardized incidence ratio
SMR	standardized mortality ratio

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LIST OF ABBREVIATIONS AND ACRONYMS (continued)

SOD	superoxide dismutase
SPF	specific-pathogen-free
SRR	standardized rate ratio
SSA/Ro52	autoantibody marker for apoptosis
STEM	scanning transmission electron microscopy
SV40	simian virus 40
TEM	transmission electron microscopy
TLC	total lung capacity
TSFE	time since first exposure
TWA	time-weighted average
UCL	upper confidence limit
UF	uncertainty factor
USGS	United States Geological Survey
VAI	vermiculite attic insulation
WHO	World Health Organization
WKY	Wistar-Kyoto rat
XRCC1	X-ray repair cross complementing protein 1
XRD	X-ray diffraction

FOREWORD

The purpose of this Toxicological Review is to provide scientific support and rationale for the hazard and dose-response assessment in IRIS pertaining to chronic inhalation exposure to Libby Amphibole asbestos, a unique mixture of asbestos fibers originating from the vermiculite mine near Libby, MT. It is not intended to be 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.

For other general information about this assessment or other questions relating to IRIS, the reader is referred to EPA's IRIS Hotline at (202) 566-1676 (phone), (202) 566-1749 (fax), or hotline.iris@epa.gov (e-mail 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,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 and other exposure durations, and a carcinogenicity assessment. This assessment reviews the potential hazards, both cancer and noncancer health effects, from exposure to Libby Amphibole asbestos and provides quantitative information for use in risk assessments: an RfC for noncancer and an inhalation unit risk addressing cancer risk. Libby Amphibole asbestos-specific data are not available to support RfD or cancer slope factor derivations for oral exposures.

An RfC is typically defined as “an estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime.” In the case of Libby Amphibole asbestos, 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 Libby Amphibole asbestos 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 Libby Amphibole asbestos. In this assessment, the estimates of hazard are derived from modeling cumulative exposures from human data, and thus for exposures of less than a lifetime the risk assessor should calculate a lifetime average concentration to compare to the RfC.

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 $\mu\text{g}/\text{m}^3$ air breathed for 70 years. For Libby Amphibole asbestos, the RfC is expressed as a Lifetime Daily Exposure in

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.

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1 fibers/cc (in units of the fibers as measured by PCM), and the IUR is expressed as cancer risk per
2 fibers/cc (in units of the fibers as measured by PCM).

3 Development of these hazard identification and exposure-response assessments for Libby
4 Amphibole asbestos has followed the general guidelines for risk assessment as set forth by the
5 National Research Council (1983). U.S. Environmental Protection Agency (EPA) Guidelines
6 and Risk Assessment Forum technical panel reports that may have been used in the development
7 of this assessment include the following: *Guidelines for the Health Risk Assessment of Chemical*
8 *Mixtures* (U.S. EPA, 1986a), *Guidelines for Mutagenicity Risk Assessment* (U.S. EPA, 1986b),
9 *Recommendations for and Documentation of Biological Values for Use in Risk Assessment*
10 (U.S. EPA, 1988), *Guidelines for Developmental Toxicity Risk Assessment* (U.S. EPA, 1991),
11 *Interim Policy for Particle Size and Limit Concentration Issues in Inhalation Toxicity* (U.S. EPA,
12 1994a), *Methods for Derivation of Inhalation Reference Concentrations and Application of*
13 *Inhalation Dosimetry* (U.S. EPA, 1994b), *Use of the Benchmark Dose Approach in Health Risk*
14 *Assessment* (U.S. EPA, 1995), *Guidelines for Reproductive Toxicity Risk Assessment* (U.S. EPA,
15 1996), *Guidelines for Neurotoxicity Risk Assessment* (U.S. EPA, 1998), *Science Policy Council*
16 *Handbook: Risk Characterization* (U.S. EPA, 2000a), *Benchmark Dose Technical Guidance*
17 *Document* (U.S. EPA, 2000b), *Supplementary Guidance for Conducting Health Risk Assessment*
18 *of Chemical Mixtures* (U.S. EPA, 2000c), *A Review of the Reference Dose and Reference*
19 *Concentration Processes* (U.S. EPA, 2002), *Guidelines for Carcinogen Risk Assessment*
20 (U.S. EPA, 2005a), *Supplemental Guidance for Assessing Susceptibility from Early-Life*
21 *Exposure to Carcinogens* (U.S. EPA, 2005b), *Science Policy Council Handbook: Peer Review*
22 (U.S. EPA, 2006a), and *A Framework for Assessing Health Risks of Environmental Exposures to*
23 *Children* (U.S. EPA, 2006b).

24 The literature search strategy employed for this assessment is based on EPA's National
25 Center for Environmental Assessment's Health and Environmental Research Outline database
26 tool (which includes PubMed, MEDLINE, Web of Science, JSTOR, and other literature
27 sources). The key search terms included the following: Libby Amphibole, tremolite, asbestos,
28 richterite, winchite, amphibole, and Libby, MT. The relevant literature was reviewed through
29 July 2011. Any pertinent scientific information submitted by the public to the IRIS Submission
30 Desk was also considered in the development of this document.

31 32 **1.1. RELATED ASSESSMENTS**

33 **1.1.1. IRIS Assessment for Asbestos (U.S. EPA, 1988)**

34 The IRIS assessment for asbestos was posted online in IRIS in 1988 and includes an IUR
35 of 0.23 excess cancers per 1 fiber/cc (U.S. EPA, 1988; this unit risk is given in units of the fibers

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1 as measured by PCM). The IRIS IUR for general asbestos is derived by estimation of excess
 2 cancers for a continuous lifetime exposure and is based on the central tendency—not the upper
 3 bound—of the risk estimates (U.S. EPA, 1988) and is applicable to exposures across a range of
 4 exposure environments and types of asbestos (CAS Number 1332-21-4). Although other cancers
 5 have been associated with asbestos (e.g., laryngeal, stomach, ovarian) (Straif et al., 2009), the
 6 IRIS IUR for asbestos accounts for only lung cancer and mesothelioma. Additionally, pleural
 7 and pulmonary effects from asbestos exposure (e.g., localized pleural thickening, asbestosis, and
 8 reduced lung function) are well documented, though, currently, there is no RfC for these
 9 noncancer health effects.

10 The derivation of the unit risk for general asbestos is based on the *Airborne Asbestos*
 11 *Health Assessment Update* (AAHAU) (U.S. EPA, 1986a). The AAHAU provides various cancer
 12 potency factors and mathematical models of lung cancer and mesothelioma mortality based on
 13 synthesis of data from occupational studies and presents estimates of lifetime cancer risk for
 14 continuous environmental exposures (0.0001 fiber/cc and 0.01 fiber/cc) (U.S. EPA, 1986a, see
 15 Table 6-3). For both lung cancer and mesothelioma, life-table analysis was used to generate risk
 16 estimates based on the number of years of exposure and the age at onset of exposure. Although
 17 various exposure scenarios were presented, the unit risk is based on a lifetime continuous
 18 exposure from birth. The final asbestos IUR is 0.23 excess cancer per 1 fiber/cc continuous
 19 exposure² and was established by the EPA Carcinogen Risk Assessment Verification Endeavor
 20 workgroup and posted on the IRIS database in 1988 (see Table 1-1) (U.S. EPA, 1988).

21
 22
 23 **Table 1-1. Derivation of the current IRIS inhalation unit risk for asbestos**
 24 **from the lifetime risk tables in the AAHAU**
 25

Gender	Excess deaths per 100,000 ^a			Risk	Unit risk
	Mesothelioma	Lung cancer	Total		
Female	183	35	218.5	2.18 × 10	
Male	129	114	242.2	2.42 × 10	
All	156	74	230.3	2.30 × 10	0.23

26
 27 ^aData are for exposure at 0.01 fibers/cc for a lifetime.
 28 AAHAU = Airborne Asbestos Health Assessment Update.
 29 Source: U.S. EPA (1988).

² An IUR of 0.23 can be interpreted as a 23% increase in lifetime risk of dying from mesothelioma or lung cancer with each 1 fiber/cc increase in continuous lifetime exposure.

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1 **1.1.2. EPA Health Assessment for Vermiculite (1991)**

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

11
12 **1.2. LIBBY AMPHIBOLE ASBESTOS-SPECIFIC HUMAN HEALTH ASSESSMENT**

13 Libby Amphibole asbestos is a complex mixture of amphibole fibers—both
14 mineralogically and morphologically (see Section 2.2). The mixture primarily includes
15 tremolite, winchite, and richterite fibers with trace amounts of magnesioriebeckite, edenite, and
16 magnesio-arfvedsonite. These fibers exhibit a complete range of morphologies from prismatic
17 crystals to asbestiform fibers (Meeker et al., 2003). Epidemiologic studies of workers exposed to
18 Libby Amphibole asbestos fibers indicate increased lung cancer and mesothelioma, as well as
19 asbestosis, and other nonmalignant respiratory diseases (Lockey et al., 1984; McDonald et al.,
20 1986a,b, 2004; Amandus and Wheeler, 1987; Amandus et al., 1987a,b; Peipins et al., 2003;
21 Sullivan, 2007; Rohs et al., 2008; Larson et al., 2010a,b; Moolgavkar et al., 2010).

22 The IRIS database has an IUR³ for asbestos based on a synthesis of 14 epidemiologic
23 studies that included occupational exposure to chrysotile, amosite, or mixed mineral exposures
24 (chrysotile, amosite, crocidolite) (U.S. EPA, 1988, 1986a). There is some uncertainty in
25 applying the resulting IUR for asbestos to exposure environments and minerals different from
26 those analyzed in the AAHAU (U.S. EPA, 1986a). There is currently no RfC, RfD, or oral slope
27 factor derived for asbestos on the IRIS database.

³For purposes of this document, termed “IRIS IUR”.

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1 2. LIBBY AMPHIBOLE ASBESTOS: GEOLOGY, USE, AND EXPOSURE POTENTIAL

2 2.1. HISTORICAL BACKGROUND

3 The term Libby Amphibole asbestos¹ refers to various mineral forms of amphibole
4 asbestos found in the rocks and ore of Zonolite Mountain, 6 miles northeast of Libby, MT (see
5 Figure 2-1). Zonolite Mountain contains a large vermiculite deposit that has been mined since
6 the early 1920s for various commercial uses. Vermiculite miners, mill workers, and those
7 working in the processing plants were exposed to these amphibole fibers, which remain within
8 the vermiculite ore and product. As amphibole asbestos is present in the geological deposit from
9 which the vermiculite ore was being mined, workers were exposed to asbestos fibers during
10 various activities such as extracting ore from the mine, transporting ore and waste rock, milling
11 operations, and shipping the final product (Meeker et al., 2003; Amandus et al., 1987a;
12 McDonald et al., 1986a). Mortality and morbidity studies on the mine and mill workers from
13 Libby have reported adverse health effects in these workers including lung cancer,
14 mesothelioma, nonmalignant respiratory disease (NMRD; e.g., asbestosis), and pleural
15 abnormalities (McDonald et al., 1986a, b, 2004; Amandus and Wheeler, 1987; Amandus et al.,
16 1987a; Sullivan, 2007; Larson et al., 2010; Moolgavkar et al., 2010). Pleural abnormalities and
17 signs of interstitial fibrosis have also been reported in workers exfoliating and processing
18 expanded Libby vermiculite in other facilities (Lockey et al., 1984; Rohs et al., 2008).

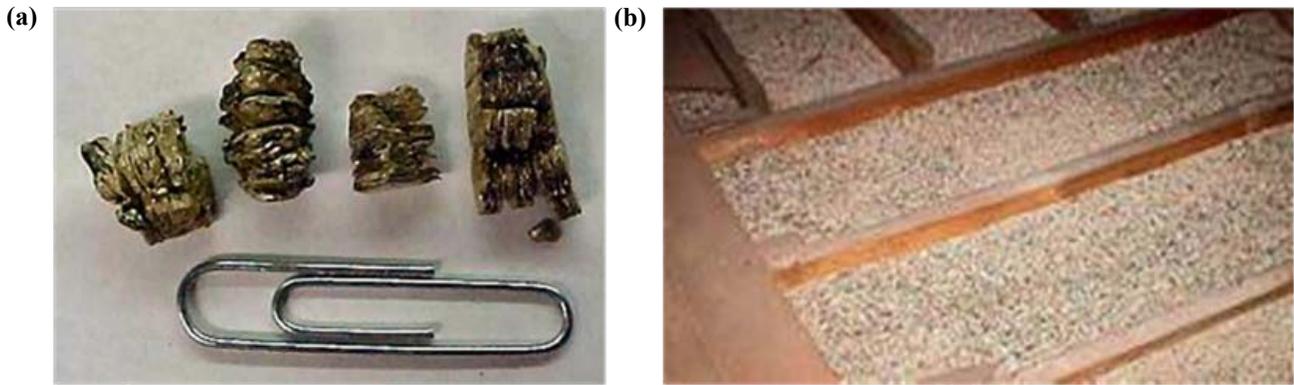
19 The primary commercial product from
20 the Zonolite mining operation was vermiculite
21 concentrate, which is produced by screening
22 and grading the ore to enrich for the raw
23 vermiculite mineral. The unexpanded mineral
24 exhibits a sheetlike structure that is seen in
25 related minerals (e.g., mica) (see Figure 2-2).
26 When heated to approximately 150°C, the
27 vermiculite mineral expands like popcorn into
28 a light porous material. This process of
29 expanding the mineral ore is termed
30 “exfoliation” or “popping” and occurs when
31 the silicate sheets within the ore are rapidly



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

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.

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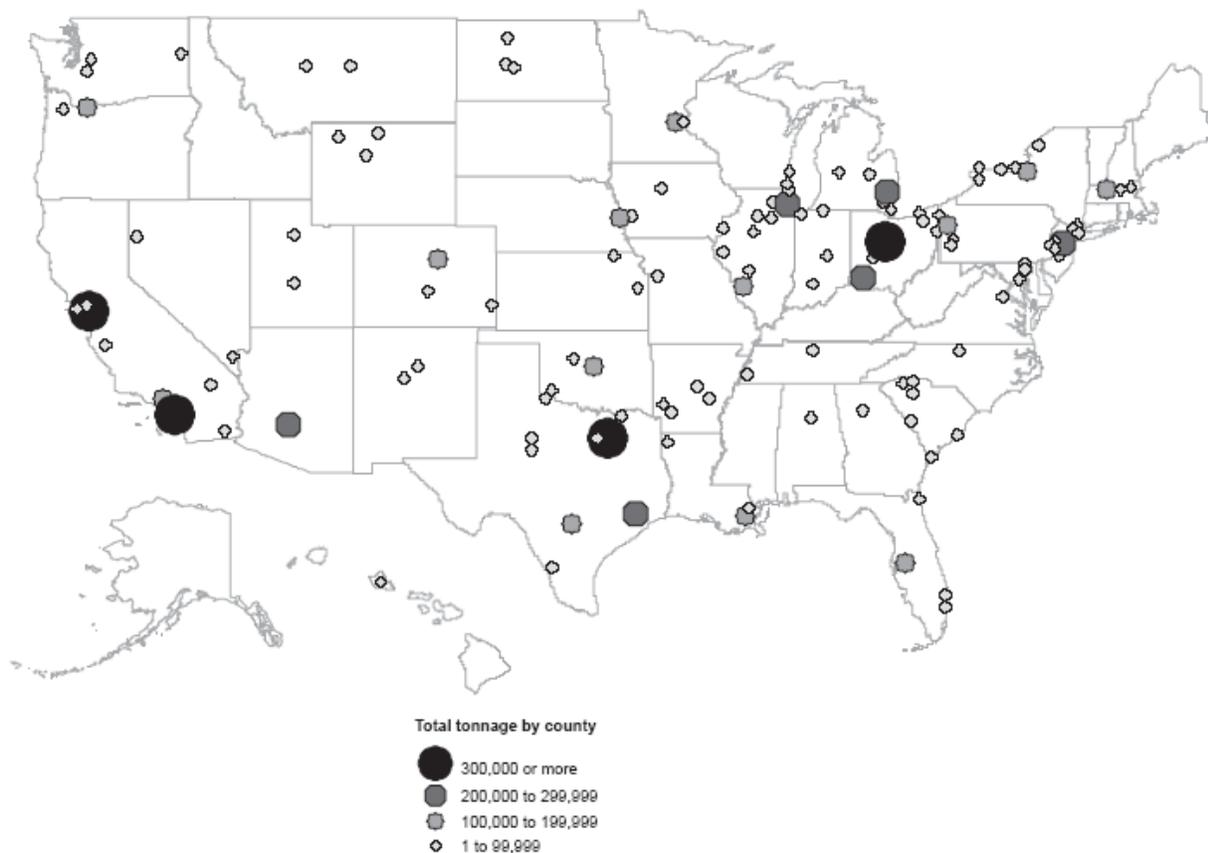
1
2 **Figure 2-2. Expanded vermiculite (a) and vermiculite attic insulation (b)**
3 **(VAI) shown in place between ceiling joists.**
4

5 dehydrated by applying high heat. Libby Amphibole asbestos fibers were released during the
6 energetic and other kinetic processing of the ore and vermiculite concentrate, potentially
7 exposing workers.

8 A portion of the vermiculite concentrate was exfoliated in Libby, MT and either used
9 locally or packaged and shipped for use elsewhere. However, most of the vermiculite
10 concentrate was transported across the country and elsewhere to expansion plants where it was
11 exfoliated and distributed. The Agency for Toxic Substances and Disease Registry (ATSDR,
12 2008) has surveyed 28 of these facilities, identifying potential community exposures both to
13 amphibole asbestos fibers from the vermiculite concentrate before exfoliation, during exfoliation,
14 and during processing and in waste rock from the processing plants (Section 4.1.4 and
15 Figure 2-3). Vermiculite from the Libby, MT mine was used commercially from the 1920s to
16 1990, and a review of company records from 1964–1990 indicates that approximately
17 6,109,000 tons of vermiculite concentrate was shipped to over 200 facilities (ATSDR, 2008).
18 Expanded vermiculite from the Libby, MT site was used in numerous consumer and construction
19 products: including attic insulation, packing material, and soil conditioners, and in the production
20 of gypsum wall board. There is also potential for exposure to Libby Amphibole asbestos in these
21 products (see Section 2.4).
22

23 **2.2. GEOLOGY AND MINERALOGY OF LIBBY AMPHIBOLE ASBESTOS**

24 A large vermiculite deposit is located on Zonolite Mountain, northeast of Libby, MT, within a
25 geologic unit known as the Rainy Creek complex. Geologic processes within the Rainy Creek
26 complex have resulted in the formation of fibrous amphiboles adjacent to igneous intrusions



1
2 **Figure 2-3. Nationwide distribution of Libby ore by county (in tons).** Data
3 on the distribution of ore are based on approximately 80,000 invoices that EPA
4 obtained from W.R. Grace that document shipments of vermiculite ore made from
5 the Libby mine between 1964 to 1990. EPA tabulated this shipping information
6 in a database.

7
8 Source: GAO (2007).
9

10
11 into the complex (veins and dikes of alkaline granite, pegmatite, and quartz) (Boettcher, 1996).
12 The amphibole fibers identified fall within the tremolite-richterite-magnesiorichterite solid
13 solution series (e.g., winchite, richterite, and tremolite) (Meeker et al., 2003). An appropriate
14 understanding of the mineralogy and geology of these materials is helpful in defining the mineral
15 fibers in Libby Amphibole asbestos.

16 Geological terms provide fiber and mineral definitions based on habit of formation and
17 fiber morphology. Conversely, the analytical methods that have been used to count fibers in air
18 samples, in both historical and current exposure environments, define microscopic fibers based
19 on dimensional characteristics and mineralogy (depending on the analytical method). Current

1 analytical methods do not have specific procedures for determining fiber morphology at the
2 microscopic level. Because the human and experimental animal data on adverse health effects of
3 asbestos rely on available analytical methods to document exposure, these definitions are
4 relevant to determining what constitutes a fiber for this health assessment. Therefore, available
5 data on the fiber morphology and fiber-size distribution of Libby Amphibole asbestos are
6 presented in the following sections.

8 **2.2.1. Silicate Minerals**

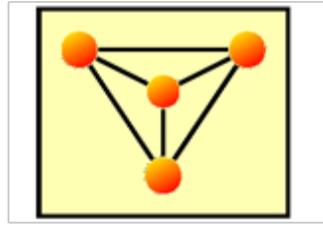
9 Silicate minerals are basically made up of oxygen and silicon, two of the most abundant
10 elements in the Earth's crust. Approximately 25% of known minerals and 40% of the common
11 minerals are silicates. Silicate minerals are hard, infusible, and have very low solubility in strong
12 mineral acids. Specific gravity ranges from fairly light to intermediate, luster is commonly
13 glassy, and most crush to a light powder even when the bulk specimen is black prior to crushing.
14 Silicates chiefly occur as components of rocks, segregations in rocks, or crystals lining cavities
15 in rocks. Most hard silicates are primary minerals (i.e., mineral forms that have not undergone
16 oxidative weathering). Secondary silicates have undergone oxidative weathering and contain
17 water of hydration (Klein and Hurlbut, 1977). Silicate minerals can be defined by chemical
18 structure, crystal structure, trace minerals, and habit of formation.

19 The basic chemical unit of silicate crystalline structure is the $[\text{SiO}_4]^{4-}$ tetrahedron-shaped
20 anionic group. The basic unit consists of four oxygen molecules at the apices of a regular
21 tetrahedron surrounding and coordinated with one silicon ion (Si^{4+}) at the center. The chemistry
22 is such that the oxygen molecules can bond to another silicon ion and, therefore, link one
23 $[\text{SiO}_4]^{4-}$ tetrahedron to another, and then another, and so forth by the process of polymerization.
24 The silicates can form as single tetrahedrons, double tetrahedrons, chains, sheets, rings and
25 framework structures (see Figure 2-4). More complex three-dimensional structures tectosilicates
26 (frameworks) may also form mineral fibers (e.g., erionite).

27 Each subclass of silicates has many mineral members. Specific minerals are defined by
28 the structure, chemistry, and morphology of the mineral. The minerals of interest in this
29 assessment are various forms of amphiboles (double-chain inosilicates) and vermiculite (a
30 phyllosilicate) (see Figure 2-4).

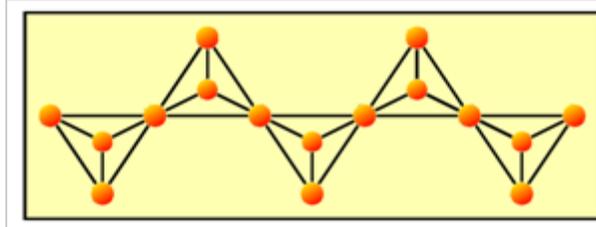
1 **(a) Nesosilicates or single tetrahedron.**

2 The single tetrahedron comprises four oxygen
3 molecules covalently bound to the silicon, at
4 the center of the $[\text{SiO}_4]^{4-}$ -tetrahedron.



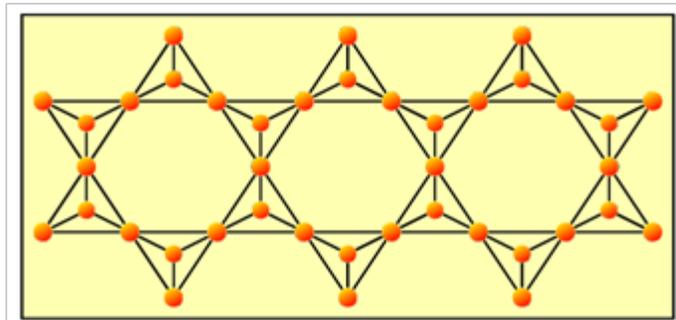
7 **(b) Inosilicates [ino (gr.) = thread] -**

8 **Single-chain silicates.** Chain silicates are
9 realized by linking $[\text{SiO}_4]^{4-}$ -tetrahedrons in a
10 way to form continuous chains. They can be
11 represented by a composition of $[\text{SiO}_3]^{2-}$. A
12 typical example is diopside $\text{CaMg}[\text{Si}_2\text{O}_6]$, in
13 which the “endless” chains are also held
14 together by Ca^{2+} and Mg^{2+} ions.



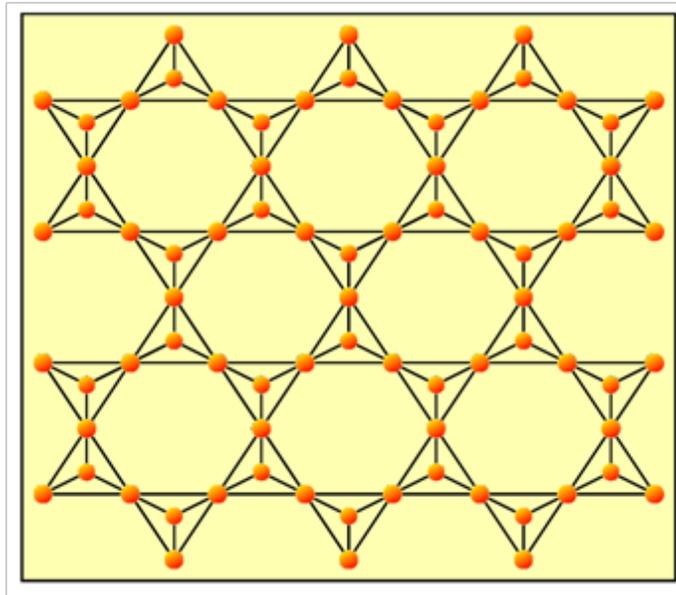
17 **(c) Inosilicates - Double-chain silicates.**

18 Two silicate chains of the inosilicates are
19 linked at the corners, forming double-chains
20 and yielding $[\text{Si}_4\text{O}_{11}]^{6-}$ ions, as realized in
21 the tremolite-ferro-actinolite series
22 $\text{Ca}_2(\text{Mg,Fe})_5\text{Si}_8\text{O}_{22}(\text{OH})_2$. Double-chain
23 silicates are commonly grouped with the
24 single-chain inosilicates.



27 **(d) Phyllosilicates [phyllo (gr.) = sheet] or**

28 **sheet silicates.** These are formed if the
29 double-chain inosilicate $[\text{Si}_4\text{O}_{11}]^{6-}$ chains are
30 linked to form continuous sheets with the
31 chemical formula $[\text{Si}_2\text{O}_5]^{2-}$. Examples of
32 sheet silicates include chrysotile
33 $\text{Mg}_3\text{Si}_2\text{O}_5(\text{OH})$ and vermiculite $[(\text{Mg},$
34 $\text{Fe,A})_3(\text{Al,Si})_2\text{O}_{10}(\text{OH})_2 \bullet 4\text{H}_2\text{O}]$.



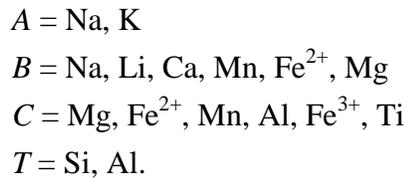
44 **Figure 2-4. Structure of the silicate minerals, illustrating silicate subclasses**
45 **by the linking of the basic silicon tetrahedron (a) into more complex**
46 **structures (b, c, or d).**

1 **2.2.1.1. Mineralogy and Structure of Amphiboles**

2 The mineralogy of amphiboles is important to understanding which mineral forms are
3 present in the Libby vermiculite mine, and, therefore, considered to be Libby Amphibole
4 asbestos. Amphibole minerals are double-chain inosilicates, meaning the chemical building
5 block for amphiboles is connected chains of the silicon tetrahedron (see Figure 2-4c).
6 Amphiboles form when edge-shared octahedra link two of the double-chain [SiO₄]⁴⁻ plates (see
7 Figure 2-4d). The specific cations between the two double-chain plates define the elemental
8 composition of the mineral, while the ratio of these cations in each location is used to classify
9 amphiboles within a solid-solution series. The cation sites are designated as A, B, and C in Eq.
10 2-1, which shows the general chemical formula for double-chain inosilicate amphiboles. The
11 Libby Amphibole asbestos is a complex mixture of mineral forms defined by the cation ratios in
12 each site (further discussed in Section 2.2.3).



17 where:



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

- 26
- 27 • Tremolite subgroup (Ca amphiboles)
 - 28 • Anthophyllite subgroup (Fe-Mg-Li orthoamphiboles)
 - 29 • Richterite subgroup (Ca-Na amphiboles)
 - 30 • Cummingtonite (Fe-Mg-Li clinoamphiboles)

31 A solid solution series includes a continuum of minerals with different cation
32 composition for each site. Solid solution series are defined by their end-members, where mineral
33 terminology can change as the proportion of cations changes within the crystalline structure. For
34 example, a solid solution series for the cation Site A will have one end-member with 100%
35 sodium ions and one end-member with 100% potassium ions. This series would include all
36 intervening ratios. Because each cation site has multiple possibilities, the elemental composition

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1 of the amphibole silicates can be quite complex. It is the complexity of the amphiboles that
2 historically has given rise to a proliferation of mineral names with no systematic basis
3 (Hawthorne, 1981). Currently, amphiboles are identified by a clear classification scheme based
4 on crystal chemistry that uses well-established names based on the basic mineralogy, with
5 prefixes and adjective modifiers indicating the presence of substantial substitutions that are not
6 essential constituents of the end-members (Leake et al., 1997). The mineral classification
7 system does not designate certain amphibole mineral as asbestos. However, some mineral
8 designations have traditionally been considered asbestos (e.g. tremolite, anthophyllite.) Other
9 commercial forms of asbestos were known by trade names (i.e. amosite) rather than
10 mineralogical terminology (i.e. an amphibole mineral in the cummingtonite-grunerite solid
11 solution series).

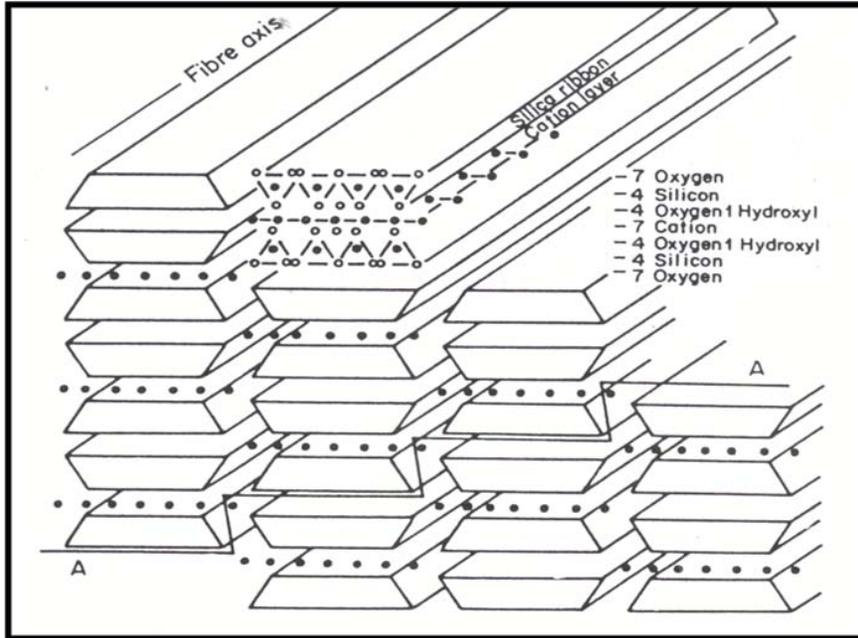
12

13 **2.2.1.2. Amphibole Morphology**

14 Mineral morphology is a function of the structural form of the silicate and the geologic
15 habit of formation, weathering and other mechanical processes. This discussion will focus on
16 morphology with respect to amphibole minerals.

17 The basic crystal structure of amphibole mineral is formed by the binding of a series of
18 double-chain plates (see Figure 2-5). Where the conditions are suitable, these crystals may form
19 as elongated particles. The morphology of the elongated crystal structure is a function of the
20 temperature, pressure, local stress field and solution chemistry conditions during
21 crystallization—*habit of formation*. Thus, morphology at this level is described in terms of the
22 crystal forms which result from different habits of formation. Individual amphibole structures
23 may be described as acicular, prismatic, or a fibrous. A fiber would be an elongated crystal with
24 parallel sides, where acicular crystals are “needlelike” in appearance and prismatic crystals may
25 have several non parallel faces (e.g. varied, faceted faces). Asbestiform morphology is present
26 where the habit of formation allows crystals to form very long individual fibrils and fibers which
27 may become visible to the naked eye (see Figure 2-6). Thus, the amphibole crystalline structure
28 may result in a range of particle morphologies, including fibers. Where conditions are not
29 conducive to the formation of individual fibers and particles, the amphibole is described as
30 massive—appearing as a solid contiguous sample. Mechanical forces that break amphibole
31 crystals along the cleavage plane create smaller pieces or cleavage fragments. These fragments
32 may be elongated, but differ from the crystals described above as at least one face of the
33 structure is the cleavage plane—not the face of a formed crystal.

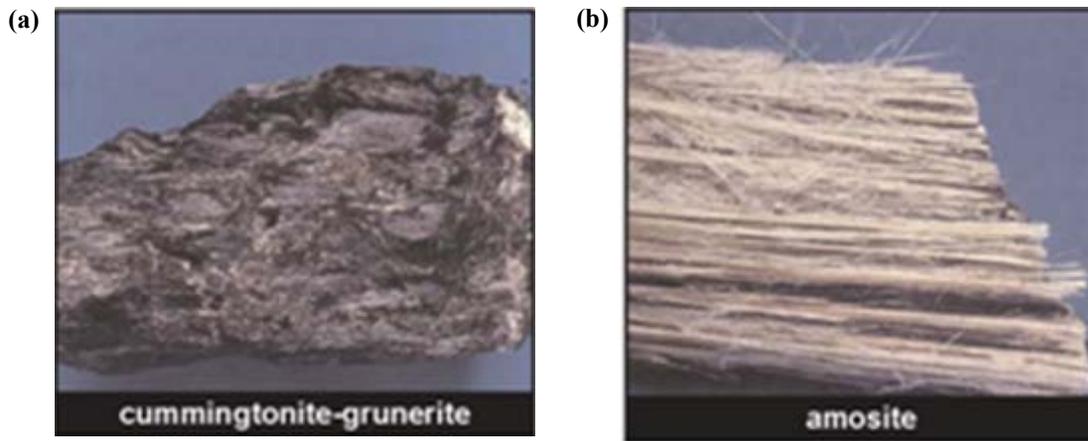
34 With respect to classifying mineral field samples, geologists applied descriptive terms
35 appropriate for viewing samples simply or at low magnification (e.g. field glass). The geologic



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Figure 2-5. Cross-section of amphibole fibers showing the silicon tetrahedrons (Δ) 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: Kirk-Othmer Encyclopedia of Chemical Technology (2010).



14 **Figure 2-6. Comparison of crystalline forms amphibole minerals.**
15 **Panel A** shows a specimen identified as an amphibole mineral in the
16 cummingtonite-grunerite solid solution series, although crystalline in form, the
17 habit of formation did not favor formation of individual particles and fibers, hence
18 its appearance as ‘massive’. **Panel B** shows an amphibole mineral with very
19 similar elemental composition but formed in a habit where very long fibers were
20 allowed to form—hence the asbestiform appearance.
21

22 Source: Adapted from NSSGA (2006).
23

24 terms for fiber morphology for classification of field samples is based on the macroscopic
25 appearance of the crystals and fibers (e.g., acicular “needle-like in form” AGI, 1972). In this
26 framework, asbestos and asbestiform fibers are defined as long, slender, hair-like fibers visible to
27 the naked eye (see Figure 2-6). This is a hallmark of commercially mined asbestos which is
28 sought after for numerous applications because of its high tensile strength, heat resistance and in
29 some cases, can be woven. Although these terms were used to describe fibers in hand samples
30 and identify commercially valuable asbestos they are only applicable at the macroscopic level. It
31 is important to realize that material defined as commercial asbestos, mined, milled, and
32 manufactured into products not only contained these visible fibers, but many smaller fibers and
33 single crystals which were not visible to the naked eye (Dement and Harris, 1979). As further
34 explained in Section 3, only these smaller fibers can enter the lung and transport to the pleura
35 where the health effects of asbestos are best characterized. Therefore, for the purposes of this
36 assessment (i.e., examining the health effects of asbestos fibers), consideration must be given to
37 how these microscopic fibers are defined. For this purpose, terms intended for describing field
38 samples may need to set aside, or redefined when applied at the microscopic level.

1 Currently there are several technologies
2 commonly used to view and identify mineral
3 structures at high magnification using light
4 microscopes or electron microscopy. As standard
5 analytical methods were developed for counting
6 mineral fibers, structures and matrices using these
7 instruments, analytical definitions to describe fibers
8 and structures were developed. Phase contrast
9 microscopy (PCM) was developed to detect fibers in
10 occupational settings and has been widely used to
11 assess worker exposure (see Text Box 2-1). The
12 definition of a PCM-fiber is based purely on its
13 dimensions. The standardization of the PCM
14 method (i.e., NIOSH 7400) and its importance in
15 applying health standards in occupational settings,

**Text Box 2-1. Fibers Viewed by Light
Microscopy**

The collection of fibers on an air filter, and visually counted under a phase contrast microscope (PCM), was first described in 1934 by the Dutch physicist Frits Zernike. The specification of a fiber as $>5\ \mu\text{m}$ in length and length-to-diameter ratio (i.e., aspect ratio) of at least 3:1 resulted from this method. As a light microscope technique, the PCM method cannot distinguish mineral fibers from other fibers.

The U.S. Public Health Service developed and tested a standard air sampling method based on PCM detection (i.e., National Institute for Occupational Safety and Health [NIOSH] Method # 7400). The NIOSH method specifies the analyst count fibers $>5\ \mu\text{m}$ in length with an aspect ratio of at least 3:1. Results from PCM analysis are reported as fibers per cubic centimeter of air (fibers/cc.)

16 results the common usage of the term ‘fiber’ to refer to those objects counted in the PCM
17 analytical method (NIOSH, 1994). However, this method cannot define the material or
18 morphology of the viewed fiber. Thus PCM-fibers may be any material, and if they are mineral
19 fibers may be any fiber morphology. If the nature of the fiber needs to be defined, NIOSH
20 Method 7402 employs electron microscopy to determine if the fibers viewed by PCM are
21 mineral fibers, and can establish the mineral composition (NIOSH, 1994a). This method does
22 not recount the fibers, but, rather, it identifies what proportion of the fibers are mineral fibers,
23 with an elemental composition consistent with asbestos, which is then used to adjust the
24 PCM-fiber count. Although the PCM-fiber definition was not based on either mineralogy or an
25 understanding of which fibers might be biologically relevant, this definition has become the basis
26 of existing health standards (e.g., U.S. EPA, 1988; OSHA, 1971[ID-160]; and MSHA, 1978).

27 Electron microscopy can view objects at much higher magnification and can be coupled
28 with other techniques which can identify the mineralogy (see Text Box 2-2). X-ray diffraction
29 (XRD) may be used with the above techniques to differentiate crystalline structure of minerals in
30 solid materials and provides information on the availability of the total mineral present. Thus,
31 XRD can determine the mineral composition of the material analyzed, identifying its solid
32 solution series and classifying the mineral per standardized nomenclature for amphibole minerals
33 (see Section 2.1.1.1).

1 With the advent of the use of electron
2 microscopy to identify mineral particles, there
3 has been an attempt to resolve the traditional
4 dimensional fiber definition(s), by describing
5 the particles examined by electron microscopy
6 and X-ray diffraction in terms that are both
7 geologically and mineralogically relevant.
8 Structures viewed by electron microscopy may
9 be described as having parallel sides, and
10 considered ‘fibers’. Where long, thin, curving
11 fibers are viewed they may be described as
12 ‘asbestiform’. Structures with nonparallel sides
13 can be considered acicular or prismatic,
14 depending on their proportions. Thus, the
15 descriptive terms used by geologists have
16 migrated into the analytical field. However, the
17 habit of formation of a single structure viewed
18 by electron microscopy cannot be determined,
19 and, while descriptive, these terms may not
20 correlate to the geologic and commercial
21 definitions of these terms. Therefore, the use of
22 these definitions to describe individual particles viewed by TEM can be problematic (Meeker et
23 al., 2003). Important characteristics such as crystal structure and surface chemistry cannot be
24 adequately categorized solely with visually determined definitions developed for the
25 classification of field samples.

26 The definition of ‘fiber’ and the appropriate application of other morphological terms is
27 an area of ongoing debate. From a public health and regulatory perspective, a PCM-fiber is the
28 fiber of interest (where confirmed as a mineral fiber with an elemental composition consistent
29 with asbestos). There is no requirement for a PCM-fiber to be asbestiform, and, in fact, the
30 method explicitly includes fibers with fairly low aspect ratios (i.e., as low as 3:1). Electron
31 microscopy identified a much broader range of fibers (having much greater resolution) and can
32 provide more specific identification of both mineralogy and the form of the structure.
33

**Text Box 2-2. Minerals Viewed by Electron
Microscopy**

Electron microscopy employs electrons—rather than light—to visualize the specimen. Furthermore, instead of using glass lenses to focus the light wavelengths, electromagnetic lenses are used to focus electrons on the sample. The analytical techniques included in electron microscopy for asbestos testing are TEM, scanning electron microscopy (SEM), and scanning transmission electron microscopy (STEM). TEM produces two-dimensional (2-D) images that generally use a magnification factor of about 500 to 500,000×. SEM produces three-dimensional (3-D) images that generally result in about 10 to 300,000× magnification. STEM can produce both 2-D and 3-D images that generally result in about 10 to 500,000× magnification.

The ISO 10312 method for analyzing air filters, enumerates structures much smaller than the PCM fibers with a minimum length requirement of 0.5 μm. Additionally, structures with an aspect ratio of at least 5:1 are considered fibers, rather than 3:1, as with PCM analysis. The ISO 10312 method also defines other structures (fiber bundles, clusters, and matrices) that are included in the structure count. Therefore, the term “structure” rather than “fiber” is used when presenting air sampling results from the ISO 10312 method where structures per cc of air (s/cc) are reported.

1 **2.2.2. Vermiculite**

2 Vermiculite is the mineralogical name given to hydrated laminar
3 magnesium-aluminum-ironsilicate, which resembles mica in appearance [see Figure 2-7; (Mg,
4 Fe,A)₃(Al,Si)₂O₁₀(OH)₂ •4H₂O] (AGI, 1972). Vermiculite is in the clay mineral group of the
5 phyllosilicates, which also includes kaolinite and montmorillonite. Mica, talc, and serpentine
6 (e.g., chrysotile asbestos) minerals are other well-known sheet silicates. These sheet-like
7 structures are produced by rings of tetrahedrons that are linked to other rings by shared oxygen
8 ions in a two-dimensional plane (see Figure 2-4d). The silicate sheet can extend broadly, and the
9 layered appearance of the mineral reflects this sheet-like structure. The symmetry of these
10 minerals is controlled primarily by the symmetry of the rings, which is usually altered to a lower
11 symmetry by other ions and other layers. Typically, crystals of this subclass are flat, platy, and
12 book-like, as in the mica group, and the sheets are then connected to each other by layers of
13 cations. These cation layers are weakly bonded and often have water molecules and other
14 neutral atoms or molecules trapped between the sheets. When subjected to heat, vermiculite has
15 the unusual property of exfoliating or expanding into “worm-like” pieces. The term vermiculite
16 is derived from the Latin *vermiculare*, which means to breed worms (The Vermiculite
17 Association, <http://www.vermiculite.org>). Vermiculite exfoliation occurs at approximately
18 150°C, producing a lightweight and highly absorbent material (AGI, 1972). Additional
19 properties of vermiculite are listed in Table 2-1. Vermiculite ore is shown in Figure 2-7.

20 Vermiculite is mined across the world, including the United States (Virginia, South
21 Carolina, and Montana); South Africa; Uganda; China; Brazil; Russia; India; and Australia
22 (British Geological Survey, 2005). The specific mineralogy and geologic formation habit of
23 vermiculite deposits vary, and although amphibole minerals are consistent with the ultramafic
24 rock formations (composed chiefly of ferromagnesian igneous rock) that bear vermiculite, not all
25 vermiculite deposits contain amphibole asbestos.

27 **2.2.3. The Mineralogy of Libby Amphibole Asbestos**

28 **2.2.3.1. Mineralogy**

29 The amphibole mineral fibers within the vermiculite ore and product have historically
30 been reported as a sodium-rich tremolite (Larsen, 1942; Boettcher, 1966; Leake, 1978, Amandis
31 et al., 1987a, McDonald 1986a). More recently, various research groups have characterized the
32 more specific mineralogical composition of amphiboles from the Rainy Creek deposit near
33 Libby, MT (Gunter and Sanchez, 2009; Sanchez et al., 2008; Meeker et al., 2003; Wylie and
34 Verkouteren, 2000; Ross, 1993; and Moatamed et al., 1986).



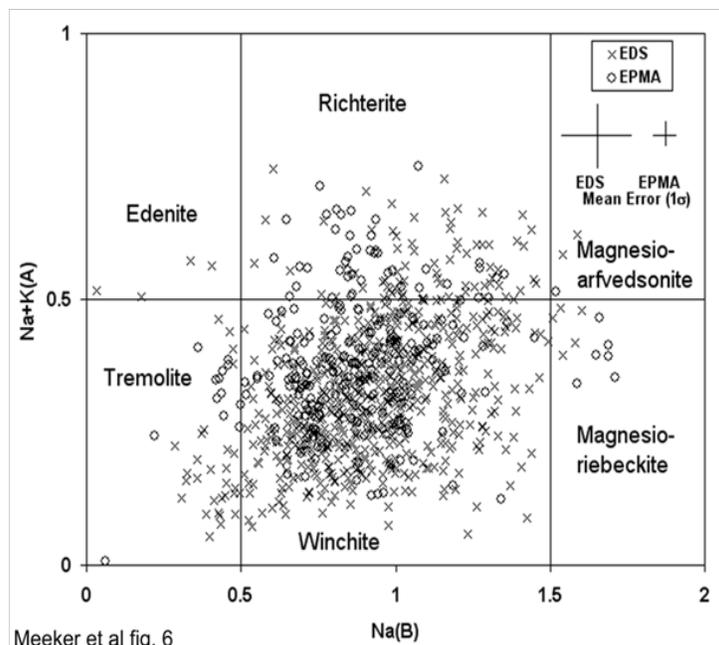
Figure 2-7. Vermiculite ore sample. Brinton's Quarry, near West Chester, Chester County, Pennsylvania, USA.

Source: Micaceous vermiculite book (<http://www.excaliburmineral.com/cdintro.htm>)
 ©Jeff Weissman/Photographic Guide to Mineral Species.

Table 2-1. Properties of vermiculite

Mineral class/subclass	Mineral silicates/phylosilicate
Chemical formula	$(\text{Mg, Fe, A})_3(\text{Al, Si})_2\text{O}_{10}(\text{OH})_2 \bullet 4\text{H}_2\text{O}$
Crystal habit of formation	Clay, scaly, aggregate
Hardness (Mohs scale)	2-3
Cleavage	Perfect
Specific gravity	2.4-2.7

EPA requested that the U.S. Geological Survey (USGS) design and conduct a study to identify the amphibole minerals in the Libby vermiculite mine. Accordingly, USGS personnel collected samples from different areas of the mine in an attempt to identify the range of materials present both geographically, as well as collecting material which represented different habits of formation (Meeker et al., 2003). Figure 2-8 shows data from 30 samples across the mine. The mineral composition of each structure determines its mineral identity (Leake et al., 1997). Here, the U.S. Geological Survey (USGS) used two different techniques to identify the mineral composition of each structure (energy dispersive X-ray analysis [EDS] and electron probe



1
2 **Figure 2-8. Mineralogy of Libby Amphibole asbestos structures from**
3 **samples taken from the Zonolite Mountain site.** An evaluation of the textural
4 characteristics shows the material to include a complete range of morphologies
5 from prismatic crystals to fibers. Each data point represents the cation
6 composition (number of occupied sites) for a single fiber. The X-axis shows the
7 number of sites occupied by Na, and the Y-axis shows the number of sites
8 occupied by Na or K. The data shown are a composite of the analysis fibers taken
9 from 30 different field samples from various locations within the mine.

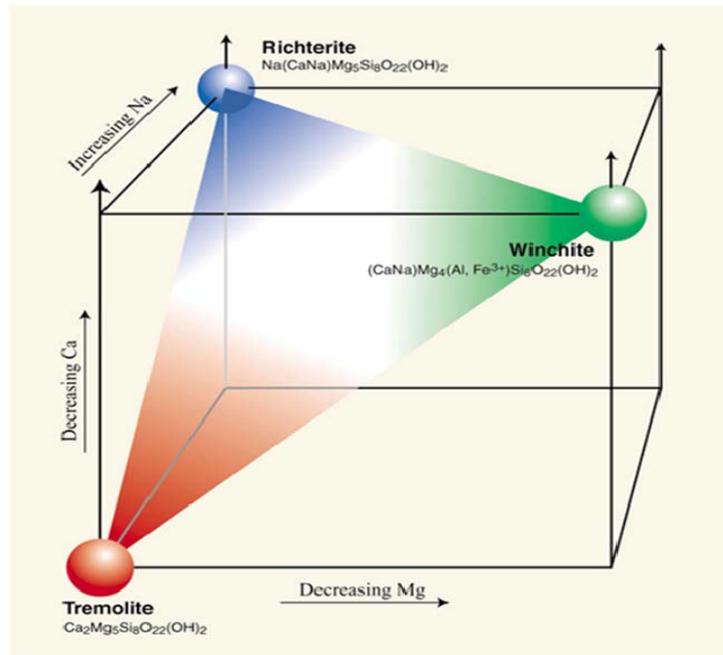
10
11 Notes: EDS is energy dispersive X-ray analysis; EPMA is electron probe microanalysis.
12 Source: Meeker et al. (2003).
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15 microanalysis [EPMA]). Similar mineral composition was determined by the two methods (see
16 Figure 2-8). Most amphibole structures are classified as winchite (84%), with lesser amounts
17 classified as richterite (11%) and tremolite (6%), based on the current mineralogical
18 nomenclature by Leake, (1997) (Meeker et al., 2003). There are also trace amounts of
19 magnesioriebeckite, edenite, and magnesio-arfvedsonite present in Libby Amphibole asbestos
20 (Meeker et al., 2003). All of these minerals are within the mineral solid solution series for
21 tremolite-richterite- magnesioriebeckite. All of the amphiboles found at the mine site, with the
22 possible exception of magnesioriebeckite, can occur in fibrous habit. It was observed these
23 amphibole materials—even when originally present as massive material—can produce abundant,
24 extremely fine fibers by gentle abrasion or crushing (Meeker et al, 2003).
25

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1 Figure 2-9 shows the compositional variations between the predominate minerals found
2 in the Libby Amphibole asbestos (winchite, richterite, and tremolite). Although each structure
3 has as discrete mineral composition, when viewed as a population, fall within solid solution
4 series shown in Figure 2-8. For example, tremolite is one end-member of the solid solution
5 series. As calcium decreases and sodium increases, the fibers transition to richterite. Similarly,
6 as fibers have decreased magnesium and calcium with respect to tremolite, they are defined as
7 winchite. The sodium content that distinguishes these amphiboles has been redefined over time
8 in the International Mineralogical Association's mineral classification system, most recently in
9 1997 (Leake, 1978; Leake et al., 1997). As a result, some amphibole fibers previously defined as
10 tremolite prior to the new classification system are currently considered winchite based on
11 chemical composition (Leake et al., 1997).

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Figure 2-9. Solution series linking tremolite, winchite, and richterite amphibole fibers.

Source: Meeker et al. (2003).

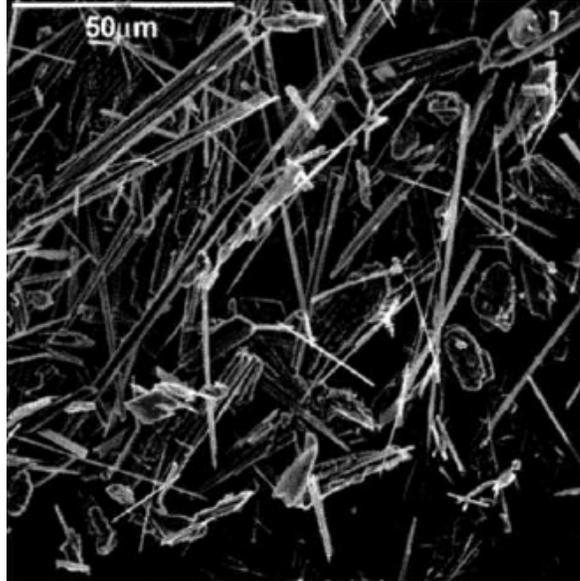
1 The mineral composition of the fibers present is not classifiable to one distinct named
2 mineral category, but, rather, the composition spans several solid-solution series. However,
3 there seems to be a consistency in the range of elemental composition found within this material.
4 Libby Amphibole asbestos is not only made up of the end-members of these solid solution series,
5 but the spectrum of minerals along the solid solution series shown. Although the majority of
6 structures analyzed fell within these solid solution series, traces of other minerals were
7 identified. The term “Libby Amphibole” is used in this document to identify the mixture of
8 amphibole minerals, of varying elemental compositions (e.g., winchite, richterite, and tremolite),
9 which have been identified in the rocks and ore of the vermiculite mine near Libby, MT, and are
10 characteristic of the elongated structures commingled with the vermiculite mined at this location
11 (Meeker et al., 2003) (i.e., present in the ore vermiculite concentrate and processed materials).
12 Libby Amphibole Asbestos refers to those elongated structures of the Libby Amphibole mineral
13 mixture, which have been identified as amphibole fibers or structures, and have been associated
14 with health effects consistent with asbestos exposure (i.e., asbestosis, pleural abnormalities, lung
15 cancer and mesothelioma)(ATSDR, 2008).

16 17 **2.2.3.2. Morphology of the Libby Amphibole Asbestos**

18 Mineral samples taken from the mine include veins of asbestiform amphibole and various
19 fiber morphologies in surrounding rock (Meeker et al., 2003). A sample viewed by scanning
20 electron microscope from the Zonolite Mountain mine illustrates the broad range of size and
21 morphologies for the mineral structures (see Figure 2-10). The USGS has described fibers
22 (including asbestiform), acicular and prismatic structures, and curved fibers all within the
23 minerals from the mine (Meeker et al., 2003). As individual fibrils and fiber bundles are viewed
24 under greater magnification under a transmission electron microscope, the range of fiber
25 morphologies can be more clearly seen (see Figure 2-11).

26 27 **2.2.3.3. Dimensional Characteristics of Libby Amphibole Asbestos**

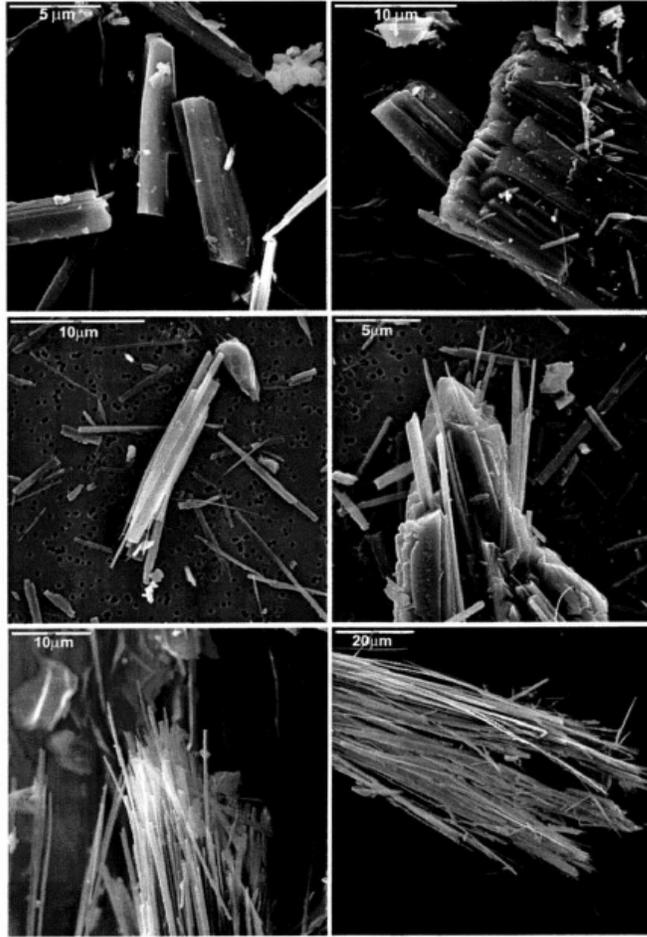
28 Cumulative particle-size-distribution frequencies (CDF) were developed for Libby ore
29 Grade 3, and Libby ore Grade 3 expanded by EPA Region 8 using the procedure described in
30 detail in Appendix C. As shown in Figure 2-12, the particle-size-distribution frequency for the
31 Libby Grade 3 ore, and the Libby Grade 3 ore expanded were similar to the
32 particle-size-distribution frequency in the ambient air monitoring samples in Libby, MT. Data
33 from ambient air monitoring in Libby are presented in Appendix B. The data to construct the
34 plot in Figure 2-11 are described in Appendices B and C. There are slight shifts towards longer
35 and thicker fibers in the ore samples compared to the air samples, with the aspect ratios being



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Figure 2-10. 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).

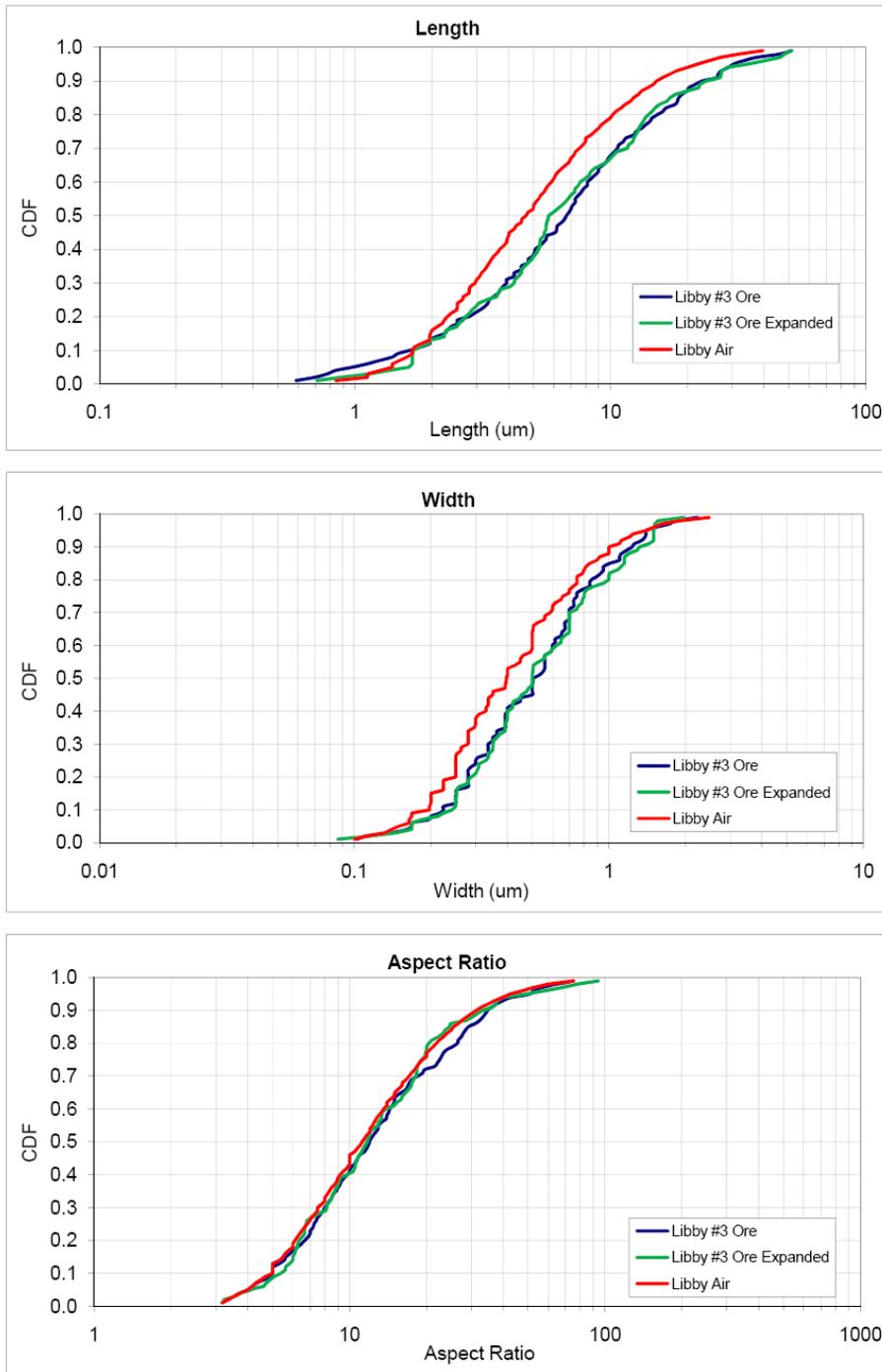


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Figure 2-11. Fiber morphology of amphibole asbestos from the Libby, MT mine viewed under a transmission electron microscope.

Source: Meeker et al. (2003).

Particle Size Distributions of LA Particles - Libby #3 Ore (N = 320),
 Libby #3 Ore Expanded (N = 108)



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Figure 2-12. 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 (2010)

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1 almost identical in the ore and air samples. However, all of these differences are minor, and the
2 majority of these fibers are respirable.

3 Mineralogical characterization of the fibers from the Libby ore Grade 3 and the expanded
4 product using energy dispersive X-ray analysis (EDS) and selected area electron diffraction
5 (SAED) provided further confirmation of the similarity between the fibers from the Libby Grade
6 3 ore and Libby Amphibole asbestos (methodology described in Section 2.3; see also
7 Appendix B). EDS spectra yielded an elemental fingerprint with sodium and potassium peaks
8 that were highly consistent with values reported for the winchite-richierite solution series
9 described for the Libby, MT ores (Meeker et al., 2003).

10 Based on these data, it is reasonable to conclude that the fibers from the Libby Grade 3
11 ore and expanded ore are similar in physical and mineralogical characteristics to the Libby
12 Amphibole asbestos fibers found in air samples from Libby, MT. The O.M. Scott facility in
13 Marysville, OH used Libby Grade 3 ore from about 1959 to 1980 (Moatamed, et. al., 1986;
14 Lockey et.al., 1984). Therefore, the exposure and health effects information from the
15 Marysville, OH facility may be used to derive an RfC that can be applied to the Libby
16 community and other sites that received vermiculite ore from Libby, MT.

17 The Marysville, OH facility also used vermiculate ore from Virginia, South Africa, and
18 South Carolina. The Virginia and South African ores were tested for the presence of fibers as
19 described in Appendix C². As described in Appendix E, the Virginia and South African ores
20 released only a small quantity of amphibole fibers. EPA was unable to obtain an ore sample
21 from South Carolina. However, vermiculite ore from the Enoree mine in South Carolina is
22 known to contain amphibole fibers (see Appendix C; U.S. EPA, 2000d; McDonald et al., 1988).

23 24 **2.3. EXPOSURE POTENTIAL**

25 Although the occurrence of Libby Amphibole asbestos is limited to a relatively small
26 geographic area, the potential for exposure to it has been greatly enhanced by the historical
27 mining, milling, and distribution of vermiculite operations in Libby, MT. Additionally, material
28 was sent to processing plants across the nation where plant workers and community contacts may
29 have been exposed. Lastly, consumer products containing vermiculite mined near Libby contain
30 Libby Amphibole asbestos, and consumers may be exposed to Libby Amphibole asbestos while
31 using the products. For example, asbestos-contaminated vermiculite attic insulation from Libby
32 remains in homes today across North America, where there is the potential for residential
33 exposures. This section summarizes the potential for current exposures to the Libby Amphibole

² Dr. Lockey, University of Cincinnati, obtained samples of the Virginia and South Africa ores from the Marysville, OH facility in 1980 and supplied these ores to the EPA for analysis.

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1 asbestos in vermiculite in the Libby community, other communities potentially impacted by
2 processing plants, and from in-place Libby vermiculite attic insulation. Historical exposures for
3 the workers in Libby, MT, and other facilities are discussed in Section 4.1, where data are
4 available.

5 There are also lifestyle, activity, and lifestage factors, which may influence one's
6 exposure potential to asbestos. For example, children may spend more hours outside and engage
7 in activities that impact exposure level compared to adults (NRC, 1993; U.S. EPA 2006). In
8 general, children inhale more air per unit body weight (U.S. EPA, 2008) and spend more time
9 outdoors than adults (Bateson and Schwartz, 2008; NRC, 1993), which could have resulted in
10 increased inhalation exposure to Libby Amphibole asbestos in children compared with adults. In
11 contrast, some adult activity patterns, such as gardening and home repair, may also result in
12 increased exposures where Libby Amphibole asbestos may be present. Thus for the various
13 environments where people may be exposed to Libby Amphibole asbestos, the potential
14 activities and pathways of exposure are discussed below, and where available, exposure
15 measurements are given for various exposure environments and activities.

16 17 **2.3.1. Libby Community**

18 The Libby community (the towns of Libby, Troy, and surrounding residences) defines the
19 area that may have been directly and indirectly impacted by mining/milling-activities. Many
20 individuals who worked in the mine lived in the surrounding areas. Facilities in the community
21 may have residual contamination from past milling and transport activities. Additionally,
22 expanded vermiculite, waste stoner rock (the waste material from exfoliation), and other
23 materials all potentially containing Libby Amphibole asbestos may have been transported off site
24 to residences and recreational areas. Taken together, there are numerous potential exposure
25 pathways for community residents, both historical and current.

26 During plant operations, individuals may have been exposed to materials inadvertently
27 transported from the workplace to vehicles, homes, and other establishments, typically on the
28 clothing, shoes, and hair of workers. This transport of material may result in "take-home
29 exposure" for the workers, their families, and other coresidents. The magnitude of these
30 exposures was not measured, so the levels to which individuals in the home might have been
31 exposed are not known. Based on studies of other industrial take-home exposures, individuals
32 doing laundry and cleaning house (often women) can be exposed to materials on workers'
33 clothing. Also, children who play on the floor might be more exposed than adults to dust from
34 take-home exposures (Kelly et al., 2006). The community health screening studies from Libby
35 showed that men were more likely to have both occupational and nonoccupational exposures,

1 while women were more likely to have household contact with exposed workers (ATSDR, 2001;
2 Peipins et al., 2003). There could also be gender differences in types of activities (e.g.,
3 household chores such as laundry and cleaning) or in intensity or duration of occupational and
4 recreational activities (Peipins et al., 2003).

5 Expanded vermiculite, as a finished product, was used as a soil amender and for attic
6 insulation. Community members may have been exposed and are possibly still exposed to these
7 consumer products. In a survey of Libby residents conducted by ATSDR in 2000–2001, almost
8 52% reported using vermiculite for gardening, 8.8% used vermiculite around the home, and 51%
9 reported handling vermiculite attic insulation (Peipins et al., 2003). As vermiculite ore, waste
10 stoner rock, and product were present in the community; numerous activities may have resulted
11 in exposure. Individuals also reported exposures from the following activities: participating in
12 recreational activities along Rainy Creek Road, the road leading to the mine (67%); playing at
13 the ball field near the expansion plant (66%); playing in the vermiculite piles (34%); heating the
14 vermiculite to make it expand/pop (38%); or other activities in which there was contact with
15 vermiculite (31%) (Peipins et al., 2003). Memoranda from Christopher Weis (U.S. EPA, 2001a)
16 state that asbestos mineral fibers were detected in outdoor sources (yard soil, garden soil,
17 driveway material, and assorted mine-waste materials) and indoor sources (dust and vermiculite
18 insulation) in Libby (U.S. EPA, 2001a, b).

19 EPA has conducted more recent exposure sampling in the Libby community. Air
20 samples were taken in the community during activities considered appropriate for various
21 potential exposure scenarios. Personal air monitors were placed on the investigator conducting
22 the activity, and a second air sample was taken from a fixed location (area sample). Asbestos
23 fibers were collected on filters and counted by two different laboratory methods: (1) PCM and
24 (2) TEM. Although TEM analysis can count smaller fibers, results are shown here for PCM size
25 fibers used to estimate risk, called PCM equivalent fibers (PCMe)³.

26 EPA continues to conduct air monitoring in the Libby community to support clean-up
27 and risk assessment activities. Ambient air monitoring conducted in 2006/2007 at 18 locations
28 across the area indicated that low levels of asbestos fibers are occasionally detected in the air,
29 even with no localized disturbance of asbestos-contaminated material (U.S. EPA, 2009b). Fibers
30 were counted by TEM, and structures⁴ $\geq 0.5 \mu\text{m}$ in length and with an aspect ratio ≥ 3 were
31 included (measured in structures per cc of air, s/cc). Average ambient air levels for the various

³ These PCM equivalent fibers (PCMe fibers) are defined as those fibers viewed on TEM that meet the PCM analytical requirements: $\geq 5 \mu\text{m}$ in length and an aspect ratio of at least 3:1. Although the PCM methodology does not specify a minimum fiber width, current PCM analytical methods reliably detect fibers of $0.25 \mu\text{m}$ in width (WHO, 1980), which EPA employs to define PCMe fibers (U.S. EPA, 2009a).

⁴ A single fiber, fiber bundle, cluster, or matrix as defined in the TEM analytical method ISO 10312.

1 sampling locations ranged from 8×10^{-6} s/cc to 1.9×10^{-5} s/cc (U.S. EPA, 2009b). Both
2 ambient and activity-based air monitoring have been completed in five community schools (U.S.
3 EPA, 2010). Outdoor activities conducted that were considered relevant to children's exposures
4 at the schools included playing sports, using playground equipment, and running/walking in
5 outdoor areas. Outdoor activities to assess exposure of the school maintenance workers included
6 digging/raking, power sweeping parking lots, and mowing and edging school lawns.
7 Additionally, ambient air samples were taken in each school (i.e., classrooms, cafeteria,
8 gymnasium, and hallways). Asbestos PCMe fibers were detected by TEM analysis in 5 of
9 63 outdoor activity-based samples, ranging from 0.0022 to 0.039 fibers/cc. No PCMe fibers
10 were detected in indoor air samples. However, 2 of 50 indoor area samples detected TEM
11 asbestos structures not considered to be PCMe fibers (5.1×10^{-4} s/cc and 5.9×10^{-4} s/cc), which
12 are within the range of analytical sensitivity for the indoor air samples (U.S. EPA, 2010). It
13 should be noted that indoor air sampling did not include any activity-based sampling to assess
14 student or employee exposures.

16 **2.3.2. Communities near Vermiculite Expansion and Processing Plants**

17 Vermiculite from the Libby, MT mine was used commercially from the 1920s to 1990,
18 and a review of company records available from (1964–1990) indicates approximately
19 6,109,000 tons of vermiculite concentrate was shipped to over 200 facilities (ATSDR, 2008).
20 The 2008 ATSDR Summary Report on the 28 Libby vermiculite expansion and processing
21 facilities stated that household residents were exposed by contact with vermiculite from the
22 workers' clothes, shoes, and hair. Workers' personal vehicles likely contained vermiculite dust
23 from the facility emissions and from vermiculite that fell from their clothing and hair on the
24 drive home after work. The O.M. Scott Company (Marysville, OH) reported that company
25 policy was to launder work clothes for their employees and to make showers available for use
26 after work. These procedures, when implemented, should greatly reduce exposure potential via
27 household contact (ATSDR, 2005). Whether other facilities made these services available or
28 how frequently they might have been used is unknown.

29 Communities near the expansion plants were subjected to some of the same exposure
30 pathways as for the Libby community. The 2008 ATSDR Summary Report observed that
31 individuals in the community could have been exposed through multiple avenues, such as living
32 near the plant and breathing emissions from the facility, disturbing waste-rock piles, having
33 direct contact with waste rock brought home, and living with indoor dust containing asbestos
34 brought in from outdoor sources (ATSDR, 2008).

1 **2.3.3. Exposures from Zonolite and Vermiculite for Homeowners, Contractors, and Other**
2 **Populations**

3 Vermiculite was most notably used as attic insulation, as a soil amender for gardening,
4 and in the manufacturing of gypsum wallboard. EPA conducted a study to estimate the potential
5 for exposure to asbestos in homes containing VAI. Air samples were taken to define exposure
6 levels in the homes under various conditions: no activity (e.g., ambient air), as well as during
7 simulated remodeling activities and removal of the VAI (U.S. EPA, 2003). Samples were taken
8 in the living space of the homes as well as the attic space.

9 Air samples were collected in five occupied homes where Zonolite VAI was in place
10 (asbestos detected from trace levels to 1.54% by bulk analysis); no fibers were detected in the air
11 samples above 0.0016 PCMe fibers/cc in these homes. However, the air samples were taken
12 when the homes were empty, and there was no disturbance of the VAI or entry/exit into the attic
13 space. Therefore, EPA conducted a number of simulations under controlled conditions to
14 estimate exposures when VAI is disturbed during normal activities (e.g., moving boxes in an
15 attic), remodeling, and removal of the VAI. Structures were built within safe containment to
16 simulate attic space above living space, and VAI was installed in the simulated attics.
17 Remodeling activities resulted in personal exposures ranging from 0.50 to 1.841 fibers/cc PCMe.
18 Stationary samples of the attic air ranged from 0.008 to 0.203 fibers/cc PCMe. For those
19 simulations that included sampling in the ‘living space’ below the attic, asbestos fibers ranged
20 from 0.001 to 0.25 fibers/cc PCMe during renovations and from 0.001 to 0.035 fibers/cc PCMe
21 in the living space after renovations were complete (U.S. EPA, 2003). These data indicate that
22 exposures to asbestos fibers may occur when disturbing Libby Amphibole asbestos-containing
23 VAI in homes.

24 A second study on potential exposures to Zonolite VAI was conducted by an
25 environmental firm hired by attorneys representing individuals with VAI in their homes (Ewing
26 et al., 2010). This study was conducted in three homes containing Zonolite VAI, and air samples
27 were taken, representing ambient conditions (no disturbance of VAI), remodeling, activity in the
28 attic, and removal of the VAI by various methods (see Table 2-2). Disturbance of the
29 asbestos-containing VAI resulted in airborne asbestos levels, both in the personal air monitors
30 and area samples (Ewing et al., 2010).

1
2
3

Table 2-2. Air sampling results for asbestos from Zonolite 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)	2.9–12.5 ^d	0.98–10.3	0.53–1.47

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^aAir sampling results reported as fibers analyzed by phased contrast microscopy (PCM).

^bAir sampling results reported as structures, PCMe as analyzed by transmission electron microscope (TEM).

^cNS—not sampled, personal samples were not taken for background levels.

^dRange 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.¹ However, to help inform the reader as to the expected toxicokinetics of Libby Amphibole asbestos, this section contains a general summary description of toxicokinetics of fibers. A more detailed discussion of fiber toxicokinetics is beyond the scope of this document and is reviewed elsewhere (NIOSH, 2011; ICRP, 1994).

The principal components of fiber toxicokinetics in mammalian systems are (1) deposition at the lung epithelial surface, and (2) clearance from the lung due to physical and biological mechanisms (including both translocation from the lung to other tissues [including the pleura]), and elimination from the body (see Figure 3-1).

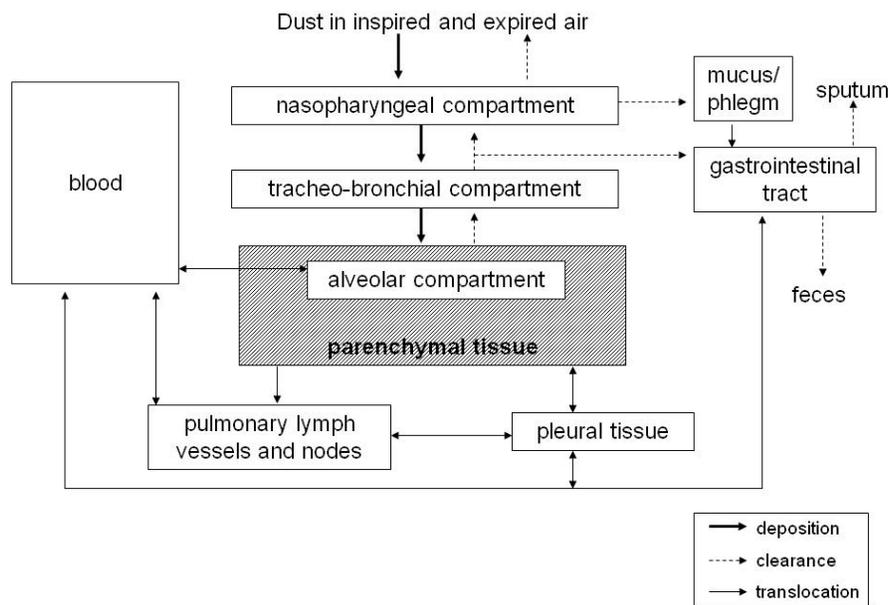


Figure 3-1. General scheme for fiber deposition, clearance, and translocation of fibers from the lung and GI tract. General scheme for fiber deposition (heavy arrows), clearance (light dotted arrows), and translocation (light arrows). Diagram of Bignon et al. (1978) derived from International Commission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

Source: ICRP (1994).

¹The 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.

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1 Libby Amphibole asbestos includes fibers with a range of mineral compositions
2 including amphibole fibers primarily identified as richterite, winchite, and tremolite (see
3 Section 2.2). Although the fiber size varies somewhat from sample to sample, a large percentage
4 (~45%) is less than 5 μm long in bulk samples examined from the Libby mine site (Meeker et al.,
5 2003). Limited data from air samples taken in the workplace also document a large percentage
6 of fibers (including both respirable² fibers as well as fibers <5 μm -long) (see Section 4.1.1.2 and
7 Table 4-3). The importance of the size of fibers and how they deposit following inhalation is
8 described below. Due to a lack of data specific to Libby Amphibole asbestos, these deposition
9 steps are discussed for general forms of asbestos.

10 The main route of human exposure to mineral fibers is through inhalation, although other
11 routes of exposure play a role. Exposure of pulmonary tissue to fibers via the inhalation route
12 depends on the fiber concentration in the breathing zone, the physical (aerodynamic)
13 characteristics of the fibers, and the anatomy and physiology of the respiratory tract. Ingestion is
14 another pathway of human exposure and occurs mainly through the swallowing of material
15 removed from the lungs via mucociliary clearance or drinking water contaminated with asbestos,
16 or eating, drinking, or smoking in asbestos-contaminated work environments (Condie et al.,
17 1983). Handling asbestos can result in heavy dermal contact and exposure. Asbestos fibers
18 could become lodged in the skin, producing a callus or corn—but generally with no serious
19 health effects (Lockey et al., 1984). Because few studies have examined the deposition and
20 clearance of fibers following ingestion of or dermal exposure to fibers, the focus of this section is
21 on the main route of exposure: inhalation.

22 Studies useful for assessing the relationship between airborne fiber concentrations and
23 respiratory disease must involve meaningful measurements of environmental exposure and an
24 understanding of how to apply these measurements to the target tissue dose. Tissue dose is a
25 more specific measure than external dose, and it is determined both by fiber characteristics of the
26 exposure environment and the exposed population. Dose to the lung is a function of airway
27 anatomy, lung volume, ventilation rate, and clearance from the lung, as well as the fiber's
28 physical and chemical characteristics (Oberdorster, 1991; U.S. EPA, 2004). Many studies have
29 examined the role of these physical and chemical characteristics in asbestos-induced disease in
30 the lung and are reviewed in more depth elsewhere (NIOSH, 2011; ATSDR, 2001; Myojo and
31 Takaya, 2001; Witschi and Last, 1996; Lippmann, 1990; Merchant, 1990; Yu et al., 1986; Griffis
32 et al., 1983; Harris and Fraser, 1976; Harris and Timbrell, 1975). Factors influencing dose to

²Respirable fibers are those that can be inhaled into the lower lung where gas exchange occurs and are defined by their aerodynamic diameter ($d_a \leq 3 \mu\text{m}$; NIOSH, 2011).

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1 other tissues in the body (e.g., pleura, peritoneum, stomach, and ovaries) are not as well known,
2 but they are discussed below where data are available.

3 4 **3.1. DEPOSITION OF FIBERS IN THE RESPIRATORY TRACT**

5 The deposition of fibers in the respiratory tract is dependent on the aerodynamic
6 properties of the fiber (length, width, and density) and the anatomy and physiology of the
7 respiratory tract (NIOSH, 2008; ATSDR, 2001; Myojo and Takaya, 2001; Witschi and Last,
8 1996; Yu et al., 1986; Griffis et al., 1983; Harris and Fraser, 1976; Harris and Timbrell, 1975).
9 The aerodynamic diameter of fibers is mostly determined by the geometric diameter and density.
10 In general, thicker fibers are deposited in the upper airways; thinner fibers are carried deeper into
11 the airways and alveolar regions. Fibers with aerodynamic diameters less than approximately
12 3 μm meet the physical criteria necessary for deposition in the terminal bronchioles and beyond
13 to the alveoli. The site of fiber deposition within the respiratory tract has implications related to
14 lung retention and surface dose of fibers.

15 The respiratory tract encompasses the extrathoracic region (nasal passages, pharynx, and
16 larynx), thoracic region (the conducting airways [trachea bronchi, bronchioles], and the
17 gas-exchange region of the lung (respiratory bronchioles, alveolar ducts, and alveoli). A full
18 review of the anatomy and architecture of the respiratory tract is beyond the scope of this
19 document but has been reviewed by ICRP (1995).

20 Fiber deposition occurs by five mechanisms: impaction, interception, sedimentation,
21 diffusion, and electrostatic precipitation (see Table 3-1):

- 22
23
- 24 **1. Impaction:** The momentum of the fiber causes it to directly impact the airway surface as
25 the airflow changes direction. This is the predominant method of deposition in the
26 nasopharyngeal region where airflow is swift and larger fibers/particles are present.
 - 27 **2. Interception:** A special case of impaction where the edge of the fiber touches the airway
28 surface and is prevented from continuing along the airway. This mechanism is important
29 in the conducting airways (trachea and bronchi), where the airflow is slower and laminar
30 flow along the airway surface is conducive to interception.
 - 31 **3. Sedimentation:** Gravitational forces and air resistance cause fibers/particles to settle out
32 of the air column onto the airway surface. For sedimentation to occur, air flow velocities
33 must be low to allow the particle/fiber to settle, and this is a predominant mechanism to
34 the smaller conducting airways.

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 **4. Diffusion:** This method of deposition is predominant in the alveolar region where air
2 movement is negligible. Diffusion occurs from interactions of the fibers with the
3 movement of air molecules; this Brownian motion increases with decreasing fiber size
4 (<0.5- μm diameter).

5 **5. Electrostatic Precipitation:** A special case of diffusion in which fiber motion towards
6 the airway surface is a function of static charge between the fiber and airway surface. As
7 with classic diffusion, this primarily occurs in the gas-exchange region where airflow is
8 negligible and electrostatic forces can predominate.
9

10
11 Aerodynamic diameter (also called aerodynamic equivalent diameter) of fibers accounts
12 for the dimensional properties that influence the movement of the fiber's center of gravity
13 through the airways, so aerodynamic diameter is important in all depositional mechanisms. The
14 aerodynamic diameter is the diameter of a unit density (1 g/cm^3) sphere that has the same
15 gravitational settling velocity as the particle of interest. Since the aerodynamic diameter informs
16 the deposition patterns of fibers, it is used in dosimetric modeling to determine the expected fiber
17 deposition in the respiratory tract. Impaction and interception, however, are also heavily
18 influenced by fiber length. Where the physical length of the fiber greatly exceeds the
19 aerodynamic diameter, impaction and interception can be underpredicted by modeling the center
20 of gravity of the fiber. Sedimentation is related to the mass of the fiber, as well as the
21 aerodynamic diameter, but generally occurs at lower velocities in smaller airways. Diffusion
22 occurs from interactions of the fibers with the movement of air molecules; this Brownian motion
23 increases with decreasing fiber size (<0.5- μm diameter). Electrostatic precipitation occurs when
24 fiber charges induce opposite charges on the airway surfaces and the fiber is drawn to the airway
25 walls (Lippmann, 1990).

26 For high aspect ratio fibers, like asbestos, the shape factor often approaches one and the
27 equation reduces to the aerodynamic diameter that is approximately equal to the nominal fiber
28 diameter.³ Therefore, in employing the information from Table 3-1 to high aspect ratio fibers,
29 one may get an idea of the depositional characteristic of fibers from the nominal diameter. By
30 definition, fibers have a greater aspect ratio than particles and as discussed, high aspect ratio
31 fibers may act significantly different than other particles with respect to some mechanisms of
32 deposition (e.g., impaction, interception, and electrostatic precipitation). Therefore, the
33 depositional characteristics of fibers are not characterized completely by aerodynamic diameter.
34 No equivalent depositional model, however, is yet available for fibers in the dimensional range

³The physical properties of a fiber that determine its aerodynamic transport are combined and defined as the aerodynamic diameter; one such property is the shape factor (ICPS, 1994).

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1 of asbestos that takes into consideration the increased sedimentation and impaction for high
2 aspect ratio particles.

3 Fibers enter the respiratory tract along with airflow through the nasal and oral passages.
4 The nasal passage, from the nostril to the pharynx, serves as a filter for some fibers with
5 diameters 5–30 μm . Clumps of fibers also could deposit in these regions. Many animal species,
6 including rats and mice, are obligate nose breathers, meaning that fibers pass only through the
7 nasal passages, and, therefore, are always subject to nasopharyngeal filtering. Humans,
8 monkeys, and dogs, among other species, breathe both orally and nasally (oronasal). Therefore,
9 larger fibers and clumps of fibers can bypass the upper respiratory tract filtering and be inhaled
10 directly into the larynx/trachea, especially during exertion (e.g., exercise or work), which may
11 further alter deposition by increased turbulence in the airways. This distinction is important
12 when comparing results of inhalation studies conducted in different species.

13 The conducting airways beyond the nasopharyngeal region include the trachea and
14 bronchi, which serially bifurcate into airways of decreasing internal diameters. The aerodynamic
15 diameter of fibers that can deposit in the tracheobronchial region is in the range of 1–5 μm .
16 Fibers with aerodynamic diameter $<1 \mu\text{m}$ can deposit in the bronchioles and the alveoli (ICRP,
17 1994).

18 Generally, fibers with aerodynamic characteristics conducive to deposition in the
19 bronchioles and alveoli can cause pulmonary fibrosis and associated disease by either retention
20 in the alveoli or penetration into the peribronchiolar space. All fibers having an aerodynamic
21 diameter that is less than approximately 2 μm , which includes Libby Amphibole asbestos, meet
22 the physical criteria necessary for deposition in the deeper regions of the respiratory tract at the
23 level of the terminal bronchioles or alveoli.

24 Deposition of fibers in the alveolar region of the lung is consistent with radiological
25 findings in humans of fibrosis in the lower lung fields at early stages of disease. Deposition of
26 fibers in the alveoli can become limited when fiber length approaches 40 μm (Morgan et al.,
27 1978). Alveolar deposition of fibers with high aspect ratios and length ranging from less than
28 1 μm to greater than 200 μm long, however, has been recorded (Morgan et al., 1978). In all
29 documented observations of fibers collected from either healthy or diseased individuals, short
30 fibers ($<5 \mu\text{m}$) were present in substantially greater numbers in lung tissue than were long fibers
31 ($>5 \mu\text{m}$) (Churg, 1982; Churg and Warnock, 1980). Although information is limited on how
32 fibers get to the pleura, fibers observed in pleural tissue from mesothelioma cases are more likely
33 to be short ($<5 \mu\text{m}$) (Suzuki et al., 2005). These observations could be due in part to the
34 increased deposition of smaller fibers or the breakage of larger fibers over time (Bernstein et al.,
35 1994; Davis, 1994).

1 The lung and nasal depositional differences are due in part to differences in airway
2 structure and breathing patterns across lifestages (i.e., children, adults), changing the depositional
3 pattern of different fiber sizes, possibly altering the site of action, and potentially resulting in
4 differential clearance and health effects (see Section 4.7).

5 Modeling of fiber deposition has been examined for various fiber types (e.g., refractory
6 ceramic fibers, chrysotile asbestos) (Sturm, 2009; Zhou et al., 2007; Lentz et al., 2003; Dai and
7 Yu, 1998; Yu et al., 1997; Coin et al., 1992), but not for Libby Amphibole asbestos. In general,
8 the pattern of deposition for fibers is expected to have some similarities to the well-studied
9 deposition pattern for essentially spherical particles (reviewed in ICRP, 1994). For example, the
10 multipath particle dose model (Jarabek et al., 2005; Brown et al., 2005) uses information on the
11 physical properties of the particles (length and width [also called bivariate distribution] and
12 density), the anatomy and architectural features of the airways, airflow patterns that influence the
13 amount and the location of the deposition of the particles, and dissolution and clearance
14 mechanisms that are operative to estimate the retained dose in the target tissue.

16 **3.2. CLEARANCE**

17 **3.2.1. Inhalation**

18 **3.2.1.1. Respiratory Tract**

19 Once fibers deposit on the surface of the respiratory tract, they may be removed (cleared)
20 from the lungs in several ways—including physical clearance, dissolution, phagocytosis, or
21 encapsulation. Some of these mechanisms, such as dissolution of the fibers or removal via the
22 mucociliary apparatus, can result in the fibers being cleared from the body (see Figure 3-1).
23 Other clearance mechanisms may remove fibers from the surface of the respiratory tract but
24 result in transport of the fibers to other tissues by translocation. Translocation of fibers from the
25 terminal bronchioles and alveoli into the peribronchiolar space, lymph nodes, and pleura has
26 been implicated in disease causation (e.g., pleural plaques, mesothelioma) (Dodson et al., 2001).
27 In human studies, the translocation of asbestos fibers following inhalation has been observed to
28 varying degrees throughout the pulmonary and extrapulmonary tissues of the respiratory system
29 (Suzuki and Kohyama, 1991; Dodson et al., 2005; Kohyama and Suzuki, 1991; Dodson et al.,
30 2001; Sebastien et al., 1980), as well as other organs, including the brain, kidney, liver
31 (Miserochi et al., 2008), and ovaries (Langseth et al., 2007). In many cases, the type of fiber
32 was not defined, and the individual exposure information is not available. Fibers that are not
33 cleared may remain at the epithelial surface or enter the parenchymal tissue of the lung.

34 Berry (1999) provided a review of the animal toxicity literature specifically for fiber
35 clearance. There are limited data on clearance patterns based on autopsy studies in humans.

1 Two studies estimated clearance half-life for amphibole asbestos (~20 years) as compared with
2 chrysotile asbestos (~10 years) (Churg and Vedal, 1994; Finkelstein and Dufresne, 1999); in
3 evaluating the data on lung fiber burden, Berry et al. (2009) estimated the range of the half-life
4 for crocidolite to be between 5 and 10 years. Generally, studies have focused on determining the
5 size and type of asbestos retained in specific tissues (Dodson et al., 1990; Gibbs et al., 1991;
6 Suzuki et al., 2005; Dumortier et al., 1998; Suzuki and Yuen, 2001; McDonald et al., 2001) and
7 did not discuss changes in fiber content since exposure. Sebastien et al. (1980) concluded that
8 lung fiber burden could not be used as an accurate reflection of pleural fiber burden.

9 10 **3.2.1.1.1. *Physical clearance of fibers***

11 Fibers deposited in the nasal passages can be removed by physical clearance. When
12 breathing occurs through the nose, many fibers are filtered by the turbulent airflow in the nasal
13 passages, impacting against the hairs and nasal turbinates, as well as becoming entrained in
14 mucus in the upper respiratory tract where they can be subsequently removed by mucociliary
15 action or reflexive actions such as coughing or sneezing. The mucociliary escalator removes
16 fibers through ciliary movement of the sticky mucus lining (Churg et al., 1989; Wanner et al.,
17 1996). Fibers removed from the conducting airways through this mechanism are coughed out or
18 swallowed and enter the digestive tract where they may adversely affect the gastrointestinal
19 tissue, enter the blood stream, or be excreted. Clearance of fibers via mucociliary action is rapid
20 and is usually complete within minutes or hours. However, the mucociliary escalator extends
21 only down to the level of the terminal bronchioles and not to the alveoli. Therefore, particles
22 that reach the alveolar region of the lung cannot be cleared through this process. Fibers can also
23 translocate due to physical forces associated with respiration (Davis, 1989).

24 Some fibers are not cleared from the lung, leading to an accumulation with time (Case et
25 al., 2000; Finkelstein and Dufresne, 1999; Jones et al., 1988). The fibers that remain in the lung
26 may undergo a number of processes including translocation, dissolution, fragmentation, splitting
27 along the longitudinal axis, or encapsulation with protein and iron. Available data indicate
28 prolonged clearance from the lung of long (>5 μm) or short amphibole fibers (Coin et al., 1994;
29 Tossavainen et al., 1994). The prolonged clearance times for long amphibole fibers have led
30 some investigators to conclude that long versus short amphibole fibers are predominant in the
31 cause of disease despite the relatively small numbers of these longer fibers in comparison to
32 short fibers (Mossman et al., 2011; ATSDR, 2003). However, others argue that fibers of all
33 lengths induce pathological responses and urge caution in excluding, based on their length, any
34 population of fibers from consideration as possibly contributing to the disease process (Aust et
35 al., 2011; Dodson et al., 2003). Respirable-sized fibers of Libby Amphibole asbestos have been

1 identified in air samples from activity-based sampling from Libby, MT, and in airborne fibers
2 suspended from both Libby vermiculite concentrate and in the exfoliated product from that
3 concentrate. Based on fibers counted by the TEM analytical method (ISO 10312), the majority
4 of counted fibers are respirable (see Figure 2-12).

6 **3.2.1.1.2. *Dissolution of fibers***

7 Dissolution, or the chemical breakdown of fibers, is another method of removal of fibers
8 from the lung. This process varies, depending on the chemical composition of the fibers, as well
9 as the physiological environment. Dissolution can occur in the lung's extracellular fluids or in
10 the macrophage phagolysosome. Studies performed in vitro to determine dissolution rate of
11 fibers attempt to mimic the extracellular lung fluids and macrophage-phagolysosome system to
12 understand the length of time that fibers remain in the system (Rendall and du Toit, 1994).
13 Studies have shown that dissolution occurs more rapidly for chrysotile fibers than for amphiboles
14 (Coffin et al., 1983). Fibers can also be physically diminished through splitting or breakage.
15 These smaller fragments are then more easily removed by phagocytosis or translocation.

17 **3.2.1.1.3. *Removal of fibers through phagocytosis***

18 The principal clearance pathway for insoluble fibers deposited in the alveoli is through
19 phagocytosis by macrophages. Alveolar macrophages that have phagocytized insoluble fibers
20 migrate to the bronchoalveolar junctions where they enter onto the mucociliary escalator for
21 removal (Green, 1973). Alternatively, alveolar macrophages that have phagocytized insoluble
22 fibers can also migrate through the epithelial wall into the interstitial space and enter the
23 lymphatics (Green, 1973).

24 Alveolar macrophage cells engulf and transport deposited particles to the mucociliary
25 escalator or through the alveolar epithelium to the interstitial tissues, where they are removed or
26 translocated by the blood or lymphatics. Durable fiber impaction in these deeper regions also
27 stimulates activation of alveolar macrophage cells. In vitro and in vivo studies clearly indicate
28 that macrophage cells play a role in the translocation of fibers (Bignon et al., 1979; Brody et al.,
29 1981; Castranova et al., 1996; Dodson et al., 2000b). These studies have demonstrated the
30 presence of asbestos fibers in cell cytoplasm where they can be transported in association with
31 cytoskeletal elements to the proximity of the cell nucleus. Small chrysotile fibers can also
32 penetrate the nuclear membrane (Malorni et al., 1990).

33 A number of processes can disrupt the normal phagocytic function of the alveolar
34 macrophages. These processes include death or dysfunction of macrophages due to phagocytosis
35 of an excessive number of particles (often termed "overload") or highly reactive particles or an

1 attempted phagocytosis of fibers of lengths that exceed the dimensional capacity of the
2 macrophage (often termed “frustrated phagocytosis”) (NIOSH, 2011). All of these processes can
3 induce inflammatory and fibrogenic responses. Limited inhalation laboratory animal studies
4 exist at nonoverloading concentrations of fibers or particles; therefore, there is insufficient
5 information to determine mechanisms at these lower doses (reviewed in Mossman et al., 2011).
6

7 **3.2.1.1.4. *Encapsulation of fibers***

8 Fibers that are too large to be easily engulfed by the alveolar macrophage can stimulate
9 the formation of “asbestos bodies.” Asbestos bodies are fibers that, during prolonged residence
10 in the lung, have become coated with proteins, iron and calcium oxalate. Due to their iron
11 content, histological stains for iron have long been used to identify them in tissue; thus, they are
12 sometimes called “ferruginous bodies.” The mechanisms that result in the formation of asbestos
13 bodies are poorly understood, although most appear to be formed around amosite fibers (Dodson
14 et al., 1996). The iron in the coating, however, is derived from the asbestos fiber, cells, or
15 medium surrounding the fiber and can remain highly reactive (Ghio et al., 1992; Lund et al.,
16 1994). Asbestos bodies can remain in the lung throughout the lifetime of the exposed individual.
17 Asbestos bodies comprise a minor portion of the overall fiber burden of the lung, and, after the
18 fiber is fully coated, these fibers might or might not participate directly in asbestos disease. The
19 presence of iron in the coating, however, could provide a source for catalysis of reactive oxygen
20 species similar to that observed with fibers.
21

22 **3.2.1.1.5. *Translocation to extrapulmonary tissues***

23 Clearance from one tissue may involve translocation to another tissue. For example,
24 following fiber deposition in the respiratory tract, fibers may then clear via translocation to
25 extrapulmonary tissues like the pleura. The specific mechanism and translocation route depend
26 both on fiber characteristics and the tissue of deposition. Whether or not fibers are translocated
27 appears to depend on their physical-chemical characteristics, including two-dimensional size
28 (length and width); durability; solubility; and reactivity. This translocation is aided by high
29 durability and an inflammation-induced increase in permeability but is hindered by fibrosis.
30 Deposition occurs in the respiratory tract as described above; translocation from the respiratory
31 tract may, in turn, lead to fibers ‘depositing’ in extrapulmonary sites.

32 Apparent translocation of fibers throughout the respiratory tract is evident from
33 experimental animal research done by several investigators following exposure by both
34 intrapleural injection and inhalation (Bignon et al., 1979; Holt, 1982; Smith et al., 1974, 1979,
35 1980; Misericchi et al., 2008). The data from most studies show that fibers can—and do—

1 translocate among tissues and organs and move by both physiological and physical mechanisms
2 (Cook and Olson, 1979; Holt, 1982, 1983). Conflicting results from another study, however,
3 indicate no evidence of fiber translocation from the central to peripheral compartments following
4 inhalation exposure in rats, although this could be due to the short duration of the study (29 days
5 postexposure) (Coin et al., 1992).

6 Translocation of fibers to extrapulmonary tissues has been studied in multiple studies;
7 however, the mechanism is still unknown. This was more recently reviewed by Miserocchi et al.
8 (2008). Fibers have been measured in extrapulmonary tissues including pleural plaques and
9 mesothelial tissue (i.e., pleural or peritoneal) in miners, brake workers, insulation workers, and
10 shipyard workers (Dodson et al., 2000a; Roggli et al., 2002; Churg et al., 1994; Kohyama and
11 Suzuki, 1991). These studies found fibers at all locations analyzed, with increased levels of
12 amphibole as compared to chrysotile in the parenchyma when subjects were exposed to a
13 mixture of both fiber types. Amphibole fibers, however, were less prevalent in the pleura and
14 mesothelial tissues (Sebastien et al., 1980, 1989; Bignon et al., 1979; Churg, 1988; Kohyama and
15 Suzuki, 1991). Few studies have examined the size distribution of fibers translocated to specific
16 tissues. For example, one early study suggested that the longer amphibole fibers predominate in
17 the lung while shorter chrysotile fibers are found in the pleura (Sebastien et al., 1980); others
18 showed that the fiber-length distribution was the same by fiber type regardless of location
19 (Kohyama and Suzuki, 1991; Bignon et al., 1979).

20 Transplacental transfer of both asbestos (chrysotile, tremolite, actinolite, and
21 anthophyllite) and nonasbestos fibers has been shown to occur in humans, as measured in the
22 placenta and in the lungs of stillborn infants (Haque and Kanz, 1988; Haque et al., 1992, 1996,
23 1998). It is hypothesized that maternal health might influence the translocation of fibers, as
24 some of the mothers had preexisting health conditions (e.g., hypertension, diabetes, or asthma)
25 (Haque et al., 1992). This group also measured transplacental translocation in a mouse study and
26 observed early translocation of crocidolite fibers through the placenta in animals exposed via
27 tail-vein injection (Haque et al., 1998) These studies did not evaluate the source or levels of
28 exposure, only the presence of fibers in the body during early lifestages in mice and humans.

29 Sebastien et al. (1980) found chrysotile was the predominant fiber in parietal pleura of
30 autopsy cases, while the amphibole fibers found in the lungs ranged from 0 to 100% (mean
31 56%). Bignon et al. (1979) found similar distributions but also found increased amphibole fibers
32 in the associated lymph nodes. In this study, chrysotile and amphibole fibers were found
33 together in the lung parenchyma and alveolar spaces. Other studies show fewer amphibole fibers
34 at the site of diseased tissue in the pleura and mesothelial tissue than chrysotile (Churg, 1988;
35 Kohyama and Suzuki, 1991). Sebastien et al. (1989) examined fiber types in lungs of chrysotile

1 textile and mining workers from South Carolina and Quebec, respectively, to better understand
2 the unknown reason for differences in disease risk in each cohort. Both groups were exposed to
3 similar material, yet the South Carolina cohort had a much greater risk of respiratory cancer.
4 This study examined only lungs, although some of those exposed had nonpulmonary cancers.
5 Overall, the number of tremolite fibers retained in the lungs was higher than that of chrysotile
6 fibers retained in the lungs in both cohorts. Size distribution showed that most fibers measured
7 were 5.8–8.0 μm long, although measurements were not made for anything smaller than this.
8 Tremolite fibers had a greater mean diameter in both cohorts (0.35 μm) as compared to
9 chrysotile (0.10 μm), while chrysotile had more “Stanton” fibers (25.2–31.8%) as compared to
10 tremolite (5.9–6.3%). Stanton fibers are defined as $>8 \mu\text{m}$ long and $<0.25 \mu\text{m}$ in diameter
11 (Stanton et al., 1981, reviewed in Appendix D).
12

13 **3.2.1.2. Pleural Cavity and Extrapulmonary Sites**

14 Studies have demonstrated fiber clearance from the respiratory tract may lead to
15 translocation to the pleural cavity and extrapulmonary sites. For example, in a study comparing
16 fiber burden in the lung, thoracic lymph nodes, and pleural plaques, Dodson et al. (1990)
17 observed that the average-length fiber found in the lung (regardless of type) was longer than
18 those found in the lymph nodes or plaques. Most fibers at all three sites were short ($<5 \mu\text{m}$). A
19 later study by this group (i.e., Dodson et al., 2000a) examined tissue from 20 individuals with
20 mesotheliomas, most with known asbestos exposures. Seventeen of the cases (85%) had
21 asbestos fibers in at least one other extrapulmonary site. The most prevalent type of asbestos in
22 the mesentery was amosite, and the second most prevalent was chrysotile. Tremolite was also
23 found, to some degree, in the mesentery and omentum, and in the lung. Dodson et al. (2005)
24 examined parenchymal lung tissue from a cohort of 54 mesothelioma patients and determined
25 the presence of asbestos in all patients analyzed. However, very little information is known
26 about the specific mechanisms of fiber clearance and/or translocation from the pleural cavity and
27 extrapulmonary sites, although many studies examining these tissues have observed fibers in
28 multiple tissue sites (reviewed in Case et al., 2011; Aust et al., 2011). Following intrapleural
29 injection of fibers in rats, Bignon et al. (1979) used transmission electron microscopic evaluation
30 following serial sacrifice to monitor migration of fibers from the pleural cavity to the lung
31 parenchyma.
32

33 **3.2.2. Ingestion**

34 Although ingestion is a potential route of exposure, limited research has examined
35 clearance (e.g., translocation) of fibers following ingestion, and no clearance studies are

1 available specific to Libby Amphibole asbestos. An early study to examine the tissue response
2 to asbestos fibers is not truly representative of a natural ingestion exposure, as the researchers
3 directly injected a suspension of amosite fibers into the duodenal wall (Meek and Grasso, 1983).
4 This study, however, also examined oral ingestion of amosite in healthy animals and those with
5 gastrointestinal ulcers to determine if translocation of fibers occurs through ulcers. Following
6 injection of amosite, granulomatous lesions were observed. Ingestion of the same material
7 resulted in no such lesions or in any other histopathological changes in either healthy or
8 compromised rats. Thus, no translocation was observed from either the healthy or the
9 compromised rat gastrointestinal tracts in this study. A later International Agency for Research
10 on Cancer study (Truhaut and Chouroulinkov, 1989) examined the effects of chrysotile and
11 crocidolite ingestion in Wistar rats. No translocation was observed. No further studies have
12 been found on clearance or translocation of fibers from the gastrointestinal tract.

13

14 **3.2.3. Dermal Contact**

15 No studies of dermal clearance or translocation have been reported in the published
16 literature.

17

18 **3.3. SUMMARY**

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

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

34 Multiple fiber characteristics (e.g., dimensions, density, and durability) play a role in the
35 toxicokinetics of fibers. For this reason, careful attention has been paid to these fiber

1 characteristics when analyzing research studies on Libby Amphibole asbestos and asbestiform
2 tremolite, an amphibole fiber that comprises part of Libby Amphibole asbestos (see
3 Appendix D). No toxicokinetic data are available specific to Libby Amphibole asbestos,
4 tremolite, richterite, or winchite. When available, this information is presented in the discussion
5 of each study in relation to the toxic endpoints described.

4. HAZARD IDENTIFICATION OF LIBBY AMPHIBOLE ASBESTOS

Several human studies are available that provide evidence for the hazard identification of Libby Amphibole asbestos.¹ This discussion focuses primarily on data derived from studies of people exposed to Libby Amphibole asbestos—either at work or in the community. The adverse health effects in humans are supported by the available Libby Amphibole asbestos experimental animal and laboratory studies. Libby Amphibole asbestos contains winchite (84%), with lesser amounts of richterite (11%) and tremolite (6%) with trace amounts of magnesioriebeckite, edenite, and magnesio-arfvedsonite (Meeker et al., 2003) (see Section 2.2.3 for a more complete discussion). Adverse health effects from tremolite exposure have been reported in both human communities and laboratory animals; these effects are consistent with the human health effects reported for Libby Amphibole asbestos. Studies examining the health effects of exposure to winchite or richterite alone were not available in the published literature. The presentation of noncancer and cancer health effects provides a comprehensive review of adverse health effects observed from exposures to Libby Amphibole asbestos.

4.1. STUDIES IN HUMANS—EPIDEMIOLOGY

The Libby Amphibole asbestos epidemiologic database includes studies conducted in occupational settings examining exposures to workers and community-based studies, which can include exposures to workers, exposures to family members of workers, and exposures from environmental sources. Occupational epidemiology studies exist for two worksites where workers were exposed to Libby Amphibole asbestos. These worksites include the mine and mill at the Zonolite Mountain operations near Libby, MT, and a vermiculite processing plant in Marysville, OH. Worker cohorts from each site and the study results are described in Section 4.1.1. Community-based studies include community health consultations for Libby, MT conducted by the Agency for Toxic Substances and Disease Registry (ATSDR), including an evaluation of cancer mortality data, and a health screening of current and former area residents—including workers—that collected medical and exposure histories, chest X-rays, and pulmonary function tests (ATSDR, 2000, 2001) (see Section 4.1.2). ATSDR, in conjunction with state health departments, also conducted health consultations for 28 other communities around vermiculite processing plants that were potentially exposed to Libby Amphibole asbestos (see Section 4.1.4). These health consultations consisted of analyses of cancer incidence or mortality data; results from nine of these studies are currently available.

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.

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1 No occupational studies are available for exposure to tremolite, richterite, or winchite
2 mineral fibers individually or as a mixture exposure, other than Libby Amphibole asbestos.
3 Communities, however, have been exposed to tremolite and other mineral fibers from natural
4 soils and outcroppings. Tremolite asbestos-containing soil has been used in whitewash in
5 interior wall coatings in parts of Turkey and Greece. Studies in these areas published as early as
6 1979 reported an increased risk of pleural and peritoneal malignant mesothelioma (Baris et al.,
7 1987; Langer et al., 1987; Baris et al., 1979; Sichletides et al., 1992). More recent studies of
8 communities exposed to tremolite and chrysotile fibers report excess lung cancer and
9 mesothelioma (1.3- and 6.9-fold, respectively) (Hasanoglu et al., 2006). Other studies reported
10 pleural anomalies in residents exposed to naturally occurring asbestos, which includes actinolite,
11 tremolite, and anthophyllite (Metintas et al., 2005; Zeren et al., 2000). Clinical observations
12 include a bilateral increase in pleural calcification accompanied by restrictive lung function as
13 the disease progresses, a condition known as “Metsovo lung,” named after a town in Greece
14 (Comkrantopoulos et al., 1985). In one community, the prevalence of pleural calcification was
15 46% (of 268 residents), increasing with age to 80% in residents over 70 (Langer et al., 1987).
16 Both tremolite and chrysotile were identified in bronchoalveolar lavage fluid of 65 residents
17 from different areas of Turkey who were environmentally exposed (Dumortier et al., 1998). The
18 health effects observed in communities with environmental and residential exposure to tremolite
19 are consistent with health effects documented for workers exposed to commercial forms of
20 asbestos.

22 **4.1.1. Studies of Libby, MT Vermiculite Mining Operation Workers**

23 Several studies of mortality from specific diseases among workers in the Libby, MT
24 mining operations have been conducted, beginning in the 1980s with the studies by McDonald
25 et al. (1986a, b) and Amandus et al. (1987a, b; Amandus and Wheeler, 1987). McDonald et al.
26 (2002, 2004) published an update with mortality data through 1999, and Sullivan (2007) updated
27 the cohort originally described by Amandus et al. (1987a, b; Amandus and Wheeler, 1987)
28 (referred to in this assessment as the Libby worker cohort) with mortality data through 2001.
29 Additionally, Larson et al. (2010a) reconstructed a worker cohort and analyzed mortality through
30 2006 in this same study population, while another study examined changes in lung abnormalities
31 using X-rays taken between 1955 and 2004 of 88 workers (Larson et al., 2010b).

32 **4.1.1.1. Description of Mining and Milling Operations**

33 The vermiculite mining and milling operations have been described in considerable detail
34 (ATSDR, 2000). An open-pit vermiculite mine began limited operations in 1923, and production
35 increased rapidly between 1940 and 1950. This mine is located on Zonolite Mountain, several

1 miles east of Libby (ATSDR, 2000). The Kootenai River runs between the town and the mine.
2 The mining and milling operations continued until 1990 (ATSDR, 2000).

3 The drilling and blasting procedures used in the strip-mining operations generated
4 considerable dust exposures, although the mining operations had lower intensity exposures
5 compared to the milling operations. Amandus et al. (1987a) noted that in 1970, a new drill with
6 a dust-control bagging system aimed at limiting workplace exposure was introduced to the
7 mining operations. Another aspect of the operations was the loading of ore for railroad
8 shipment. From 1935–1950, railroad box cars were loaded at a station in Libby. In 1950, the
9 loading station was moved to a loading dock on the Kootenai River, 7 miles east of town. Tank
10 cars were used from 1950–1959 and then switched to enclosed hopper cars in 1960.

11 The milling operations used a screening or sifting procedure to separate vermiculite
12 flakes from other particles and increase the concentration of vermiculite from approximately
13 20% in the bulk ore to 80–95% in the resulting product. A dry mill began operating in 1935, and
14 a wet mill began operating in the 1950s in the same building as the dry mill. One of the primary
15 changes in the conditions in the dry mill was the installation of a ventilation fan in 1964.
16 Exposure to asbestos inside the mill was estimated to be 4.6 times higher preceding this
17 installation (McDonald et al., 1986a). This ventilation fan resulted in higher amphibole fiber
18 exposures in the mill yard until 1968, when the exhaust stack for the fan was moved. Other
19 changes to the milling operations in the 1970s included replacement of hand bagging and sewing
20 with an automatic bagging machine (1972), pressurization of the skipper control room used for
21 transferring the ore concentrate from the mill to a storage site (1972), and construction of a new
22 wet mill (1974). Closing of the old dry and wet mills in 1976 had a substantial impact on
23 exposures at the worksite. In 1974, a new screening plant used to size-sort the ore concentrate
24 was constructed at the loading dock near the river. Two processing plants operated within the
25 town of Libby (ATSDR, 2001). These expansion or exfoliation plants heated the ore
26 concentrate, resulting in additional release of the Libby Amphibole asbestos fibers in the area.

27 28 **4.1.1.2. Exposure Estimation**

29 In the early 1980s, two research groups conducted parallel studies of the mortality
30 experienced by workers in the Libby mining and milling operations. One study was undertaken
31 by the National Institute of Occupational Safety and Health (NIOSH) (Amandus et al., 1987a, b;
32 Amandus and Wheeler, 1987) and the other by researchers from McGill University (McDonald
33 et al., 1986a, b). The exposure assessment procedures used by the two groups relied on the same
34 exposure measurements and used similar assumptions in creating exposure estimates for specific
35 job activities and time periods (see Table 4-1). In brief, available air sampling data were used to

1 construct a job-exposure matrix assigning daily exposures (8-hour time-weighted average) for
2 identified job codes based on sampling data for specific locations and activities. Varying job
3 codes and air exposures were used for different time periods as appropriate to describe plant
4 operations. Individual exposure metrics (e.g., cumulative exposure) were calculated using the
5 work history of each individual in the study in conjunction with the plant job-exposure matrix.
6 The specific study details for the Libby, MT worker cohort are described in more detail below,
7 with differences between the research groups highlighted.

8 Before 1970, exposure estimates were based on midget impinger samples taken primarily
9 in the dry mill by state and federal inspectors. Total dust samples were measured as million
10 particles per cubic foot (mppcf) by the midget impinger method. Amandus et al. (1987a)
11 describe the period during which most of the midget impinger measurements were made as
12 1962–1967, and McDonald et al. (1986a) describe this period as 1962–1969, with a few
13 additional measures in earlier years.² The number of samples available before 1970 was
14 336 (Amandus et al., 1987a). Membrane-filter air samples for fibers, taken at various locations
15 within the operations, began in 1967, and data are available from company records as well as
16 State and Federal Agencies (see Table 4-2). Stationary and short-term (i.e., 20-minute to less
17 than 4-hour) measurements were primarily used prior to 1974. The number of membrane-filter
18 samples available was 4,116. Air samples collected through membrane filters were analyzed by
19 phase contrast microscopy (PCM) to visually count fibers greater than >5- μm long and having an
20 aspect ratio >3:1 (Amandus et al., 1987a).³ PCM methods from the 1960s allowed reliable
21 characterization of fibers with widths greater than approximately 0.4 μm (Skikne, 1980;
22 Amandus et al., 1987a). Further standardization of the PCM method provides better
23 visualization of thinner fibers, and 0.25 μm width is considered the limit of resolution for fiber
24 width (WHO, 1986).

² Amandus et al. (1987a) indicates that one sample was available from 1942, and additional samples were available after 1956; McDonald et al. (1987a) indicates that additional samples were available from 1944, 1956, and 1958.

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

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Table 4-1. Exposure assessment methodologies used in evaluations of Libby, MT (see Section 4.1.1) and Marysville, OH (see Section 4.1.2) worker cohorts

Operation and study cohort	Asbestos fiber quantification and job-exposure classification	Studies using methodology
Libby, MT mining and milling operations; NIOSH cohort	Exposure based on phase-contrast microscopy of fibers >5 µm long and aspect ratio >3:1 (1967–1982), and midjet impinger data (1956–1969). 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. Cumulative exposure reported in units of fiber-years (equivalent to the unit of fibers/cc-years EPA is using for all studies).	Amandus et al., 1987a, b; Amandus and Wheeler, 1987
Libby, MT mining and milling operations; NIOSH cohort	Modification to Amandus et al. (1987a) job classification: laborers and “unknown” jobs assigned 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.	Sullivan, 2007; Moolgavkar et al., 2010
Libby, MT mining and milling operations; ATSDR cohort assembled from W.R. Grace & Co. records	Extension of Amandus et al. (1987a) exposure data, with additional application of exposure estimates to job titles from early 1980s through 1993.	Larson et al., 2010a, b
Libby, MT mining and milling operations; McGill University cohort	Similar to Amandus et al. (1987a), except with 28 “occupation locations,” and conversion ratio = 4.6 for dry mill pre- and post 1964. Cumulative exposure reported in units of fibers/ml-years (equivalent to the unit of fibers/cc-years EPA is using for all studies).	McDonald et al., 2004, 2002, 1986a, b
Marysville, OH fertilizer production facility using Libby, MT vermiculite	Libby, MT vermiculite ore used in the plant from around 1960 to 1980. ^a Industrial hygiene monitoring began 1972 (based on fibers >5-µm long, diameter <3 µm, aspect ratio ≥3:1). Breathing zone samples used after 1976. Fiber analysis by PCM.	Lockey et al., 1984; Rohs et al., 2008

^aRohs et al. (2008) use 1963 as the beginning date of the use of Libby, MT vermiculite at the Marysville, OH plant, based on information from ATSDR (ATSDR, 2008, 2005). Lockey et al. (1984) used 1957 as the beginning date. Subsequent to these publications, additional information was used to conclude that the beginning date for use of Libby vermiculite ore was 1959 (see Appendix F).

NIOSH = National Institute for Occupational Safety and Health; PCM = phase contrast microscopy.

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

Source	Unit of measurement	Years	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

^aMillion particles per cubic foot of air, sampled by a midget impinger apparatus and examined by light microscopy.

^bFibers per cc of air drawn through a filter and examined under a phased contrast light microscope. Objects >5 μ and with an aspect ratio >3 were reported as fibers (see Section 2 for details).

^cMESA: U.S. Mining and Enforcement and Safety Administration (former name of MSHA).

^dMSHA: U.S. Mining and Safety Administration.

Source: Amandus et al. (1987a).

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The samples taken from specific work locations within the plant were used to estimate exposures in specific jobs and time periods based on professional consideration of temporal changes in facilities, equipment, and job activities. The analysis by McDonald et al. (1986a) was based on 28 occupation locations, while the work of Amandus et al. (1987a) was based on 25 occupation locations. These were defined to categorize tasks and locations across the mining, milling, and shipping operations to group like tasks, with respect to exposure potential, for evaluation. Both research groups established similar location operations for the Libby cohort. For the years after 1968, data from filter samples were available for all locations, and NIOSH researchers used the average (arithmetic mean) exposure when more than one sample was available for a given location or job task and time period. McDonald et al. (1986a) used an alternative procedure described by Oldham (1965) to estimate the mean of log-normal distributions.

For exposures occurring prior to 1968, different procedures had to be used to estimate exposures at the various locations because measures from sample filters were not available from this earlier period. McDonald et al. (1986a) estimated pre-1968 exposure measurements for 26 location operations; assumptions were made and estimates based on data from later years or related operations, although these assumptions are not stated by the authors. McDonald et al. (1986a) did recognize the uncertainty in these calculations, and, for four areas, (drilling, ore loading, river dock, and bagging plant), provided high and low estimates. Amandus et al. (1987a) interviewed company employees, considered relative exposure levels between locations

1 post 1968 employing best available judgment to estimate task specific exposure levels.
2 Amandus et al. (1987a) expanded the procedures described in McDonald et al. (1986a, 1987a) to
3 estimate pre-1968 exposures for four location operations (drilling, ore loading, river dock, and
4 bagging plant). “Low” and “high” estimates were generated using different assumptions; the
5 detailed results for the various assumptions were not presented, but the differences between them
6 were described by the authors as “slight,” and the results presented were based on the high
7 estimate of exposure. Their decisions and specific assumptions are detailed (Amandus et al.,
8 1987a). The authors acknowledge there is uncertainty in exposure estimates prior to 1968 for
9 many of these locations. They do note that variability in sample results for the midget impinger
10 was low and that, in general, sample variability was low for fiber air-sampling results for areas
11 where the greatest numbers of employees worked (mill, service area, loading and bagging).

12 To estimate dry mill exposures prior to 1967, when fiber counts from phase contrast
13 microscopy air samples began to be used to measure exposures, Amandus et al. (1987a)
14 established a conversion factor from total dust counts (mmpcf) to fiber counts (fibers/cc). The
15 conversion ratio was based on a comparison of 336 impinger samples taken in 1965–1969 and
16 81 filter samples taken in 1967–1971. Both sets of samples were taken in the dry mill. Using
17 different subsets of the samples (i.e., different years) resulted in ratios that ranged from
18 1.9 fibers/cc:1.0 mppcf to 11.5 fibers/cc:1.0 mppcf. The ratio based on the average fiber counts
19 from air samples (1967–1971) to the average total dust measurements in sample years
20 1965–1969 was 4.0 fibers/cc:1.0 mppcf. This was the ratio used in the analyses in the NIOSH
21 studies (Amandus et al., 1987a, b; Amandus and Wheeler, 1987) because it allowed for the use
22 of the greatest amount of data from overlapping time periods, while controlling for the reduced
23 exposure levels after 1971 where fiber count based on phase contrast microscopy—but not
24 midget impinger data—were available. This dust-to-fiber conversion factor was only used to
25 estimate exposures in the dry mill. The resulting exposure concentrations of 168 fibers/cc in
26 1963 and all prior years and 35.9 fibers/cc in 1964–1967 were applied to dry mill exposures
27 (Amandus et al., 1987a).

28 McDonald et al. (1986a) used a different procedure, based on the estimated reduction in
29 dust exposure with the installation of the ventilation system in 1964. Rather than develop a
30 direct dust-to-fiber conversion factor, they observed that total dust levels dropped approximately
31 4.6-fold after the installation of ventilation in the dry mill. Therefore, exposures in the dry mill
32 prior to 1965 were calculated as 4.6 times the fiber exposures measured by PCM between 1970
33 and 1974 (22.1 fibers/cc) resulting in estimated dry mill exposures of 101.5 fibers/cc prior to
34 1965 (McDonald et al., 1986a).

1 Exposure estimates for each location operation derived from sampling data and history of
2 changes in control measures were used to develop a job-exposure matrix that estimated exposure
3 in fibers/cc for each job code during several calendar time periods. Jobs were mapped to
4 operation/location based on estimated time spent in different job tasks, thus estimating an 8-hour
5 time-weighted average exposure for each job during several calendar time periods. Job histories
6 from date of first employment to 1982 were used with the job-exposure matrix to develop
7 cumulative exposure estimates for each worker.

8 9 **4.1.1.2.1. *Characteristics of historical fiber exposures***

10 The resulting exposure estimates presented by both research groups, and the job-exposure
11 matrices used in calculating cumulative exposure for the cohort are based on fiber counts by
12 phase contrast microscopy analysis of air filters. As discussed in Section 2 (see Text Box 2-1),
13 phase contrast microscopy analysis does not distinguish between fiber mineralogy or
14 morphology and all fibers $>5\ \mu\text{m}$ in length with an aspect ratio of 3:1 or greater are included.
15 Both researcher groups analyzed fibers available at the facility in order to identify the mineral
16 fibers in the air samples.

17 Transmission electron microscopy⁴ (TEM) analysis of airborne asbestos fibers indicated
18 a range of fiber morphologies—including long fibers with parallel sides, needlelike fibers, and
19 curved fibers (McDonald et al., 1986a). Of the fibers examined by TEM, $>62\%$ were $>5\ \mu\text{m}$ in
20 length and a wide range of dimensional characteristic were noted: length (1–70 μm), width
21 (0.1–2 μm), and aspect ratios from 3–100. Energy dispersive spectroscopy used to determine the
22 mineral analysis indicated that the fibers were in the actinolite-tremolite solid-solution series, but
23 sodium rich (McDonald et al., 1986a). This analysis is consistent with the current understanding
24 of amphibole asbestos found in the Libby mine (see Section 2.2.3).

25 At the time of their study, when exposure concentrations were reduced to generally less
26 than 1 fiber/cc, Amandus et al. (1987a) obtained eight air filters from area air samples collected
27 in the new wet mill and screening plant (provided by the mining company). These samples were
28 analyzed by phase contrast microscopy using the appropriate analytical method for the time
29 (NIOSH Physical and Chemical Analytical Method No. 239). From early method development
30 through current PCM analytical techniques, the Public Health Service, Occupational Safety and
31 Health Administration and NIOSH methods have defined a fiber by PCM analysis as having an
32 aspect ratio $\geq 3:1$ (Edwards and Lynch, 1967; NIOSH, 1994). Amandus et al. (1987a) reported

⁴ Transmission electron microscopy (TEM) utilizes a high-energy electron beam to irradiate the sample. This allows visualization of structures much smaller than can be 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: energy dispersive spectroscopy (EDS) and selected area electron diffraction (SAED).

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1 the dimensional characteristics of the fibers from these filters including aspect ratio, width, and
 2 length (see Table 4-3). Data for 599 fibers from the 8 area air samples collected in the wet mill
 3 and screening plant are provided. These data are limited in one sense by the minimum diameter
 4 and length cutoffs (>4.98- μm long, >0.44- μm wide, aspect ratio >3.0).⁵ Even with these greater
 5 than 10:1, with 16% greater than 50:1 aspect ratio. Only 7% of the fibers had a width greater
 6 than 0.88 μm , with one fiber reported of the 559 with a width greater than 1.76. It should be
 7 noted that as NIOSH was examining PCM visible fibers, these data do not give the full fiber-size
 8 distribution of Libby Amphibole asbestos fibers (see Section 2.2.3).

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Table 4-3. Dimensional characteristic 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	Percent (%)	Range	Total counted	Percent (%)	Range	Total counted	Percent (%)
4.98–7.04	54	9	0.44–0.62	406	68	5–10	24	4
7.04–9.96	109	18	0.62–0.88	151	25	10–20	176	29
9.96–14.08	107	18	0.88–1.24	27	5	20–50	305	51
14.08–19.91	111	19	1.24–1.76	14	2	50–100	84	14
19.91–28.16	90	15	1.76–2.49	0	0	>100	10	2
28.16–39.82	65	11	>2.49	1	0			
39.82–66	46	8						
66–88	10	2						
>88	7	1						

^aFibers were viewed and counted by Phase Contrast Microscopy.

Source: Amandus et al. (1987a).

11

12 **4.1.1.2.2. Descriptions of cohorts**

13 The cohort studies conducted in the 1980s were similar in terms of exposure assessment
 14 (as described in the previous section, Table 4-1), and other aspects of the study design (see
 15 Table 4-4). Both studies included workers who had worked for at least 1 year. Amandus and
 16 Wheeler (1987) included men hired before 1970 ($n = 575$), with follow-up through
 17 December 31, 1981. McDonald et al. (1986a) included men hired before 1963 ($n = 406$) with

⁵ See footnote 3, page 4–6.

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1 follow-up through 1983. A later analysis (McDonald et al., 2004) extended this follow-up
2 through 1999.

Table 4-4. Respiratory (lung) cancer mortality and exposure-response analyses based on studies of the vermiculite mine workers in Libby, MT^a

Reference(s)	Inclusion criteria and design details	Standardized mortality ratio (SMR) (95% CI)	Exposure-response analyses—lung cancer
Amandus and Wheeler, 1987	Men, hired before 1970, worked at least one year, follow-up through 1982 ($n = 575$); 161 deaths (159 with death certificates). Mean duration: 8.3 years (0 worked less than 1 year). Mean fiber-years: 200.3. 12 female workers not included in this analysis.	<i>No exclusions:</i> All cancer ($n = 38$) SMR: 1.3 (0.9, 1.8) Lung ($n = 20$) SMR: 2.2 (1.4, 3.4) <i>20 or more years since first hire (latency):</i> Lung ($n = 12$) SMR: 2.3 ($p < 0.05$)	<i>No exclusions:</i> <u>Cumulative Exposure</u> <u>n</u> <u>SMR (95% CI)^b</u> 0.0–49 fibers/cc-yrs 6 1.5 (not reported) 50–99 fibers/cc-yrs 2 1.6 (not reported) 100–399 fibers/cc-yrs 2 1.1 (not reported) ≥400 fibers/cc-yrs 10 5.8 (not reported, but $p < 0.01$) <i>20 or more years since first hire (20-year latency)</i> <u>Cumulative Exposure</u> <u>n</u> <u>SMR (95% CI)^b</u> 0.0–49 fibers/cc-yrs 2 0.85 (not reported) 50–99 fibers/cc-yrs 2 2.3 (not reported) 100–399 fibers/cc-yrs 1 1.1 (not reported) ≥400 fibers/cc-yrs 7 6.7 (not reported, but $p < 0.01$) In a linear regression analysis of data with at least 20 years latency, the results per fiber-year were: beta (standard error) = 0.60 (0.13) and 0.58 (0.08) for threshold and nonthreshold models. Using a survival (Cox) model, the corresponding estimate is 0.11 (0.04). All estimates are statistically significant ($p < 0.05$).
McDonald et al. 2004; McDonald et al., 1986a	Men, hired before 1963, worked at least one year ($n = 406$); 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 years (0 worked less than 1 year). Mean fiber-yrs: 144.6.	Respiratory ($n = 44$) SMR: 2.4 (1.7, 3.2)	<i>Excluding first 10 years of follow-up:</i> <u>Cumulative Exposure</u> <u>n</u> <u>RR (95% CI)^d</u> 0.0–11.6 fibers/cc-yrs 5 1.0 (referent) 11.7–25.1 fibers/cc-yrs 9 1.7 (0.58, 5.2) 25.2–113.7 fibers/cc-yrs 10 1.9 (0.63, 5.5) ≥113.8 fibers/cc-yrs 163 3.2 (1.2, 8.8) per 100 fibers/cc-yrs increase 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.

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1 A more recent analysis of the Libby, MT workers expanded the cohort to include all
2 workers, regardless of duration of employment (Sullivan, 2007). The total sample
3 ($n = 1,672$ white men) included 808 workers who had worked for less than 1 year. These
4 short-term workers had been excluded from the previous studies in Table 4-4. Analyses
5 presented in the report were based on follow-up from 1960–2001. This beginning point was
6 chosen because comparison rates for asbestosis, an outcome of interest, were not available before
7 1960 in the NIOSH Life-Table Analysis System, the analytic software used in the analysis
8 (Sullivan, 2007). Few deaths had occurred before 1960 (95 men dead or lost to follow-up before
9 1960 were excluded), so this exclusion criterion would not be expected to result in a substantial
10 loss of outcomes. Because mesothelioma was not coded separately until 1999, the mesothelioma
11 risk analysis is based on data from 1999–2001.

12 In the study by Sullivan (2007), comparison rates for standardized mortality ratio (SMR)
13 analyses were calculated from U.S. population cause-specific mortality data (limited to white
14 males) and adjusted for age and calendar year of follow-up (using 5-year groups). McDonald
15 et al. (2004) also used comparison rates from the U.S. population and included additional
16 analyses for the category of respiratory cancers using Montana population rates.

17 Larson et al. (2010a) reconstructed a worker cohort based on company records and
18 analyzed mortality risks through 2006. This study included 1862 workers; inclusion and
19 exclusion criteria are not stated, and, thus, it is not clear whether this analysis excluded females
20 or specific ethnic groups. The exposure assessment methodology was based on the methods
21 described by Amandus et al. (1987a)—without the modification used by Sullivan (2007).
22 Multiple causes of death (i.e., from any mention on the death certificate) were used, rather than
23 underlying cause of death. Because multiple causes of death are used, more than one cause of
24 death can be coded for an individual.

25 The studies of the Libby worker cohort by Amandus and Wheeler (1987), Sullivan
26 (2007), and Larson et al. (2010a) defined lung-cancer mortality based on more specific causes of
27 death codes compared to the broader classification of “all respiratory cancer” used by McDonald
28 et al. (1986a, 2004). For example, the International Classification of Diseases (ICD) codes used
29 for deaths due to cancers of the trachea, bronchus, and lung occurring during the applicable years
30 in the NIOSH cohort in Sullivan (2007) were ICD-7 162.0–162.1, 162.8, 163, ICD-8 162, and
31 ICD-9 162. In the first McDonald et al. (1986a) analysis, ICD-8 codes 160–163 for respiratory
32 cancer were used, which also included cancer of the larynx (ICD-8 code 161) and some types of
33 “other” respiratory cancers (ICD-8 code 160). The updated follow-up for 1999 included ICD-9
34 codes 160–165 for respiratory cancer, adding the “other” respiratory cancer group (ICD-9 codes
35 164 and 165). In the national Surveillance, Epidemiology, and End Results (SEER) cancer data

1 from 2003–2007, the age-adjusted mortality rate for cancer of the larynx was 1.2, compared to
2 52.5 per 100,000 person-years for lung and bronchial cancer (NCI, 2011). Thus, these additional
3 categories (larynx and “other” respiratory cancers) represent a relatively small proportion of
4 respiratory cancers, but they could be a source of some misclassification of the outcome if these
5 other cancers are not related to asbestos exposure.

6 The classification of mesothelioma was more difficult because of the lack of a unique
7 ICD code for mesothelioma prior to the 10th revision, implemented in the United States in 1999.
8 The updated NIOSH study by Sullivan (2007) identified 15 deaths for which mesothelioma was
9 mentioned on the death certificate. Only two of these deaths occurred between 1999 and 2001;
10 these were coded using the ICD-10 mesothelioma coding (C45). Larson et al. (2010a) classified
11 all death certificates listing mesothelioma as ICD-10 code C45. The updated McGill study
12 (McDonald et al., 2004) (with analysis through 1998) noted that the classification of
13 mesothelioma was based on a nosologist’s review of death certificates; only 5 of the 12 cases
14 classified as mesothelioma had a cause of death listed as pleural cancer (ICD-9 code 163).

16 **4.1.1.3. Cancer Mortality Risk**

17 **4.1.1.3.1. Lung cancer**

18 The results within and among the papers in these two sets of studies (Amandus and
19 Wheeler, 1987; Sullivan, 2007; Larson et al. 2010a; McDonald et al., 1986a, 2004) show similar
20 effects in terms of the increased risk seen for lung (or respiratory) cancer (see Table 4-4).
21 Exposure-response analyses from these studies demonstrated increasing mortality with
22 increasing exposure, using categorical and continuous measures of exposure, different lag
23 periods, and different exposure metrics. Because of the congruence in results and overlapping of
24 study participants among these studies, the most recent studies are discussed in detail below.

25 The analysis of McDonald et al. (2004) is limited to 406 male workers who were hired
26 before 1963 and who were employed for at least 1 year. The mean duration of work was
27 8.7 years. Cause of death data were obtained from the National Death Index for deaths from
28 1983 to 1998 and were based on ICD-8 coding by a nosologist using death certificates obtained
29 for deaths before 1983. Expected rates were based on age-, race- and sex- specific rates. A total
30 of 44 deaths due to respiratory cancers were observed, for an SMR = 2.4 (95% confidence
31 interval [CI]: 1.7, 3.2). A pattern of increasing mortality with increasing cumulative exposure
32 was seen, with relative risks (RRs) of 1.0 (referent), 1.7, 1.9, and 3.2 in categories of 0.0–11.6,
33 11.7–25, 25.2–113.7, and ≥ 113.8 fibers/cc-years, respectively (see Table 4-4). The estimated
34 linear increase in RR of respiratory cancer risk per 100 fibers/cc-years cumulative exposure was
35 0.36 (95% CI: 0.03, 1.2) ($p = 0.02$). McDonald et al. (2004) reported that similar results were

1 obtained with measures of exposure intensity and measures of residence-weighted exposure, but
2 the data were not presented in the paper.

3 Sullivan (2007) included 1,672 white male workers who were alive in 1960 or hired after
4 1960. There was no minimum duration of employment required for inclusion in this analysis,
5 and approximately 50% of the cohort ($n = 808$) had worked less than 1 year. Mortality follow-up
6 was conducted through 2001, with 767 identified deaths. The exposure assessment protocol was
7 based on that described by Amandus et al. (1987a), with a modification to the estimated intensity
8 of exposure to laborers and to those with “unknown” jobs. Sullivan (2007) assigned
9 weighted-average exposure for all unskilled jobs in a department (if known) during a calendar
10 time period, rather than lower mill yard exposure used by Amandus et al. (1987a). The weights
11 are based on the number of workers assigned to unskilled jobs during the same calendar time
12 period. In the Sullivan (2007) follow-up, SMRs, using underlying cause-of-death data (based on
13 death certificates) obtained through the National Death Index and from individual states, and
14 expected mortality based on national age-, race-, and sex-specific rates, were calculated. Using a
15 15-year exposure lag, SMRs were increased for lung cancer ($n = 89$, $SMR = 1.7$, 95% CI: 1.4,
16 2.1) and for all cancer mortality ($n = 202$, $SMR = 1.4$, 95% CI: 1.2, 1.6) (see Table 4-4).
17 Additionally, an internal referent group was used for analyses of risk in relation to cumulative
18 exposure and duration. The results of these internal analyses are presented as standardized rate
19 ratios (SRR) for white men, controlling for age group. Increasing risks across categories of
20 cumulative exposure and duration were observed with both types of analyses, indicating a
21 positive exposure-response relationship. The SMR estimates for lung-cancer mortality were 1.5,
22 1.6, 1.8, and 1.9 in the 1- to 4.49-, 4.5- to 22.9-, 23.0- to 99.0-, and ≥ 100 fibers/cc-year exposure
23 categories, respectively. The SRR estimates were 1.0, 1.1, 1.4, and 1.5, respectively, across
24 these same exposure categories (see Table 4-4). For comparison to the earlier work by
25 McDonald et al. (1986a), an SMR was provided for all respiratory cancer in those employed at
26 least 1 year ($SMR = 2.0$, 95% CI: 1.5–2.5). For the full cohort employed at least 1 day, the SMR
27 for all respiratory cancer was 1.7 (95% CI: 1.4–2.1) (Sullivan, 2007).

28 Amandus and Wheeler (1987) provide some information on the smoking history of a
29 sample of 161 male workers employed during 1975–1982 with at least 5 years of employment in
30 the Libby cohort study and comparison data based on surveys conducted in the United States
31 from 1955–1978. Among the workers, 35% were current smokers, and 49% were former
32 smokers. This smoking information was obtained from questionnaires the company
33 administered to workers after 1975. Assuming the definitions are similar to those of the national
34 surveys, however, the prevalence of current smokers is similar in the worker cohort compared to
35 the U.S. white male population data (ranging from 37.5–41.9% current smokers between 1975

1 and 1978). The only year in this range with data on former smokers in the national survey is
2 1975, and, at that time, the prevalence of former smokers in the population data was 29.2%,
3 about 20% lower than among the workers. Using an estimated RR of lung cancer of 14 among
4 smokers, Amandus and Wheeler (1987) estimated that the difference in smoking rates between
5 workers and the comparison population could have resulted in a 23% increase in the observed
6 risk ratio and commented that the increased risk observed in the lower dose range
7 (<50 fiber-years) could be the result of confounding by smoking status.

8 Smoking patterns in the U.S. population changed considerably over the period
9 corresponding to the data reported by Amandus and Wheeler (1987). In the National Health
10 Interview Surveys conducted between 1974 and 1983, the prevalence of smoking in males
11 age 20 and older decreased from 42.1 to 35.5% (DHHS, 1989, p.269). In addition, the
12 prevalence of former smokers can depend on the definition used. Based on 1986 survey data, the
13 percentage of adults age 17 and older classified as former smokers varied between 14.7 and
14 25.8% using different definitions for time since last smoked (e.g., from quitting 5 or more years
15 ago to quitting within the past 3 months) (DHHS, 1989). Thus, given the lack of information
16 pertaining to the period in which smoking information was collected and the specifics of the
17 sources that were used, EPA concludes there is considerable uncertainty regarding the evidence
18 for differences in smoking rates between the workers and the external comparison population.

19 Larson et al. (2010a) evaluated multiple causes of death, and, therefore, more than one
20 cause of death can be coded for an individual. A total of 104 lung or bronchus cancer deaths
21 were observed, for an SMR of 1.6 (95% CI: 1.3, 2.0) using an external comparison of United
22 States cause of death data from 1960 to 2002 (Larson et al., 2010a). A higher risk was seen in
23 the higher cumulative exposure categories using Cox proportional hazards modeling with an
24 internal referent group: relative risk 1.0 (referent), 1.1 (95% CI: 0.6, 2.1), 1.7 (95% CI: 1.0, 3.0),
25 and 3.2 (95% CI: 1.8, 5.3) respectively, for <1.4 (referent), 1.4 to <8.6, 8.6 to <44.0 and ≥ 44.0
26 fibers/cc-years. Larson et al. (2010a) used data from a health screening program conducted in
27 Libby by ATSDR in 2000–2001 (described in Section 4.1.2.2) pertaining to smoking history to
28 estimate that the proportion of smokers ranged from 50% to 66% in the unexposed group
29 (defined as exposure <8.6 fibers/cc-years) and between 66% and 85% among the exposed
30 (defined as ≥ 8.6 fibers/cc-years). Larson et al. (2010a) used these estimates in a Monte Carlo
31 simulation to estimate the potential bias in lung cancer risks that could have been introduced by
32 differences in smoking patterns. The bias-adjustment factor ($RR_{unadjusted}/RR_{adjusted} = 1.3$) reduced
33 the overall RR estimate for lung cancer from 2.4 to 2.0.

34

1 4.1.1.3.2. *Mesothelioma*

2 Data pertaining to mesothelioma risk from the available studies are summarized in
3 Table 4-5. McDonald et al. (2004) presented dose-response modeling of mesothelioma risk
4 based on 12 cases. Using Poisson regression, the mesothelioma mortality rate across increasing
5 categories of exposure was compared to the rate in the lowest exposure category. Note that the
6 referent group was also at excess risk of dying from mesothelioma; that is, one to three cases of
7 mesothelioma were observed in the referent group, depending on the exposure index. Three
8 exposure indices were used in analysis: average intensity over the first 5 years of employment,
9 cumulative exposure, and residence-weighted cumulative exposure. Because of the requirement
10 for 5 years of employment data, 199 individuals (including three mesothelioma cases) were
11 excluded from the analysis of average intensity. The residence-weighted cumulative exposure
12 was based on the summation of exposure by year, weighted by years since the exposure. This
13 metric gives greater weight to exposures that occurred a longer time ago. Although evidence of
14 an excess risk of dying from mesothelioma was seen in all groups, there was little evidence of
15 increasing RR with increasing average intensity or cumulative exposure. For the
16 residence-weighted cumulative exposure, an RR of 1.57 was observed among those with
17 500.1–1,826.8 fibers/cc-years exposure, and an RR of 1.95 was observed among workers with
18 higher residence-weighted cumulative exposure. Sullivan (2007) identified 15 deaths from
19 mesothelioma through a manual review of death certificates, with 14 classified as “pleural or
20 unspecified,” and 1 classified as “peritoneal.” Only two of these deaths occurred between 1999
21 and 2001, the period for which comparison data using the ICD-10 classification criteria were
22 available. Based on these two mesothelioma deaths, the SMR was 14.1 (95% CI: 1.8, 54.4).
23 Larson et al. (2010a) identified 19 mesothelioma deaths (coding any mention of mesothelioma
24 on the death certificate as the ICD-10 classification of C45). Comparison data were based on
25 multiple-causes-of-death data (1960 to 2002). The SMR for mesothelioma was 94.8 (95% CI:
26 57.0, 148.0), and an increasing risk was seen across quartiles of exposure (see Table 4-5). The
27 comparison rates for the SMR analysis are based on multiple cause of death data for the U.S.
28 population from 1960–2002; only a small portion of this period included the ICD-10 coding
29 scheme for mesothelioma. Thus, the expected rates could be underestimated, biasing the effect
30 estimates upward.

31

Table 4-5. 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 year, follow-up through 1982 (<i>n</i> = 575); 161 deaths (159 with death certificates). Mean duration: 8.3 years (0 worked less than 1 year). Mean fiber-years: 200.3. Twelve female workers not included in this analysis.	2 mesothelioma deaths observed (hired in 1946, 33 years latency, exposure >300 fibers/cc-years); 1.2% of all deaths
McDonald et al. 2004; McDonald et al., 1986a	Men, hired before 1963, worked at least 1 year (<i>n</i> = 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 years (0 worked less than 1 year). Mean fiber-yrs: 144.6.	12 mesothelioma deaths observed; 4.2% of all deaths <i>Excluding first 10 years of follow-up:</i> <u>Cumulative Exposure</u> <i>n</i> <u>RR (95% CI)^b</u> 0.0–11.6 fibers/cc-yrs 1 1.0 (referent) 11.7–25.1 fibers/cc-yrs 4 3.7 (0.41, 33.5) 25.2–113.7 fibers/cc-yrs 3 3.4 (0.35, 33.2) ≥113.8 fibers/cc-yrs 4 3.7 (0.41, 33.2) per 100 fibers/cc-yrs increase 0.10 (<0, 1.81) <i>(p</i> > 0.20) <u>Intensity Category</u> <i>n</i> <u>RR (95% CI)^b</u> 0.0–11.6 fibers/cc-yrs 1 1.0 (referent) 11.7–25.1 fibers/cc-yrs 4 3.4 (0.37, 30.9) 25.2–113.7 fibers/cc-yrs 2 2.3 (0.21, 26.1) ≥113.8 fibers/cc-yrs 2 2.1 (0.19, 23.9) per 100 fibers/cc-yrs increase 0.02 (<0, 1.08) <i>(p</i> > 0.20) <u>Residence-weighted</u> <i>n</i> <u>RR (95% CI)^b</u> 0.0–25.1 fibers/cc-yrs 3 1.0 (referent) 25.2–113.7 fibers/cc-yrs 4 1.57 (0.35, 7.07) ≥113.8 fibers/cc-yrs 5 1.95 (0.41, 8.51) per 100 fibers/cc-yrs increase 0.03 (<0, 6.4) <i>(p</i> > 0.20)
Sullivan, 2007	White men, enumerated in 1982, alive in 1960 or hired after 1960, worked at least 1 day, follow-up 1960–2001 (<i>n</i> = 1,672); 767 deaths (95% with known cause of death). Mean duration: 4.0 years (808, ~50% worked less than 1 year). Median fibers/cc-years: 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 <i>N</i> = 2 for 1999–2001: SMR: 15.1 (95% CI: 1.8, 54.4) Pleural (<i>n</i> = 4) SMR: 23.3 (95% CI: 6.3, 59.5)

This document is a draft for review purposes only and does not constitute Agency policy.

Table 4-5. Mesothelioma mortality risk based on studies of the vermiculite mine workers in Libby, MTa (continued)

Reference(s)	Inclusion criteria and design details	Results																		
Larson et al. (2010a)	Inclusion criteria not described ($n = 1,862$); follow-up through 2006; 952 deaths (80% with known cause of death). Median duration: 0.8 years; Median fibers/cc-yr = 4.3. Immediate and underlying cause of death data (i.e., multiple causes of death) from death certificates or National Death Index-Plus.	19 mesothelioma deaths observed SMR: 94.8 (95% CI: 57, 248) <i>20 year exposure lag:</i> <u>Cumulative Exposure</u> <table border="1"> <thead> <tr> <th></th> <th><i>n</i></th> <th>RR (95% CI)^c</th> </tr> </thead> <tbody> <tr> <td><1.4 fibers/cc-yrs</td> <td>1</td> <td>1.0 (referent)</td> </tr> <tr> <td>1.4 to <8.6 fibers/cc-yrs</td> <td>2</td> <td>1.9 (0.31, 13.6)</td> </tr> <tr> <td>8.6 to <440 fibers/cc-yrs</td> <td>5</td> <td>4.5 (0.8, 24.6)</td> </tr> <tr> <td>≥44.0 fibers/cc-yrs</td> <td>11</td> <td>17.1 (3.7, 78.1)</td> </tr> <tr> <td>per 100 fibers/cc-yrs increase</td> <td></td> <td>1.15 (1.03, 1.28) ($p = 0.0134$)</td> </tr> </tbody> </table>		<i>n</i>	RR (95% CI) ^c	<1.4 fibers/cc-yrs	1	1.0 (referent)	1.4 to <8.6 fibers/cc-yrs	2	1.9 (0.31, 13.6)	8.6 to <440 fibers/cc-yrs	5	4.5 (0.8, 24.6)	≥44.0 fibers/cc-yrs	11	17.1 (3.7, 78.1)	per 100 fibers/cc-yrs increase		1.15 (1.03, 1.28) ($p = 0.0134$)
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^aIncludes miners, millers, and processors; workers in the screening plant, loading docks, and expansion plants; and office workers.

^bIn McDonald et al. (2004), the RR is based on Poisson analysis using an internal referent group.

^cIn 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.

1 **4.1.1.3.3. Other cancers**

2 Larson et al. (2010a) presented data on cancers other than respiratory tract and
3 mesothelioma. The category of malignant neoplasms of digestive organs and peritoneum
4 included 39 observed deaths, for an SMR of 0.8 (95% CI: 0.6, 1.1). No risk in relation to
5 asbestos exposure was seen with a 20-year lag. The potential for underascertainment of specific
6 causes of death should be noted, however, given the 10% loss to follow-up and missing cause of
7 death data for 9% of the identified deaths.

8
9 **4.1.1.3.4. Summary of cancer mortality risk in Libby, MT vermiculite mining operation**
10 **workers**

11 The studies conducted in the 1980s (Amandus and Wheeler, 1987; McDonald et al.,
12 1986a) as well as the extended follow-up studies published in more recent years (Sullivan, 2007;
13 McDonald et al., 2004; Larson et al., 2010) provide evidence of an increased risk of lung-cancer
14 mortality and of mesothelioma mortality among the workers in the Libby vermiculite mining and
15 processing operations. The lung cancer analyses using an internal referent group in the larger
16 follow-up studies (Larson et al., 2010a; Sullivan, 2007; McDonald et al., 2004) observed
17 increasing risks with increasing cumulative exposure exposures when analyzed using quartiles or
18 as a continuous measure. Increased risks are also seen in the studies reporting analyses using an

1 external referent group (i.e., standardized mortality ratios [Sullivan, 2007; Amandus and
2 Wheeler, 1987; McDonald et al., 1986a]).

3 **4.1.1.4. *Noncancer Effects: Respiratory and Cardiovascular Disease***

4 **4.1.1.4.1. *Asbestosis and other nonmalignant respiratory disease mortality***

5 The studies described previously also reported noncancer mortality data, with a specific
6 focus on respiratory diseases (see Table 4-6). In Sullivan (2007), the SMR for asbestosis
7 (ICD-9 code 501) was 166 (based on $n = 22$, underlying cause of death compared to a U.S. white
8 male referent group). In Larson et al. (2010a), the SMR was 143 (95% CI: 111, 181), based on
9 69 observed asbestosis-related deaths using multiple-causes-of-death data. Increasing
10 cumulative exposure was observed to increase the risk for asbestosis mortality in both of these
11 analyses (see Table 4-6). A two- to threefold increase was also seen for other categories of
12 nonmalignant respiratory disease in Larson et al. (2010a), with an SMR of 2.4 (95% CI: 2.2, 2.6)
13 for all nonmalignant respiratory disease, and SMR = 2.8 (95% CI: 2.3, 3.4) for diseases other
14 than asbestosis, chronic obstructive pulmonary disease, and silicosis. These results are similar to
15 the nonmalignant respiratory disease mortality data from studies of this cohort using underlying
16 cause-of-death data. A markedly higher risk of nonmalignant respiratory disease mortality was
17 also observed in the cumulative exposure category of ≥ 300 or ≥ 400 fibers/cc-years, respectively
18 in Sullivan (2007) and Amandus and Wheeler (1987). Larson et al. (2010) used a Monte Carlo
19 simulation to estimate the potential bias in nonmalignant respiratory disease risk that could have
20 been introduced by differences in smoking patterns between exposed and unexposed workers in
21 the cohort. The bias-adjustment factor ($RR_{\text{unadjusted}}/RR_{\text{adjusted}} = 1.2$) reduced the overall RR
22 estimate for nonmalignant respiratory mortality from 2.1 to 1.8.

23

Table 4-6. Nonmalignant respiratory mortality studies of the vermiculite mine workers in Libby, MT^a

Reference(s)	Respiratory disease (SMR, 95% CI)	Dose-response analyses: Nonmalignant respiratory diseases and asbestosis																																											
Amandus and Wheeler, 1987 (NIOSH)	<p><i>No exclusions:</i> Nonmalignant respiratory diseases ($n = 20$) SMR: 2.4 (1.5, 3.8)</p> <p><i>20 year latency:</i> Nonmalignant respiratory diseases ($n = 12$) SMR: 2.5 ($p < 0.05$)</p>	<p><i>No exclusions:</i> Nonmalignant respiratory diseases</p> <table border="1"> <thead> <tr> <th>Cumulative Exposure</th> <th>n</th> <th colspan="2">SMR (95% CI)^b</th> </tr> </thead> <tbody> <tr> <td>0.0–49 fibers/cc-yrs</td> <td>8</td> <td colspan="2">2.2 (not reported)</td> </tr> <tr> <td>50–99 fibers/cc-yrs</td> <td>2</td> <td colspan="2">1.7 (not reported)</td> </tr> <tr> <td>100–399 fibers/cc-yrs</td> <td>3</td> <td colspan="2">1.8 (not reported)</td> </tr> <tr> <td>≥400 fibers/cc-yrs</td> <td>10</td> <td colspan="2">4.0 (not reported, but $p < 0.01$)</td> </tr> </tbody> </table> <p><i>20 or more years since first hire (latency):</i> Nonmalignant respiratory diseases</p> <table border="1"> <thead> <tr> <th>Cumulative Exposure</th> <th>n</th> <th colspan="2">SMR (95% CI)^b</th> </tr> </thead> <tbody> <tr> <td>0.0–49 fibers/cc-yrs</td> <td>7</td> <td colspan="2">3.3 (not reported, but $p < 0.05$)</td> </tr> <tr> <td>50–99 fibers/cc-yrs</td> <td>2</td> <td colspan="2">2.8 (not reported)</td> </tr> <tr> <td>100–399 fibers/cc-yrs</td> <td>0</td> <td colspan="2">0 (not reported)</td> </tr> <tr> <td>≥400 fibers/cc-yrs</td> <td>3</td> <td colspan="2">2.8 (not reported)</td> </tr> </tbody> </table>				Cumulative Exposure	n	SMR (95% CI) ^b		0.0–49 fibers/cc-yrs	8	2.2 (not reported)		50–99 fibers/cc-yrs	2	1.7 (not reported)		100–399 fibers/cc-yrs	3	1.8 (not reported)		≥400 fibers/cc-yrs	10	4.0 (not reported, but $p < 0.01$)		Cumulative Exposure	n	SMR (95% CI) ^b		0.0–49 fibers/cc-yrs	7	3.3 (not reported, but $p < 0.05$)		50–99 fibers/cc-yrs	2	2.8 (not reported)		100–399 fibers/cc-yrs	0	0 (not reported)		≥400 fibers/cc-yrs	3	2.8 (not reported)	
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McDonald et al. 2004; McDonald et al., 1986a (McGill)	<p>Nonmalignant respiratory diseases ($n = 51$) SMR: 3.1 (2.3, 4.1)</p>	<p><i>Excluding first 10 years of follow-up:</i> Nonmalignant respiratory diseases</p> <table border="1"> <thead> <tr> <th>Cumulative Exposure</th> <th>n</th> <th colspan="2">RR (95% CI)^d</th> </tr> </thead> <tbody> <tr> <td>0.0–11.6 fibers/cc-yrs</td> <td>5</td> <td colspan="2">1.0 (referent)</td> </tr> <tr> <td>11.7–25.1 fibers/cc-yrs</td> <td>13</td> <td colspan="2">2.5 (0.88, 7.2)</td> </tr> <tr> <td>25.2–113.7 fibers/cc-yrs</td> <td>14</td> <td colspan="2">2.6 (0.93, 7.3)</td> </tr> <tr> <td>≥113.8 fibers/cc-yrs</td> <td>19</td> <td colspan="2">3.1 (1.2, 8.4)</td> </tr> <tr> <td>per 100 fibers/cc-yrs</td> <td>–</td> <td colspan="2">0.38 (0.12, 0.96) ($p = 0.0001$)</td> </tr> </tbody> </table>				Cumulative Exposure	n	RR (95% CI) ^d		0.0–11.6 fibers/cc-yrs	5	1.0 (referent)		11.7–25.1 fibers/cc-yrs	13	2.5 (0.88, 7.2)		25.2–113.7 fibers/cc-yrs	14	2.6 (0.93, 7.3)		≥113.8 fibers/cc-yrs	19	3.1 (1.2, 8.4)		per 100 fibers/cc-yrs	–	0.38 (0.12, 0.96) ($p = 0.0001$)																	
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Sullivan, 2007 (NIOSH)	<p><i>15 year exposure lag:</i> Asbestosis ($n = 22$) SMR: 166 (104, 251)</p> <p>Nonmalignant respiratory diseases ($n = 111$) SMR: 2.4 (2.0, 2.9)</p> <p>Chronic obstructive pulmonary disease ($n = 53$) SMR: 2.2 (1.7, 2.9)</p> <p>Other nonmalignant respiratory diseases ($n = 19$) SMR: 2.7 (1.6, 4.2)</p>	<p><i>15 year exposure lag:</i> Asbestosis</p> <table border="1"> <thead> <tr> <th>Cumulative Exposure</th> <th>n</th> <th>SMR (95% CI)^b</th> <th>SRR (95% CI)^c</th> </tr> </thead> <tbody> <tr> <td>0.0–49.9 fibers/cc-yrs</td> <td>3</td> <td>37 (7.5, 122)</td> <td>1.0 (referent)</td> </tr> <tr> <td>50.0–249.9 fibers/cc-yrs</td> <td>8</td> <td>213 (91.6, 433)</td> <td>7.3 (1.9, 28.5)</td> </tr> <tr> <td>≥250 fibers/cc-yrs</td> <td>11</td> <td>749 (373, 1,368)</td> <td>25.3 (6.6, 96.3)</td> </tr> </tbody> </table> <p>linear trend test ($p < 0.01$)</p> <p><i>15 year exposure lag:</i> Nonmalignant respiratory diseases</p> <table border="1"> <thead> <tr> <th>Cumulative Exposure</th> <th>n</th> <th>SMR (95% CI)^b</th> <th>SRR (95% CI)^c</th> </tr> </thead> <tbody> <tr> <td>0.0–4.49 fibers/cc-yrs</td> <td>18</td> <td>1.8 (1.1, 2.8)</td> <td>1.0 (referent)</td> </tr> <tr> <td>4.5–19.9 fibers/cc-yrs</td> <td>24</td> <td>2.0 (1.3, 3.0)</td> <td>1.2 (0.6, 2.3)</td> </tr> <tr> <td>20.0–84.9 fibers/cc-yrs</td> <td>26</td> <td>2.2 (1.5, 3.3)</td> <td>1.5 (0.8, 2.9)</td> </tr> <tr> <td>85.0–299.9 fibers/cc-yrs</td> <td>20</td> <td>2.6 (1.6, 4.0)</td> <td>1.4 (0.7, 2.7)</td> </tr> <tr> <td>≥300 fibers/cc-yrs</td> <td>23</td> <td>4.8 (3.1, 7.3)</td> <td>2.8 (1.3, 5.7)</td> </tr> </tbody> </table>				Cumulative Exposure	n	SMR (95% CI) ^b	SRR (95% CI) ^c	0.0–49.9 fibers/cc-yrs	3	37 (7.5, 122)	1.0 (referent)	50.0–249.9 fibers/cc-yrs	8	213 (91.6, 433)	7.3 (1.9, 28.5)	≥250 fibers/cc-yrs	11	749 (373, 1,368)	25.3 (6.6, 96.3)	Cumulative Exposure	n	SMR (95% CI) ^b	SRR (95% CI) ^c	0.0–4.49 fibers/cc-yrs	18	1.8 (1.1, 2.8)	1.0 (referent)	4.5–19.9 fibers/cc-yrs	24	2.0 (1.3, 3.0)	1.2 (0.6, 2.3)	20.0–84.9 fibers/cc-yrs	26	2.2 (1.5, 3.3)	1.5 (0.8, 2.9)	85.0–299.9 fibers/cc-yrs	20	2.6 (1.6, 4.0)	1.4 (0.7, 2.7)	≥300 fibers/cc-yrs	23	4.8 (3.1, 7.3)	2.8 (1.3, 5.7)
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Table 4-6. Nonmalignant respiratory mortality studies of the vermiculite mine workers in Libby, MT^a (continued)

Reference(s)	Respiratory disease (SMR, 95% CI)	Dose-response analyses: Nonmalignant respiratory diseases and asbestosis			
Larson et al., 2010a	Asbestosis (<i>n</i> = 69) SMR: 143 (111, 181)	<i>20 year exposure lag:</i> Asbestosis			
		<u>Cumulative Exposure</u>	<u><i>n</i></u>	<u>SMR (95% CI)^b</u>	<u>RR (95% CI)^e</u>
	Nonmalignant respiratory diseases (<i>n</i> = 425) SMR: 2.4 (2.2, 2.6)	<1.4 fibers/cc-yrs	4	(not reported)	1.0 (referent)
		1.4– <8.6 fibers/cc-yrs	8	(not reported)	2.8 (1.0, 7.6)
		86– <44.0 fibers/cc-yrs	25	(not reported)	8.0 (3.2, 19.5)
		≥44.0 fibers/cc-yrs	32	(not reported)	11.8 (4.9, 28.7)
	Chronic obstructive pulmonary disease (<i>n</i> = 152) SMR: 2.2 (1.9, 2.6)	Per 100 fibers/cc-yrs increase			1.18 (1.12, 1.23) (<i>p</i> < 0.001)
		<i>20 year exposure lag:</i> Nonmalignant respiratory diseases			
	Other nonmalignant respiratory (<i>n</i> = 120) SMR: 2.8 (2.3 3.4)	<u>Cumulative Exposure</u>	<u><i>n</i></u>	<u>SMR (95% CI)^b</u>	<u>RR (95% CI)^e</u>
		<1.4 fibers/cc-yrs	43	(not reported)	1.0 (referent)
		1.4– <8.6 fibers/cc-yrs	46	(not reported)	1.4 (0.9, 2.1)
		86– <44.0 fibers/cc-yrs	56	(not reported)	1.8 (1.3, 2.7)
		≥44.0 fibers/cc-yrs	58	(not reported)	2.5 (1.7, 3.6)
		Per 100 fibers/cc-yrs increase			1.08 (1.03, 1.13) (<i>p</i> = 0.0028)

^aIncludes miners, millers, and processors; workers in the screening plant, loading docks, and expansion plants; and office workers.

^bSMR based on external referent group.

^cIn 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-years 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.

^dIn McDonald et al. (2004), the RR is based on Poisson analysis using internal referent group.

^eIn Larson et al. (2010), 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.

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3 **4.1.1.4.2. Radiographic abnormalities**

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Respiratory disease risk is also evidenced by chest radiographs showing pleural and parenchymal abnormalities in the Libby, MT worker cohorts (see Table 4-7). Two of these studies were conducted in the 1980s and were based on X-rays of a subset of workers taken for either an annual workplace screening (Amandus et al., 1987b) or as part of a study examination (McDonald et al., 1986b). The subset of McDonald et al. (1986b) included 164 workers currently employed at the Libby facility, 80 former employees, and 47 area residents without known dust exposure. The subset selected by Amandus et al. (1987b) included workers with at least 5 years tenure who had worked at Libby at some time during 1975–1982. The most recent

1 X-ray film for each worker, which NIOSH obtained from the Libby hospital that performed the
2 screening, was independently read by three qualified readers using the International Labor Office
3 (ILO) classification system. For the analysis, the classification indicating pleural abnormalities
4 by at least two of the three readers was used to determine the presence of pleural abnormalities,
5 while the median reading was used to determine the profusion category of small opacities. In the
6 McDonald et al. (1986b) study, all three readings agreed for about 90% of the chest X-rays that
7 showed evidence of pleural calcification, obliteration of the costophrenic angle, and pleural
8 thickening on the diaphragm. Similarly, all three readings agreed for about 80% of chest X-rays
9 that showed evidence of small opacities, pleural plaques, or diffuse thickening. Amandus et al.
10 (1987b) provided a more detailed breakdown of the correspondence between readers for the
11 rating of small opacities (by category). The prevalences of any opacities (category 1/0 or more)
12 were 10, 16, and 10% for Readers A, B, and C. This difference among raters was similar to that
13 seen in other studies. Other design details are described in Table 4-7.

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 on July 1, 1983 ($n = 164$). Former male employees living within 200 miles; hired before 1963 ($n = 80$), worked at least 1 year (80 participants from 110 eligible); 43 had a previous X-ray. Men without known dust exposure ($n = 47$); X-rays taken for other reasons (mostly employment related) at same place during study period; 24 had a previous X-ray. Data from nine women employed on July 1, 1983 not included in this report.	Pleural thickening of the chest wall observed in 15.9% of current employees and 52.5% of past employees. Small opacities ($\geq 1/0$) observed in 9.1% of current employees and 37.5% of past employees. Both abnormalities increased with age. Age-adjusted and age-stratified (>60 years old) analyses showed increasing risk of both abnormalities with increasing cumulative exposure.
Amandus et al. (1987b)	Men, employed during 1975–1982 with at least 5 years tenure ($n = 191$); 184 with previous chest X-rays; 121 with smoking questionnaires. Annual radiographs taken since 1964; most recent radiograph evaluated. Mean employment duration: 14 years. Mean fiber-years: 123 (all workers), 119 (workers with radiographs).	Pleural thickening of the chest wall observed in 13%. Small opacities ($\geq 1/0$) observed in 10%. Both abnormalities increased with increasing cumulative exposure.
Whitehouse (2004)	$n = 123$ (86 former employees of W.R. Grace & Co., 27 family members of employees, and 10 Libby residents with only environmental exposures). Average age: 66 years; 80% males. Fifty-six patients had interstitial abnormalities at profusion category 0/1 or 1/0. Chest X-rays and/or HRCT scans; pulmonary function tests (FVC, TLC, and DLCO).	Average yearly loss ($n = 123$): FVC 2.2% TLC 2.3% DLCO 3.0%
Larson et al. (2010b)	Men with 2 or more X-rays spanning a period of 4 or more years. Most recent X-ray read independently by each of 3 NIOSH B-readers; each series of X-rays (for a given participant) then read by the panel for a consensus determination of time of first appearance of the detectable abnormality ($n = 84$).	Latency (time from hire to observed change), median (25 th , 75 th percentile) years: Localized pleural thickening 8.6 (1.4, 14.7) Any pleural calcification 17.5 (8.1, 24.2) Diffuse pleural thickening 27.0 (10.7, 29.8)

DLCO = single breath carbon monoxide diffusing capacity; FVC = forced vital capacity; TLC = total lung capacity, HRCT = high resolution computed tomography.

1 Although both research groups utilized the ILO 1980 guidelines, McDonald et al (1986b)
2 reported pleural thickening on the chest wall (both pleural plaques and diffuse) but excluding
3 other sites. Amandus et al (1987b) report “any pleural change” (both pleural plaques and
4 diffuse, defined as “...any unilateral or bilateral pleural change, which included pleural plaque,
5 diffuse pleural thickening of the chest wall, diaphragm or other site, but excluded costophrenic

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1 angle obliteration...”), which included all sites as well as a second category of “pleural
2 thickening of the chest wall.”

3 Amandus et al. (1987b) reported pleural thickening of the chest wall in 13% and small
4 opacities ($\geq 1/0$) in 9.1% of current employees. Similar data were reported by McDonald et al.
5 (1986b), with 15.9 and 10% with pleural thickening of the chest wall and small opacities,
6 respectively. In both studies, prevalence of these abnormalities increased with increasing
7 cumulative exposure. McDonald et al. (1986b) also included 80 former employees in their
8 study. The prevalence of pleural thickening of the chest wall (52.5%) and small opacities
9 (37.5%) was higher in these workers compared with current workers. These groups differed by
10 age, however, with only one of the 80 former workers < age 40 years compared with 80 of
11 164 current workers. Within the age category 40 to 59 years, the prevalences of chest wall
12 pleural thickening were 20.3 and 40.0% in current and former employees, respectively, and, in
13 the ≥ 60 -years age group, the prevalences were 40.0 and 61.2%, respectively. The authors
14 attribute these differences in prevalence rates in current compared with former employees to
15 differences in cumulative exposure. Among the 47 area residents without known dust exposure
16 in an occupational setting in the study by McDonald et al. (1986b), the prevalence of pleural
17 thickening was 8.5% ($n = 4$), and the prevalence of small opacities was 2.1% ($n = 1$).

18 Both Amandus et al. (1987b) and McDonald et al. (1986b) provided categorical
19 exposure-response data as well as logistic models for various endpoints (e.g., small opacities,
20 pleural calcification, pleural thickening of the chest wall, and “any pleural change”). In
21 McDonald et al. (1986b), exposure and age were both predictive of pleural thickening along the
22 chest wall, and the regression coefficient for cumulative exposure (fibers-years/cc) was
23 0.0024 per unit increase in cumulative exposure for the log odds of the presence of pleural
24 thickening, adjusting for age and smoking. Exposure, age, and smoking status were all
25 predictive of small opacities, with a beta of 0.0035 per unit increase in cumulative exposure. In
26 contrast, although categorical analysis reported by Amandus et al. (1987b) indicated a positive
27 exposure response relationship for both “any pleural change” and pleural thickening along the
28 chest wall, exposure was not a significant predictor in regression analysis controlling for age
29 (regardless of smoking status). The estimated relationship between exposure and prevalence of
30 small opacities in Amandus et al. (1987b) was similar to that reported by McDonald et al.
31 (1986b).

32 Whitehouse (2004) examined changes in pulmonary function measures in 123 patients
33 seen in a pulmonary disease practice serving the Libby, MT area, with a mean follow-up time of
34 35 months. This study population included 86 former employees of W.R. Grace & Co.,
35 27 family members of employees, and 10 Libby residents with only environmental (i.e.,

1 nonoccupational, nonfamily-related) exposures. The average age at the time of the first
2 pulmonary study was 66 years, and 80% were male. Chest X-rays or high resolution computed
3 tomography scans revealed no evidence of interstitial changes in 67 (55%) of the 123 patients,
4 and 56 patients (45%) were found to have interstitial changes at profusion category 0/1 or 1/0.
5 Pulmonary function tests included forced vital capacity (FVC), total lung capacity (TLC), and
6 the single breath carbon monoxide diffusing capacity (DLCO). The average yearly loss was
7 2.2% for FVC, 2.3% for TLC, and 3.0% for DLCO. The subset of 94 patients who experienced a
8 loss of FVC was characterized as the group with worsening lung function. Among this group,
9 the average yearly loss was 3.2% for FVC, 2.3% for TLC, and 3.3% for DLCO.

10 Larson et al. (2010b) analyzed data from a subset of workers for whom pleural and/or
11 parenchymal abnormalities were seen on the most recently available X-ray and who had one or
12 more previous X-rays covering a span of at least 4 years available for comparison. Three
13 NIOSH B-readers independently reviewed the most recent of the available X-rays for each
14 individual in the study using ILO criteria (ILO, 2000). If pleural or parenchymal abnormalities
15 consistent with asbestos exposure were seen by each of the readers, the full series of X-rays for
16 that participant was evaluated to identify the time at which changes were first seen. For this set
17 of analyses, the readers worked as a consensus panel, examining each of the available X-rays in
18 reverse chronological order to determine the latency (i.e., length of time between first exposure,
19 as measured by date of hire and observed abnormality), and the degree of progression by type of
20 abnormality. Stored X-rays were found for 184 workers, and 84 were included in the analysis.
21 Exclusions were based on the following: 76 did not have at least two X-rays over the span of at
22 least 4 years, 20 declined to participate, unanimous classification of the most recent X-ray was
23 not reached for 3, and 1 worker did not have any detectable abnormality. Localized pleural
24 thickening was seen in 83 of these 84 workers who were known to have had pleural and/or
25 parenchymal abnormalities at a median latency of 8.6 years. Any pleural calcification was seen
26 in 37 workers, with a median latency of 17.5 years, and diffuse pleural thickening was seen in
27 12 workers (median latency: 27.0 years). The latency period increased with increasing profusion
28 categories, from a median of 18.9 years for $\geq 1/0$, 33.3 years for progression to $\geq 2/1$, and
29 36.9 years for progression to $\geq 3/2$.

30 31 **4.1.1.4.3. Cardiovascular-related mortality**

32 Larson et al. (2010a) presents data on mortality due to cardiovascular diseases, with
33 SMRs of 0.9 (95% CI: 0.9, 1.0) seen for heart disease ($n = 552$) and 1.4 (95% CI: 1.2, 1.6) seen
34 for circulatory system diseases ($n = 258$). Deaths due to heart diseases were further categorized
35 into ischemic heart disease ($n = 247$) and other heart disease ($n = 120$, for pericarditis,

1 endocarditis, heart failure, and ill-defined descriptions and complications of heart disease), with
2 SMRs of 0.7 (95% CI: 0.6, 0.8) and 1.5 (95% 1.2, 1.8), respectively. Circulatory diseases
3 included hypertension without heart disease ($n = 42$), with an SMR of 1.7 (95% CI: 1.2, 2.4) and
4 diseases of arteries, veins, or lymphatic vessels ($n = 136$), SMR = 1.6 (95% CI: 1.4, 2.0). The
5 combined category of cardiovascular-related mortality resulted in modestly increased risks
6 across quartiles of exposure, with RR of 1.0 (referent), 1.3 (95% CI: 1.0, 1.6), 1.3 (95% CI: 1.0,
7 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
8 ≥ 44.0 fibers/cc-years, respectively. Larson et al. (2010) used a Monte Carlo simulation to
9 estimate the potential bias in cardiovascular disease risk that could have been introduced by
10 differences in smoking patterns between exposed and unexposed workers in the cohort. The
11 bias-adjustment factor ($RR_{unadjusted}/RR_{adjusted} = 1.1$) reduced the overall RR estimate from 1.6 to
12 1.5. Because Larson et al. (2010) analyzed multiple causes of death, the observed association
13 between exposure and cardiovascular disease-related mortality may reflect, at least in part, a
14 consequence of an underlying respiratory disease.

15

16 **4.1.1.4.4. Summary of noncancer risk in Libby, MT vermiculite mining operation workers**

17 The risk of mortality related to asbestosis and other forms of nonmalignant respiratory
18 disease is elevated in the Libby vermiculite mining and processing operations, with increasing
19 risk seen with increasing exposure to Libby Amphibole asbestos fibers in studies conducted in
20 the 1980s (Amandus and Wheeler, 1987; McDonald et al., 1986a) and in the extended follow-up
21 studies published in more recent years (Sullivan et al., 2007; McDonald et al., 2004; Larson
22 et al., 2010). The analyses using an internal referent group in the larger follow-up studies
23 (Larson et al., 2010; Sullivan, 2007; McDonald et al., 2004)⁶ observed increasing risks with
24 increasing cumulative exposure exposures when analyzed using tertiles or quartiles, or as a
25 continuous measure. Increased risks are also seen in the studies reporting analyses using an
26 external referent group, i.e., standardized mortality ratios (Sullivan, 2007; Amandus and
27 Wheeler, 1987; McDonald et al., 1986a). Radiographic evidence of small opacities (evidence of
28 parenchymal damage) and pleural thickening (both discrete and diffuse) has also been shown in
29 studies of Libby workers (McDonald et al., 1986b; Amandus et al., 1987b; Whitehouse, 2004;
30 Larson et al., 2010b).

31

32 **4.1.2. Libby, MT Community Studies**

33 In addition to worker exposures, the operations of the Zonolite Mountain mine are
34 believed to have resulted in both home exposures and community exposures. Potential pathways

⁶ See also reanalysis of Sullivan (2007) data by Moolgavar et al. (2010).

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1 of exposure (discussed below) range from release of airborne fibers into the community,
2 take-home exposure from mine workers (e.g., clothing), and recreational activities including
3 gardening and childhood play activities. Due to a potential for a broader community concern,
4 ATSDR conducted several studies and health actions responding to potential asbestos
5 contamination in the Libby, MT area.

7 **4.1.2.1. Geographic Mortality Analysis**

8 ATSDR conducted a location-specific analysis of mortality risks and a community health
9 screening for asbestos in the Libby area (see Table 4-8). The mortality analysis was based on
10 death certificate data from 1979–1998, with geocoding of current residence at time of death. The
11 six geographic areas used in the analysis were defined as the Libby city limits (1.1 square miles
12 around the downtown); the extended boundary of Libby (2.2 square miles around the
13 downtown); the boundary based on air modeling (16 square miles, based on computer modeling
14 of asbestos fiber distribution); the medical screening boundary (25 square miles, including the
15 town of Libby and areas along the Kootenai River); the Libby valley (65 square miles); and
16 central Lincoln County (314 square miles, based on a 10-mile radius around downtown Libby)
17 (ATSDR, 2000).

18 The 1990 population estimates were 2,531, 3,694, 4,300, 6,072, 8,617, and 9,512,
19 respectively, for these six areas. Age-standardized SMRs were calculated using underlying
20 cause-of-death information obtained from death certificates issued during the study period
21 for 413 of 419 identified decedents, and Montana and U.S. populations were used as reference
22 groups. Increased SMRs were observed for both asbestosis and pulmonary circulation diseases
23 (see Table 4-8). The SMR for lung cancer ranged from 0.9–1.1 and 0.8–1.0 in the analyses for
24 each of the six geographic boundaries using Montana and U.S. reference rates, respectively. In
25 addition, four deaths due to mesothelioma were observed during the study period. These
26 analyses did not distinguish between deaths among workers and deaths among other community
27 members.

Table 4-8. Cancer mortality and nonmalignant respiratory disease mortality in the Libby, MT community

Reference(s)	Inclusion criteria and design details	Results
ATSDR, 2000	<p>1979–1998, underlying cause of death from death certificates; 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). Inquiries to postmaster were required because of P.O. Box address for 8% ($n = 32$); information on 47 of 91 residents of elderly care facilities resulted in reclassification of 16 of 47 (34%) to nonresidents of Libby.</p> <p>U.S. Census data corresponding to the same six geographic boundaries of Libby, MT.</p> <p>419 decedents identified, 418 death certificates obtained, 413 with geocoding.</p> <p>Age-standardized SMRs based on Montana and U.S. comparison rates. Asbestosis SMRs were somewhat higher using the U.S. referent group, but choice of referent group had little difference on SMRs for most diseases.</p> <p>Four deaths from mesothelioma observed in the study area.</p>	<p>Lung cancer ($n = 82$) SMR (95% CI)</p> <p>Comparison area (Montana reference rates):</p> <p>Libby city limits 1.1 (0.8, 1.5)</p> <p>Extended Libby boundary 1.1 (0.8, 1.5)</p> <p>Air modeling 1.0 (0.8, 1.4)</p> <p>Medical screening 0.9 (0.7, 1.2)</p> <p>Libby valley 0.9 (0.7, 1.2)</p> <p>Central Lincoln County 0.9 (0.7, 1.1)</p> <p>Pancreatic cancer ($n = 10$) SMR (95% CI)</p> <p>Comparison area (Montana reference rates):</p> <p>Libby city limits 1.0 (0.5, 2.1)</p> <p>Extended Libby boundary 0.9 (0.4, 1.7)</p> <p>Air modeling 0.7 (0.3, 1.4)</p> <p>Medical screening 0.7 (0.3, 1.2)</p> <p>Libby valley 0.6 (0.3, 1.0)</p> <p>Central Lincoln County 0.5 (0.3, 1.0)</p> <p>Asbestosis ($n = 11$) SMR (95% CI)</p> <p>Comparison area (Montana reference rates):</p> <p>Libby city limits 40.8 (13.2, 95.3)</p> <p>Extended Libby boundary 47.3 (18.9, 97.5)</p> <p>Air modeling 44.3 (19.1, 87.2)</p> <p>Medical screening 40.6 (18.5, 77.1)</p> <p>Libby valley 38.7 (19.3, 69.2)</p> <p>Central Lincoln County 36.3 (18.1, 64.9)</p> <p>Comparison area (U.S. reference rates):</p> <p>Libby city limits 63.5 (20.5, 148)</p> <p>Extended Libby boundary 74.9 (30.0, 154)</p> <p>Air modeling 71.0 (30.6, 140)</p> <p>Medical screening 66.1 (30.2, 125)</p> <p>Libby valley 63.7 (31.7, 114)</p> <p>Central Lincoln County 59.8 (29.8, 107)</p> <p>Pulmonary circulation ($n = 14$) SMR (95% CI)</p> <p>Comparison area (Montana reference rates):</p> <p>Libby city limits 2.3 (1.1, 4.4)</p> <p>Extended Libby boundary 1.9 (0.9, 3.7)</p> <p>Air modeling 1.8 (0.9, 3.3)</p> <p>Medical screening 1.6 (0.8, 2.9)</p> <p>Libby valley 1.6 (0.9, 2.7)</p> <p>Central Lincoln County 1.5 (0.8, 2.5)</p>

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4.1.2.2. Community Screening—Respiratory Health

The ATSDR community health screening was conducted from July–November 2000 and July–September 2001 with 7,307 total participants (see Table 4-9; ATSDR, 2001). 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; the population of Libby, MT in 2000 was

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1 approximately 10,000. In addition to a standardized interview regarding medical history,
2 symptoms, work history, and other potential exposures, clinical tests included spirometry (forced
3 expiratory volume in one second [FEV1] and FVC) and chest X-rays (for participants aged
4 18 years and older). Moderate to severe restriction (defined by the researchers as FVC <70%
5 predicted value) was observed in 2.2% of the men and 1.6% of women but was not observed in
6 individuals less than age 18.

7 Two board-certified radiologists (B readers) examined each radiograph, and a third reader
8 was used in cases of disagreement. Readers were aware that the radiographs were from
9 participants in the Libby, MT health screening but were not made aware of exposure histories
10 and other characteristics (Peipins et al., 2003; Price, 2004; Peipins, 2004). The radiographs
11 revealed pleural abnormalities in 17.9% of participants, with prevalence increasing with
12 increasing number of “exposure pathways” (defined on the basis of potential work and
13 residential exposure to asbestos within Libby and from other sources) (see Table 4-9). Detailed
14 results of an analysis excluding the former Libby workers cohort were not presented, but the
15 authors noted that the relationship between number of exposure pathways and increasing
16 prevalence of pleural abnormalities was somewhat attenuated with this exclusion. The
17 prevalence of pleural anomalies decreased from approximately 35% to 30% in individuals with
18 12 or more exposure pathways when these workers were excluded from the analysis. Among
19 individuals with no definable exposure pathways, the prevalence of pleural anomalies was 6.7%,
20 which is higher than reported in other population studies (Price, 2004; Peipins, 2004). The direct
21 comparability between study estimates is difficult to make; the possibility of over- or
22 underascertainment of findings from the X-rays based on knowledge of conditions in Libby was
23 not assessed in this study. No information is provided regarding analyses excluding all potential
24 work-related asbestos exposures.

Table 4-9. Pulmonary function and chest radiographic studies in the Libby, MT community

Reference(s)	Inclusion criteria and design details	Results																																																																																																				
Peipins et al., 2003; ATSDR, 2001	Resided, worked, attended school, or participated in other activities in Libby for at least 6 months before 1991 (including mine employees and contractors). Health screening between July and November 2000. Conducted interviews (<i>n</i> = 6,149, 60% of Libby residents based on 2000 Census data) and chest X-rays (<i>n</i> = 5,590, 18 years and older), and determined spirometry—forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC1), and ratio (FEV1/FVC). 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. Chest X-rays read by 1980 ILO classifications (3 views; posterior-anterior, right- and left- anterior oblique). Peipins et al. (2003) similar to ATSDR, 2001 except longer screening period (July–November 2000 and July–September 2001). Conducted interviews (<i>n</i> = 7,307) and chest X-rays (<i>n</i> = 6,668).	Peipins (2003) and ATSDR (2001): 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 (2001): Moderate-to-severe FVC1 restriction (FVC <70% predicted): 2.2% of men >17 years old; 1.6% of women >17 years old; 0.0% of men or women <18 years old. Also includes data on self-reported lung diseases and symptoms.																																																																																																				
Weill et al. (2010)	Participants in the ATSDR community health screening (see first row in table). Analysis limited to ages 25 to 90 years, excluding individuals with history of other asbestos-related work exposures, with spirometry, consensus reading of chest X-ray, smoking data, and exposure pathway data (<i>n</i> = 4,397). Analysis based on five exposure categories: (1) W.R. Grace worker, (2) other vermiculite worker (contractor work), (3) other dusty occupation, (4) household (combination of three household categories), and (5) environmental (“no” to work and household exposures in Categories 1–6). Chest X-rays read by 1980 ILO classifications (frontal view).	<table border="1"> <thead> <tr> <th></th> <th>Profusion ≥1/0</th> <th>Plaque</th> <th>DPT/ CAO</th> </tr> </thead> <tbody> <tr> <td colspan="4">Prevalence (%), ages 25 to 40 years:</td> </tr> <tr> <td>1) W.R. Grace</td> <td>0.0</td> <td>20.0</td> <td>5.0</td> </tr> <tr> <td>2) Other</td> <td>0.8</td> <td>0.8</td> <td>0.0</td> </tr> <tr> <td>3) Dusty</td> <td>0.0</td> <td>3.8</td> <td>0.4</td> </tr> <tr> <td>4) Household</td> <td>0.0</td> <td>2.2</td> <td>0.0</td> </tr> <tr> <td>5) Environment</td> <td>0.0</td> <td>0.4</td> <td>0.0</td> </tr> <tr> <td colspan="4">Prevalence (%), ages 41 to 50 years:</td> </tr> <tr> <td>1) W.R. Grace</td> <td>0.0</td> <td>26.2</td> <td>5.0</td> </tr> <tr> <td>2) Other</td> <td>0.5</td> <td>7.8</td> <td>1.0</td> </tr> <tr> <td>3) Dusty</td> <td>0.0</td> <td>2.8</td> <td>0.9</td> </tr> <tr> <td>4) Household</td> <td>0.0</td> <td>11.1</td> <td>0.4</td> </tr> <tr> <td>5) Environment</td> <td>0.0</td> <td>1.9</td> <td>0.2</td> </tr> <tr> <td colspan="4">Prevalence (%), ages 51 to 60 years:</td> </tr> <tr> <td>1) W.R. Grace</td> <td>3.2</td> <td>34.9</td> <td>3.2</td> </tr> <tr> <td>2) Other</td> <td>0.6</td> <td>13.7</td> <td>0.6</td> </tr> <tr> <td>3) Dusty</td> <td>0.6</td> <td>12.6</td> <td>0.0</td> </tr> <tr> <td>4) Household</td> <td>1.0</td> <td>20.1</td> <td>1.5</td> </tr> <tr> <td>5) Environment</td> <td>0.0</td> <td>7.7</td> <td>0.9</td> </tr> <tr> <td colspan="4">Prevalence (%), ages 61 to 90 years:</td> </tr> <tr> <td>1) W.R. Grace</td> <td>11.1</td> <td>45.7</td> <td>8.6</td> </tr> <tr> <td>2) Other</td> <td>0.6</td> <td>24.8</td> <td>8.5</td> </tr> <tr> <td>3) Dusty</td> <td>1.1</td> <td>21.9</td> <td>3.3</td> </tr> <tr> <td>4) Household</td> <td>2.4</td> <td>38.3</td> <td>5.7</td> </tr> <tr> <td>5) Environment</td> <td>1.3</td> <td>12.7</td> <td>2.2</td> </tr> </tbody> </table>		Profusion ≥1/0	Plaque	DPT/ CAO	Prevalence (%), ages 25 to 40 years:				1) W.R. Grace	0.0	20.0	5.0	2) Other	0.8	0.8	0.0	3) Dusty	0.0	3.8	0.4	4) Household	0.0	2.2	0.0	5) Environment	0.0	0.4	0.0	Prevalence (%), ages 41 to 50 years:				1) W.R. Grace	0.0	26.2	5.0	2) Other	0.5	7.8	1.0	3) Dusty	0.0	2.8	0.9	4) Household	0.0	11.1	0.4	5) Environment	0.0	1.9	0.2	Prevalence (%), ages 51 to 60 years:				1) W.R. Grace	3.2	34.9	3.2	2) Other	0.6	13.7	0.6	3) Dusty	0.6	12.6	0.0	4) Household	1.0	20.1	1.5	5) Environment	0.0	7.7	0.9	Prevalence (%), ages 61 to 90 years:				1) W.R. Grace	11.1	45.7	8.6	2) Other	0.6	24.8	8.5	3) Dusty	1.1	21.9	3.3	4) Household	2.4	38.3	5.7	5) Environment	1.3	12.7	2.2
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Table 4-9. Pulmonary function and chest radiographic studies in the Libby, MT community (continued)

Reference(s)	Inclusion criteria and design details	Results
Vinikoor et al. (2010)	Participants in the ATSDR community health screening (see first row in table). Analysis limited to $n = 1,003$ ages 10–29 years at time of health screening (\leq age 18 in 1990 when the mining/milling operations closed). Excluded if worked for W.R. Grace, or for a contractor of W.R. Grace, exposed to dust at other jobs, or exposed to vermiculite at other jobs. Exposure characterized by 6 activities (never, sometimes, or frequently participated in 1–2 or ≥ 3 activities). Analysis of history of respiratory symptoms and spirometry data (obstructive, restrictive, or mixed).	Little difference across exposure levels in prevalence of physician-diagnosed lung disease or abnormal spirometry. Odds Ratio (95% CI) seen between ≥ 3 activities and Usual cough 2.93 (0.93, 9.25) Shortness of breath 1.32 (0.51, 3.42) Bloody phlegm 1.49 (0.41, 5.43)

OR = odds ratio; DPT = diffuse pleural thickening; CAO = costophrenic angle obliteration.

1 Weill et al. (2010) used the ATSDR community health screening data to analyze the
2 prevalence of X-ray abnormalities in relation to age, smoking history, and types of exposures.
3 From the 6,668 participants with chest X-rays, 1,327 individuals with a history of
4 asbestos-related work (other than with the Grace mining or related vermiculite operations) were
5 excluded, along with 817 excluded based on age (<25 or >90 years) or lack of spirometric data,
6 smoking data, or exposure pathway data. An additional 127 were excluded because a consensus
7 agreement (2 out of 3 readers) was not reached regarding the X-ray findings, leaving $n = 4,397$ in
8 the analysis. Analysis was based on five exposure categories: (1) Grace worker ($n = 255$),
9 (2) other vermiculite worker (e.g., secondary contractor worker for Grace or other jobs with
10 vermiculite exposure ($n = 664$), (3) other dusty occupation (e.g., plumber, dry wall finisher,
11 carpenter, roofer, electrician, welder, shipyard work or ship construction or repair ($n = 831$),
12 (4) household, including household with other vermiculite or dusty work (lived with a Grace
13 worker combination of three household categories) ($n = 880$), and (5) environmental (“no” to
14 work and household exposures in Categories 1–4) ($n = 1,894$). The frontal views (posterior-
15 anterior) of the chest X-rays were used in this analysis (in contrast to the use of frontal and
16 oblique views in Peipins et al., 2003). As expected, lung function (FEV_1 , FVC, and FEV_1/FVC)
17 was lower among ever smokers compared with never smokers (within each age group) and
18 decreased with age (within each smoking category). The prevalence of X-ray abnormalities
19 (plaques, or diffuse pleural thickening, and/or costophrenic angle obliteration) also generally
20 increased with age (divided into 25–40, 41–50, 51–60, and 61–90 years) within each of the
21 exposure categories (see Table 4-9), with the highest prevalence seen among Grace workers. For
22 a given age, the prevalence among those with environmental exposure only (i.e., no household or

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1 occupational exposures) was similar to the prevalence among those with non-Grace occupational
2 or household exposures in the next youngest age category. The prevalence among the household
3 contact category was similar or higher than the prevalence among the other vermiculite and dusty
4 job categories. This household contact category includes individuals who lived with a Grace
5 worker with no personal history of vermiculite or dust work ($n = 594$) and those who also had a
6 history of other vermiculite ($n = 114$) or dusty ($n = 172$) jobs. The authors noted the prevalence
7 rates were similar among these groups, and so the analysis was based on the combination of
8 these three groups. Mean FVCs (\pm SE) percentage predicted were 78.76 (\pm 3.64), 82.16 (\pm 3.34),
9 95.63 (\pm 0.76), and 103.15 (\pm 0.25), respectively, in those with diffuse pleural thickening and/or
10 costophrenic angle obliteration, profusion $\geq 1/0$, other pleural abnormalities, and no pleural
11 abnormalities. The strongest effects of diffuse pleural thickening and/or costophrenic angle
12 obliteration on FVC were seen among men who had never smoked (-23.77 , $p < 0.05$), with
13 smaller effects seen among men who had smoked (-9.77 , $p < 0.05$) and women who had smoked
14 (-6.73 , $p < 0.05$).

15 Vinikoor et al. (2010) used the 2000–2001 health screening data to examine respiratory
16 symptoms and spirometry results among 1,224 adolescents and young adults who were 18 years
17 or younger in 1990 when the mining/milling operations closed. At the time of the health
18 screening, the ages in this group ranged from 10 to 29 years. Exclusion criteria for this analysis
19 included previous work for W.R. Grace, work for a contractor of W.R. Grace, exposure to dust at
20 other jobs, or exposure to vermiculite at other jobs. The total number of exclusions was 221,
21 leaving 1,003 in the analysis. The potential for vermiculite exposure was classified based on
22 responses to questions about six activities (handling vermiculite insulation, participation in
23 recreational activities along the vermiculite-contaminated gravel road leading to the mine,
24 playing at the ball fields near the expansion plant, playing in or around the vermiculite piles,
25 heating the vermiculite to “pop” it, and other activities involving vermiculite). The medical
26 history questionnaire included information on three respiratory symptoms: usually have a cough
27 ($n = 108$, 10.8%); troubled by shortness of breath when walking up a slight hill or when hurrying
28 on level ground ($n = 145$, 14.5%); coughed up phlegm that was bloody in the past year
29 ($n = 59$, 5.9%). A question on history of physician-diagnosed lung disease ($n = 51$, 5.1%) was
30 also included. The spirometry results were classified as normal in 896 (90.5%), obstructive in 62
31 (6.3%), restrictive in 30 (3.0%), and mixed in 2 (0.2%). Information on smoking history was
32 also collected in the questionnaire: 15.8% and 7.3% were classified as current and former
33 smokers, respectively. Approximately half of the participants lived with someone who smoked.
34 The analyses adjusted for age, sex, personal smoking history, and living with a smoker. For
35 usually having a cough, the odds ratios (ORs) were 1.0 (referent), 1.88 (95% CI: 0.71, 5.00),

1 2.00 (95% CI: 0.76, 5.28) and 2.93 (95% CI: 0.93, 9.25) for never, sometimes, frequently
2 participated in 1–2 activities, and frequently participated in ≥ 3 activities, respectively. For
3 shortness of breath, the corresponding ORs across those exposure categories were 1.0 (referent),
4 1.16 (95% CI: 0.55, 2.44), 1.27 (95% CI: 0.61, 2.63) and 1.32 (95% CI: 0.51, 3.42), and for
5 presence of bloody phlegm in the past year the ORs were 1.0 (referent), 0.85 (95% CI: 0.31,
6 2.38), 1.09 (0.41, 2.98), and 1.49 (95% CI: 0.41, 5.43). For history of physician-diagnosed lung
7 disease and abnormal spirometry results, there was little difference in the odds ratios across the
8 exposure categories: for lung disease, the ORs were 1.0 (referent), 1.95 (95% CI: 0.57, 6.71),
9 1.51 (95% CI: 0.43, 5.24) and 1.72 (95% CI: 0.36, 8.32) for the categories of never, sometimes,
10 frequently participated in 1–2 activities, and frequently participated in ≥ 3 activities, respectively.
11 For abnormal spirometry (i.e., obstructive, restrictive, or mixed, $n = 94$ cases), the ORs were
12 1.0 (referent), 1.34 (95% CI: 0.60, 2.96), 1.20 (95% CI: 0.53, 2.70) and 1.33 (95% CI: 0.42,
13 4.19) across these exposure groups.

14 Two other studies examining autoimmune disease and autoantibodies in residents of
15 Libby, Montana are described in Section 4.3.

16

17 **4.1.2.3. Other Reports of Asbestos-Related Disease Among Libby, MT Residents**

18 Whitehouse et al. (2008) recently reviewed 11 cases of mesothelioma diagnosed between
19 1993 and 2006 in residents in or around Libby, MT ($n = 9$) and in family members of workers in
20 the mining operations ($n = 2$). Three cases were men who might have had occupational asbestos
21 exposure through construction work (Case 1), working in the U.S. Coast Guard and as a
22 carpenter (Case 5), or through railroad work involving sealing railcars in Libby (Case 7). One
23 case was a woman whose father had worked at the mine for 2 years; although the family lived
24 100 miles east of Libby, her exposure may have come through her work doing the family
25 laundry, which included laundering her father's work clothes. The other seven cases
26 (four women, three men) had lived or worked in Libby for 6–54 years, and had no known
27 occupational or family-related exposure to asbestos. Medical records were obtained for all
28 11 patients; pathology reports were obtained for 10 of the 11 patients. The Centers for Disease
29 Control estimated the death rate from mesothelioma, using 1999 to 2005 data, as approximately
30 14 per million per year (CDC, 2009), approximately five times higher than the rate estimated by
31 Whitehouse et al., (2008) for the Libby area population based on the estimated population of
32 9,500 for Lincoln County and 15 years (or 150,000 person-years) covered by the analysis.
33 Whitehouse et al. (2008) stated that a W.R. Grace unpublished report of measures taken in 1975
34 indicated that exposure levels of 1.1 fibers/cc were found in Libby, and 1.5 fibers/cc were found
35 near the mill and railroad facilities. Because the mining and milling operations continued to

1 1990, and because of the expected latency period for mesothelioma, Whitehouse et al. (2008)
2 suggests that additional cases can be expected to occur within this population.

3 4 **4.1.2.4. Summary of Respiratory Health Effects in Libby, MT Community Studies**

5 The geographic-based mortality analysis of 1997–1998 mortality data indicates that
6 asbestosis-related mortality is substantially increased in Libby, MT, and the surrounding area,
7 with rates 40 times higher compared with Montana rates and 60–70 times higher compared with
8 U.S. rates (ATSDR, 2000). These data provide evidence of the disease burden within the
9 community; however, because this analysis did not distinguish between deaths among workers
10 and deaths among other community members, it is not possible based on these data to estimate
11 the risk of asbestos-related mortality experienced by residents who were not employed at the
12 mining or milling operations. The community health screening studies provide more detailed
13 information regarding exposure pathways in addition to occupation (ATSDR, 2001). Data from
14 the ATSDR community health screening study indicate that the prevalence of pleural
15 abnormalities, identified by radiographic examination, increases substantially with increasing
16 number of exposure pathways (Peipins et al., 2003). In addition, the prevalence of some
17 self-reported respiratory symptoms among 10 to 29-year-old adolescents and young adults was
18 associated with certain exposure pathways. These participants were \leq age 18 in 1990 when the
19 mining/milling operations closed (Vinikoor et al., 2010). A better understanding of the
20 community health effects and the examination of the potential progression of adverse health
21 effect in this community would benefit from additional research to establish the clinical
22 significance of these findings. The observation by Whitehouse et al. (2008) of cases of
23 mesothelioma among individuals with no direct occupational exposure to the mining and milling
24 operations indicates the need for continued surveillance for this rare cancer.

25 26 **4.1.3. Marysville, OH Vermiculite Processing Plant Worker Studies**

27 Libby vermiculite was used in the production of numerous commercial products,
28 including as a potting soil amender and a carrier for pesticides and herbicides. A Marysville, OH
29 plant that used Libby vermiculite in the production of fertilizer beginning around 1960 to 1980 is
30 the location of the two related studies described in this section.

31 The processing facility had eight main departments, employing approximately
32 530 workers, with 232 employed in production and packaging of the fertilizer and 99 in
33 maintenance; other divisions included research, the front office, and the polyform plant (Lockey,
34 1985). Six departments were located at the main facility (trionizing, packaging, warehouse,
35 plant maintenance, central maintenance, and front offices). Research and development and a

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

7 Information about exposure assessment at the Marysville, OH plant is summarized in the
8 final row of Table 4-1. Industrial hygiene monitoring at the plant began in 1972. Lockey et al.
9 (1984) noted that the limited availability of data that would allow for extrapolation of exposures
10 for earlier time periods possibly resulted in the underestimation of exposures before 1974.⁷
11 Task-level air samples were conducted, and measurements were determined using scanning
12 electron microscopy and transmission electron microscopy (based on particles >5- μ m-long,
13 <3- μ m-diameter, and \geq 3:1 aspect ratio).

14 Based on measurements and knowledge of plant operations, three categories of exposure
15 levels were defined. Group I was considered to be the nonexposed group and consisted of the
16 chemical processing, research, and front office workers. The chemical process plant was about a
17 quarter mile from the main vermiculite facility, but the same chemicals were used in both
18 locations. The 8-hour time-weighted average vermiculite exposure in this group, both before and
19 after 1974, was estimated as 0.049 fiber/cc (based on a single stationary sample taken outside the
20 main facility), which was characterized as similar to the background levels in the community.
21 Group II was the “low exposure” category and included central maintenance, packing, and
22 warehouse workers. The 8-hour time-weighted average vermiculite exposures in this group were
23 estimated as approximately 0.1–0.4 fibers/cc before 1974 and 0.03–0.13 fibers/cc in and after
24 1974. Group III was the “highest exposure” category, and included vermiculite expanders, plant
25 maintenance, and pilot plant workers. The 8-hour time-weighted average vermiculite exposures
26 in this group were approximately 1.2–1.5 fibers/cc before 1974 and 0.2–0.375 fibers/cc in and
27 after 1974. Cumulative fiber exposure indexes, expressed as fibers-year/cc, were derived for
28 each worker from available industrial hygiene data and individual work histories. Those with
29 less than 1 fiber/cc-year were assumed to be equivalent to a community population (in terms of
30 exposure) and were used as the comparison group. The estimated cumulative exposure for the
31 work force, including Group I workers, ranged from 0.01 to 28.1 fibers/cc-years using an 8-hour

⁷ Subsequent exposure assessment efforts by this team of investigators are described in Appendix F.

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1 workday and an assumed 365 days of exposure per year.⁸ Exposure was assumed to occur from
2 1957 to 1980 in this study. Exposure after work hours was assumed to be zero.

3 The first study of pulmonary effects in the Ohio plant workers was conducted in 1980
4 and involved 512 workers (97% of the 530 workers previously identified with past vermiculite
5 exposure) (see Table 4-10; Lockey et al., 1984). Physical examination (for detection of
6 pulmonary rales and nail clubbing), spirometry, and chest-X-rays were performed, and
7 information pertaining to smoking history, work history at the plant, and other relevant work
8 exposures was collected using a trained interviewer. Radiographs were read independently by
9 two board-certified radiologists (B-readers), with a reading by a third reader when the initial
10 two readings did not agree. The number of workers within each exposure group was 112, 206,
11 and 194 in Groups I, II, and III, respectively. Approximately 44% were current smokers,
12 20% former smokers, and 35% lifetime nonsmokers, but smoking history (i.e., smoking status,
13 pack-years) did not differ by exposure group. Mean cumulative fiber estimates were 0.45, 1.13,
14 and 6.16 fibers/cc-years in Groups I, II, and III, respectively. An increased risk of costophrenic
15 angle blunting ($n = 11$), pleural, and parenchymal abnormalities ($n = 11$), or any of these
16 outcomes ($n = 22$) was observed in Group III compared with Group I; the prevalence of any
17 radiographic change was 2.8% in Group I, 3.9% in Group II, and 5.8% in Group III. Using the
18 cumulative fiber metric, the prevalence of any radiographic change was 2.4% in the
19 <1 fiber/cc-year, 5.0% in 1–10 fibers/cc-year, and 12.5% in the >10 fibers/cc-year groups.

⁸ Lockey et al. (1984) reported the maximum value for this group as 39.9 fibers/cc-years, but this estimate was later corrected to exclude work from 1947 to 1956, prior to the use of vermiculite at the plant. Information provided in personal communication from J. Lockey to Robert Benson, U.S. EPA, June 7, 2011.

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Table 4-10. Pulmonary function and chest radiographic studies of the Marysville, OH vermiculite processing plant workers

Reference(s)	Inclusion criteria and design details	Results
Lockey et al., 1984; Lockey, 1985 ^a	1980, <i>n</i> = 512 (from 530 identified employees with past vermiculite exposure; nonparticipants included 9 refusals and 9 unavailable due to illness or vacation). Smoking history, work history at the plant, and other asbestos and fiber mineral work history data were collected. Chest exam (rales), nail clubbing, spirometry, forced vital capacity, forced expiratory volume, single-breath carbon monoxide diffusing capacity, and chest X-rays (available for 502 participants) were analyzed. Mean employment duration: 10.2 years ^b Three exposure groups, based on jobs and area: Mean cumulative exposure ^b Group I 0.45 fibers/cc-years Group II 1.13 fibers/cc-years Group III 6.16 fibers/cc-years	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. Pleural thickening in 10 workers (2%); bilateral, small opacities in 1 (0.2%). Abnormality (combined outcomes) increased with increasing cumulative exposure.
Rohs et al., 2008	2002–2005, interviews and chest X-rays conducted, <i>n</i> = 298; 280 with interviews and readable chest X-rays (from 431 workers in the 1980 study group, of which, 513 were alive in 2004 ^c ; 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). Age, smoking, asbestos exposure measure (at this plant), and other asbestos exposure data used to compare participants and nonparticipants. Libby, MT vermiculite ore used in the plant from 1963–1980.	Pleural abnormalities in 80 workers (28.7%). Small opacities ($\geq 1/0$) in 8 workers (2.9%). Increasing risk of pleural abnormalities with increasing cumulative fiber exposure: odds ratios (adjusting for date of hire, body mass index) by exposure quartile were 1.0 (referent), 2.7, 3.5, and 6.9.

^aLockey et al. (1984) is the published paper based on the unpublished thesis (Lockey, 1985).

^bCalculated based on stratified data presented in Table 2 of Lockey et al. (1984).

^cRohs et al. (2008) identified one additional eligible worker from the original 512 employees identified in Lockey et al. (1984).

1 A follow-up study of this cohort was conducted in 2002–2005 (Rohs et al., 2008) (see
2 Table 4-10). This study included 298 workers, of which 280 completed the study interview and
3 chest X-ray. Details of the reasons for nonparticipation rates are described in Table 4-10. The
4 evaluation of each worker included an interview to determine work and health history,
5 spirometry, pulmonary examination, and chest X-ray. The study interview included information
6 about smoking history and asbestos exposure at the Marysville, Ohio plant and other worksites.
7 Exposure was estimated using the procedure previously described using the data on fiber levels
8 (Lockey et al., 1984). Exposure was assumed to occur from 1963 to 1980 in this study,

1 assuming an 8-hour workday and 365 days of exposure per year (J. Lockey, University of
2 Cincinnati, personal communication to R. Benson, U.S. EPA, July, 2007). Each worker supplied
3 a detailed work history (start and end date for each area within the facility). The exposure
4 reconstruction resulted in a cumulative exposure estimate for each individual. The estimated
5 cumulative exposure for this follow-up study ranged from 0.01 to 19.03 fibers/cc-years
6 (mean = 2.48). The time from first exposure ranged from 23 to 47 years. Twenty-eight workers
7 reported previous occupational exposure to asbestos. Exposure outside of work was assumed to
8 be zero.

9 Three board-certified radiologists independently classified the radiographs using the ILO
10 classification system (ILO, 2000). Radiologists were blinded to all identifiers. Pleural
11 thickening (all sites) was reported as either localized pleural thickening or diffuse pleural
12 thickening. Diffuse pleural thickening of the chest wall may be reported as in-profile or face-on,
13 and is recorded on the lateral chest wall “only in the presence of and in continuity with, an
14 obliterated costophrenic angle” (ILO 2000). Localized pleural thickening may also be viewed
15 in-profile or face-on and was described by Rohs et al. (2008) as “...{pleural} thickening with or
16 without calcification, excluding solitary costophrenic angle blunting” consistent with current
17 ILO classification. Interstitial abnormalities were considered present if the reader identified
18 irregular opacities of profusion 1/0 or greater (ILO, 2000). For the analysis, a chest X-ray was
19 defined as positive for pleural abnormality and/or interstitial abnormality when the median
20 classification from the three readings was consistent with such effects. Radiographs classified as
21 unreadable were not used. Radiographic abnormalities found in the study population are
22 summarized in Tables 4-11 and 4-12.

Table 4-11. Prevalence of pleural radiographic abnormalities according to quartiles of cumulative fiber exposure in 280 participants

Exposure quartile	Exposure, fiber-yr/cc, and (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)

^aTwo 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.

^bSignificant trend, $p < 0.001$.

^cTypographical error in publication corrected.

The 80 workers with pleural thickening include 68 with localized pleural thickening (85%) and 12 with diffuse pleural thickening (15%).

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. Lockety, University of Cincinnati (personal communication to Robert Benson, U.S. EPA).

Table 4-12. 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 on or before 1973	186	70 (37.6)	5.07	2.47–10.41	<0.001
Hired after 1973	94	10 (10.6)	Reference		
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					
Yes	184	55 (29.9)	1.21	0.70–2.11	0.50
No	96	25 (26.04)	Reference		
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

^an = 239 for Body Mass Index due to 38 persons undergoing phone interview and 3 persons with onsite interviews who were not measured for height and weight.

^bSmoking 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)

1 Pleural thickening was observed in 80 workers (28.7%), and small opacities ($\geq 1/0$) were
2 observed in 8 (2.9%). Six of the 8 participants with small opacities also had pleural thickening
3 (4 as LPT, 2 as DPT). The prevalence of pleural thickening increased across exposure quartiles
4 from 7.1% in the first quartile to 24.6%, 29.4%, and 54.3% in the second, third, and
5 fourth quartiles, respectively (see Table 4-11). The range of exposures was estimated as
6 0.01–0.28, 0.29–0.85, 0.86–2.20, and 2.21–19.03 fiber/cc-years in the first, second, third, and
7 fourth quartiles, respectively (Rohs et al., 2008).

8 Pleural thickening was associated with hire on or before 1973 and age at time of
9 interview but was not associated with body mass index (BMI) or smoking history (ever smoked)
10 (see Table 4-12). Body mass index is a potentially important confounder because fat pads can
11 sometime be misclassified as localized pleural thickening. A hire date of on or before 1973 and

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1 ages at time of interview are each highly correlated with cumulative exposure to fibers. The
2 small number of females ($n = 16$) in the cohort limits the analysis of the association with sex.
3 Modeling of odds ratios with cumulative fiber exposure and including various cofactors (age,
4 hired before 1973, or BMI) with the first exposure quartile as the reference was also conducted.
5 Each model demonstrated the same trend: increased prevalence of pleural thickening with
6 increasing cumulative exposure to fibers. Adjusting for age, date of hire, and body mass index
7 resulted in odds ratios of 2.7, 3.5, and 6.9 for the second, third, and fourth quartiles, respectively.
8 Age-adjusted and BMI-adjusted results were included in Table 4-11. There was no evidence of
9 significant interactions using this modeling.

10 There was potential coexposure to a number of herbicides, pesticides, and other
11 chemicals in the facility (personal communication to Robert Benson, EPA Region 8, from Ivan
12 Smith, The Scotts Company, June 7, 2007). The herbicides and pesticides used during the time
13 when Libby ore was used included atrazine, benomyl, bensulide, chloroneb, chlorothalonil,
14 chlorpyrifos, 2,4-D, dacthal, diazinon, dicamba, dephenamid, disodium methanearsonate, dyrene,
15 ethoprop, linuron, MCPP, monuron, neburon, oxadiazon, terrachlor, pentachlorophenol,
16 phenylmercuric acetate, siduron, terrazole, thiophannate-methyl, thiram. Other chemicals used
17 included ammonium hydroxide, brilliant green crystals, caustic soda, corncobs, ferrous
18 ammonium sulfate, ferrous sulfate, florex RVM, frit-504, frit-505, hi sil, lime, magnesium
19 sulfate, mon-a-mon, potash, potassium sulfate, sudan orange, sudan red, sulfur, sulfuric acid,
20 UFC, urea, and Victoria green liquid dye. No quantitative information on exposure to these
21 chemicals is available. However, the addition of the other chemicals to the vermiculite carrier
22 occurred in a different part of the facility after expansion of the vermiculite ore. Industrial
23 hygiene monitoring in these areas showed very low levels of fibers in the air. In addition, none
24 of these other chemicals is volatile. Thus, it is unlikely that workers would be coexposed by
25 inhalation to these other chemicals. EPA has no information indicating that exposure to any of
26 these individual chemicals causes pleural thickening or evidence of small opacities typical of
27 those found in workers employed in the Marysville facility. The spectrum of radiographic
28 abnormalities observed in the lung and pleura are the same in the Marysville workers, the Libby
29 workers (see Section 4.1.1.4.2, Table 4-7), and the Libby community survey {including
30 workers} (see Section 4.1.2.2, Table 4-9).

31 This study demonstrates that exposure to Libby Amphibole asbestos can cause
32 radiographic evidence of pleural thickening and parenchymal abnormalities (small opacities) in
33 exposed workers. The prevalences of radiographic abnormalities involving the pleura were
34 28.7% in 2004 (80/280), compared to a 2% prevalence observed in 1984 (10/501). This apparent
35 increase in prevalence is most likely due to the additional time between the two studies giving

1 additional time for the abnormalities to become apparent in conventional X-rays. The follow-up
2 study also shows an increasing prevalence of pleural thickening with increasing cumulative
3 exposure to Libby Amphibole asbestos.

4 The influence of some potential sources of selection bias in Rohs et al. (2008) is difficult
5 to qualitatively or quantitatively assess. One type of selection is the loss due to the death of
6 84 of the 513 (16%) workers in the first study; this group may represent less healthy or more
7 susceptible population. Exclusion of the very sick or susceptible may imply that the population
8 of eligible participants was somewhat healthier than the whole population of workers; this
9 exclusion may result in an underestimation of risk. Another type of selection is the loss due to
10 nonparticipation among the 431 individuals identified as alive in 2004 ($n = 135$ refusals and
11 nonresponders; 31%). Participation rates in epidemiologic studies can be associated with better
12 health status, and participation is often higher among nonsmokers compared with smokers. This
13 type of selection of a relatively healthier group (among the living) could also result in an
14 underascertainment of the risk of observed abnormalities within the whole exposed population.
15 However, if participation was related differentially based on exposure and outcome (i.e., if
16 workers experiencing pulmonary effects and who were more highly exposed were more likely to
17 participate than the highly exposed workers who were not experiencing pulmonary effects), the
18 result would be to overestimate the exposure response. This latter scenario is less likely to occur
19 for asymptomatic effects (i.e., abnormalities detected by chest X-ray), such as those that are the
20 focus of this study than for symptoms such as shortness of breath or chest pain.

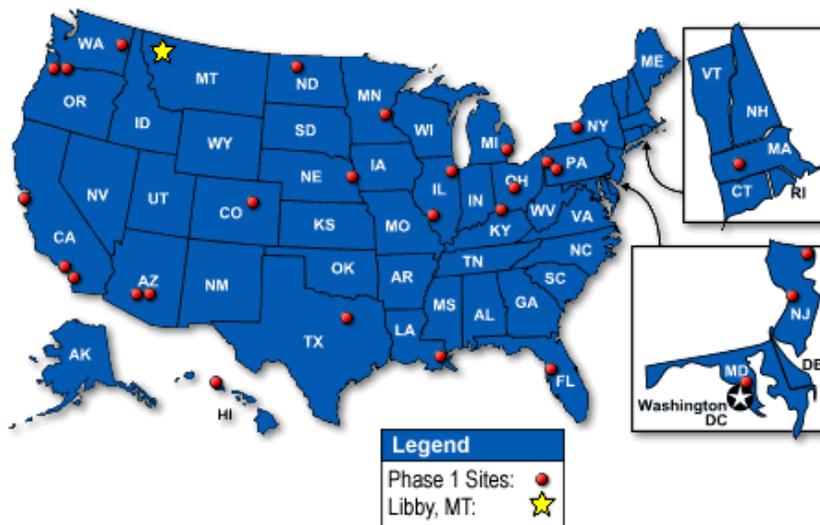
21 Some information is available on differences by participation status in the Rohs et al.
22 (2008) study. Although current age was similar (mean: 59.1 and 59.4 years, respectively, in
23 participants and living nonparticipant groups, $p = 0.53$), participants were more likely to have
24 been hired before or during 1973 (66.4 and 49.7%, respectively, $p = 0.001$), and had higher mean
25 exposure levels (mean cumulative exposure: 2.48 and 1.76 fiber/cc-years, respectively, $p = 0.06$).
26 Participants were also somewhat less likely to be ever smokers (58.6%) compared with the living
27 nonparticipants (66.2%). Using a conservative assumption that all living nonparticipants would
28 have had normal X-rays, resulted in estimated prevalences of pleural abnormalities of 3.7, 13.9,
29 18.5, and 38.3%, respectively, in the lowest-to-highest exposure quartile, with corresponding
30 odds ratios of 1.0 (referent), 4.19 (95% CI: 1.34, 13.08), 5.91 (95% CI: 1.95, 17.93), and 16.15
31 (95% CI: 5.53, 47.17). This pattern is similar to that observed in the analysis that excludes the
32 living nonparticipants, indicating the observed trend with exposure was not an artifact of a bias
33 introduced by differences in participation rates among the workers.

1 **4.1.3.1. Summary of Marysville, OH Vermiculite Processing Plant Worker Studies**

2 The studies conducted in the 1980s (Lockey et al., 1984) and the follow-up of the cohort
3 (Rohs et al., 2008) indicate that pleural thickening can be seen among workers in this plant, with
4 increasing prevalence with increasing cumulative exposure. Radiographic evidence of small
5 opacities (interstitial changes in the lung) increased from 0.2% in the original study to 2.9% and
6 radiographic evidence of pleural thickening increased from 2 to 28.6% of participants in the
7 follow-up study. No effects on lung function were found in the original study (Lockey et al.,
8 1984). Lung function was not reported for the cohort follow-up, despite greater prevalence of
9 radiographic abnormalities (Rohs et al., 2008).

10
11 **4.1.4. Community Studies from Other Vermiculite Processing Plants**

12 ATSDR has completed community evaluations of 28 sites, in addition to Libby,
13 surrounding exfoliation plants that require further evaluation by EPA because of current
14 contamination or evidence (based on a database of invoices) that the plant processed more than
15 100,000 tons of vermiculite from the Libby, MT mine (see Figure 4-1). Nine of these
16 evaluations included analyses conducted in conjunction with state health departments using
17 death certificate data (see Table 4-13). These community-level evaluations do not address
18 individual exposures or residential histories; therefore, the evidence in these evaluations
19 pertaining to disease risk is somewhat limited.



21 **Figure 4-1. Location of 28 sites included in the Phase 1 community evaluations conducted by ATSDR.**

Source: ATSDR (2008) http://www.atsdr.cdc.gov/asbestos/sites/national_map/.

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Table 4-13. Description of study areas in ATSDR health consultations evaluating cancer incidence and mortality^a

Site, exposure period	Study area (<i>n</i> from 1990 census)	Year of report
Los Angeles, CA, 1950–1977	Incidence: census tract (<i>n</i> = 21,945) Mortality: zip code (<i>n</i> = 57,615)	2007
Newark, CA, 1967–1992	Incidence: census tract (<i>n</i> = 7,785) Mortality: zip code (<i>n</i> = 37,861)	2005
Santa Ana, CA, 1972–1993	Census tract (35,000)	2003
West Chicago, IL, 1974–1996	Mortality: zip code (<i>n</i> = 14,796)	2003
Dearborn, MI, early 1950s–1989	City limits (<i>n</i> = 89,015)	2005
St. Louis, Missouri, 1956–1988	Census tracts (<i>n</i> = 20,112)	2006
Trenton, NJ, 1920s–1990	Census tracts and areas (<i>n</i> = 26,762)	2005
Edgewater, NJ, not reported	Not reported	2005
Marysville, OH, 1963–1980 ^c	City limits (<i>n</i> = 9,656)	2005

^aAll incidence studies used Surveillance, Epidemiology, and End Results (SEER) data as comparison group except New Jersey, which used New Jersey state rates. All mortality studies used U.S. rates from the National Center for Health Statistics.

^bThe Agency for Toxic Substances and Disease Registry (ATSDR, 2008) report presented incidence data from 1979–2000, but the 1986–1995 incidence data and the mortality data were obtained from the report of the New Jersey Department of Health and Social Services.

^cThe start date for the use of the Libby, MT vermiculite was given as variously described as 1963 or 1967 in the ATSDR health consultation report (ATSDR, 2008); the studies by Lockey et al. (1984) and Rohs et al. (2008) used 1957 and 1963, respectively, as the start date.

1 The lung cancer standardized incidence ratios for these evaluations range from
2 0.74–1.07, and the SMRs range from 0.74–1.1, indicating little evidence of an increased risk of
3 lung cancer among these studies (see Table 4-14). As expected from the small number of
4 observations, the standardized incidence ratios for mesothelioma or the category of cancer of the
5 peritoneum, retroperitoneum, and pleura (excluding mesothelioma, but which could reflect some
6 misdiagnoses) are more variable, ranging from approximately 0.5–2.5. Breast and prostate
7 cancer were selected as negative controls (i.e., cancers that have not previously been associated
8 with asbestos exposure) in these evaluations. For breast cancer, the standard incidence ratios
9 (SIRs) ranged from 0.73 to 1.25, and for prostate cancer, the SIRs ranged from 0.58 to 1.11,
10 similar to the variability seen among the estimates for lung cancer. In summary, these studies do
11 not provide evidence of an increased risk of lung cancer in the communities surrounding plants
12 that processed vermiculite contaminated with Libby Amphibole asbestos; the small numbers of
13 mesothelioma cases and potential contribution of other asbestos-related sites in some areas make
14 it very difficult to interpret these data. A major limitation of these studies is the lack of
15 information on exposure. Selection of the study population is based on geographic area, with no

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1 site-specific or individual-level assessment of relevant exposure pathways. Thus, the extent to
2 which community members were exposed around these facilities is unknown. The use of this
3 type of broad exposure characterization would be expected to result in considerable exposure
4 misclassification. As a result, more refined study designs are needed to evaluate risk to
5 individuals potentially exposed to Libby Amphibole asbestos in their community due to
6 operations at the expansion plants.

7

8

Table 4-14. Incidence and mortality results for potential asbestos-related cancers (by cancer site) in communities in the vicinity of vermiculite-processing facilities (with ATSDR health consultations evaluating potential pathways of exposure)

Study area ^c	Incidence ^a				Mortality ^b			
	Observed	Expected ^c	SIR	(95% CI)	Observed	Expected ^c	SMR	(95% CI)
Lung and bronchus								
Los Angeles, CA ^d	100	117.4	0.85	(0.69, 1.04)	210	285.0	0.74	(0.64, 0.84)
Newark, CA ^d	29	27.2	1.07	(0.71, 1.53)	125	124.3	1.01	(0.84, 1.2)
Santa Ana, CA ^d	79	95.4	0.83	(0.66, 1.03)	–	–	–	–
West Chicago, IL	–	–	–	–	95	98.6	0.96	(0.78, 1.18)
Dearborn, MI	757	764.4	0.99	(0.92, 1.06)	1,133	1,261.3	0.90	(0.85, 0.95)
St. Louis, MO	–	–	–	–	319	286.6	1.1	(1.0, 1.2)
Trenton, NJ	496	671.0	0.74	(0.68, 0.81)	976	1,100.3	0.89	(0.83, 0.94)
Edgewater, NJ	35	30.7	1.14	(0.80, 1.59)	51	50	1.02	(0.76, 1.34)
Marysville, OH	–	–	–	–	106	98.1	1.1	(0.9, 1.3)
Mesothelioma								
Los Angeles, CA ^d	1	1.9	0.53	(0.01, 2.96)	–	–	–	–
Newark, CA ^d	1	0.4	2.49	(0.03, 13.9)	–	–	–	–
Santa Ana, CA ^d	4	1.5	2.68	(0.72, 6.87)	–	–	–	–
West Chicago, IL	–	–	–	–	–	–	–	–
Dearborn, MI	8	12.3	0.65	(0.28, 1.28)	–	–	–	–
St. Louis, MO	–	–	–	–	–	–	–	–
Trenton, NJ	6	10.6	0.57	(0.21, 1.24)	–	–	–	–
Edgewater, NJ	1	0.5	2.11	(0.03, 11.7)	–	–	–	–
Marysville, OH	–	–	–	–	–	–	–	–
Peritoneum, retroperitoneum, and pleura								
Excluding mesothelioma					Including mesothelioma			
Los Angeles, CA ^d	1	3.1	0.32	(0.00, 1.78)	0	2.1	0.0	–
Newark, CA ^d	3	0.7	4.06	(0.82, 11.9)	0	0.9	0.0	(0, 4.10)
Santa Ana, CA ^d	6	2.7	2.24	(0.82, 4.87)	–	–	–	–
West Chicago, IL	–	–	–	–	1	0.8	1.28	(0.02, 7.12)
Dearborn, MI	16	19.1	0.84	(0.48, 1.36)	9	9.6	0.93	(0.43, 1.77)
St. Louis, MO	–	–	–	–	3	2.3	1.3	(0.3, 3.8)
Trenton, NJ	10	16.7	0.60	(0.29, 1.10)	18	8.3	2.17	(1.29, 3.43)
Edgewater, NJ	1	0.8	1.28	(0.02, 7.13)	0	0.2	0.0	–
Marysville, OH	–	–	–	–	0	0.8	0.0	–

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Table 4-14. Incidence and mortality results for potential asbestos related cancers (by cancer site) in communities in the vicinity of vermiculite processing facilities (with ATSDR health consultations evaluating potential pathways of exposure) (continued)

^aAll incidence studies used Surveillance, Epidemiology, and End Results (SEER) data as the comparison group except New Jersey, which used New Jersey state rates; incidence period in all analyses was 1986–1995. An additional analysis compared the Hamilton, NJ mesothelioma rates to SEER rates; standard incidence ratio (SIR) was reported to be “increased slightly but remained under 1.0.” Incidence data, ICD-10 (International Classification of Diseases) codes: lung and bronchus, C340:C349; mesothelioma, M-9050:9053; peritoneum, retroperitoneum, and pleura, C480:C488, C384; respiratory system and intrathoracic organs, C320:C399-excluding mesothelioma; selective digestive organs, C150:C218, C260-C269-excluding mesothelioma.

^bAll mortality studies used U.S. rates from the National Center for Health Statistics. Mortality period was 1989–1998 in the Los Angeles and Newark, CA analyses and was 1979–1998 in all analyses. Mortality data, ICD-9 codes: lung and bronchus, 162.2–162.9; peritoneum, retroperitoneum, and pleura, 158, 163; respiratory system and intrathoracic organs, 161–165; selective digestive organs, 150–154, 159.

^cExpected values have been rounded.

^dSimilar results were observed in the CA analyses using alternative methods to calculate standardized risk ratios for incidence and mortality.

CI = confidence interval.

Source: ATSDR (2008).

1 **4.1.4.1. Summary of Community Studies from Other Vermiculite Processing Plants**

2 The community-based mortality studies around the 28 exfoliation plants that processed
3 vermiculite contaminated with Libby Amphibole asbestos provide little evidence of an increased
4 risk of asbestos-related cancers in the surrounding communities. These studies are quite limited,
5 however, by the broad exposure classification and the inability to limit the analysis to individuals
6 who had resided in the specific areas during the relevant exposure periods. Additional studies
7 would be needed to more fully examine the potential risks associated with residential exposures
8 from these sources.

9
10 **4.1.5. Case Reports**

11 Progressive disease from exposure to Libby Amphibole was noted in a case report of fatal
12 asbestosis in an individual who died 50 years after working at a vermiculite processing plant for
13 a few months at about age 17 (Wright et al., 2002). In another case report, exposures that
14 stemmed from playing for a few years as a child in contaminated vermiculite waste materials
15 around a former Libby vermiculite processing facility was reportedly associated with the
16 development of asbestosis and fatal lung cancer (Srebro and Roggli, 1994).

17

1 **4.2. SUBCHRONIC AND CHONIC STUDIES AND CANCER BIOASSAYS IN**
2 **ANIMALS—ORAL, INHALATION AND OTHER ROUTES OF EXPOSURE**

3 Laboratory animal studies with exposure to Libby Amphibole or tremolite asbestos show
4 effects similar to those observed in occupationally exposed human populations including pleural
5 pathology, mesothelioma, and lung cancer. Tremolite is an amphibole asbestos fiber that is a
6 component of Libby Amphibole asbestos (~6%). Also, in early studies Libby Amphibole
7 asbestos was defined as tremolite. Therefore, laboratory animal studies examining the effect of
8 tremolite exposure have been reviewed and are summarized below to potentially increase
9 understanding of the effects and mechanisms of Libby Amphibole asbestos. Detailed study
10 summaries can be found in Appendix D and summarized in Tables 4-15 and 4-16. No inhalation
11 studies have been performed for Libby Amphibole asbestos, but chronic intrapleural injection
12 studies in hamsters demonstrate carcinogenicity following exposure. The chronic inhalation and
13 intrapleural injection laboratory animal studies with tremolite asbestos demonstrated pleural
14 pathology and carcinogenicity in rats. These studies support the epidemiology studies of Libby
15 Amphibole asbestos exposure (see Section 4.1), and aid in informing the mechanisms of Libby
16 Amphibole asbestos-induced disease.

17
18 **4.2.1. Oral**

19 No studies in laboratory animals with oral exposure to Libby Amphibole were found in
20 the literature. However, one chronic cancer bioassay was performed following oral exposure to
21 tremolite. McConnell et al. (1983a) describe part of a National Toxicology Program study (NTP,
22 1990a) performed to evaluate the toxicity and carcinogenicity of ingestion of several minerals,
23 including tremolite. The tremolite (Gouverneur Talc Co, Gouverneur, New York) used was not
24 fibrous. No significant tumor induction was observed in the animals with oral exposure to
25 tremolite animals. Although nonneoplastic lesions were observed in many of the aging rats,
26 these were mostly in the stomach and occurred in both controls and exposed animals. The
27 observed lesions included chronic inflammation, ulceration, and necrosis of the stomach
28 (McConnell et al., 1983a). McConnell et al. (1983a) suggested that nonfibrous tremolite could
29 account for the lack of toxicity following exposure in this group of animals. Also, oral studies of
30 asbestos, in general, show decreased toxicity and carcinogenicity as compared to inhalation and
31 implantation/injection studies (Condie, 1983).

Table 4-15. In vivo data following exposure to Libby Amphibole asbestos

Species (sex)	Exposure route	Fiber type	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)	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	Libby Amphibole asbestos (Six Mix) and crocidolite	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	Libby Amphibole asbestos (Six Mix) and crocidolite	Collagen gene expression and protein levels increased following exposure to both forms of asbestos (~1 mo post exposure).	Smartt et al., 2009
Wistar Kyoto rats (M) (n = 12/group) Spontaneously Hypertensive (SH) (n = 6/group) SH Heart Failure (SHHF) (n = 6/group)	Intratracheal instillation (once) 1 d, 1 wk, 1 mo 0.25 or 1.0 mg/rat	Libby Amphibole asbestos (Six Mix)	Strain-related differences observed in biomarkers of inflammation following exposure to Libby Amphibole asbestos. No differences were observed in histopathology.	Shannahan et al., 2011a

Table 4-15. In vivo data following exposure to Libby Amphibole asbestos (continued)

Species (sex)	Exposure route	Fiber type	Effects ^a	Reference
Spontaneously Hypertensive (SH) (M) (n = 8/group)	Intratracheal instillation (once) 4 h, 1 d 1.0 mg deferoxamine (DEF); 21 µg FeCl ₃ ; 0.5 mg LA, 0.5 mg FeLA; 0.5 mg LA + 1 mg DEF in 300 µL saline	Libby Amphibole asbestos (Six Mix)	Statistically significant increases in neutrophils was observed in BALF in animals exposed to LA, FeLA and LA + DEF with the greatest increase observed in the LA+DEF animals.	Shannahan et al., 2011b
Fisher 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	Libby Amphibole asbestos (Six Mix) Amosite	Statistically significant increases in inflammatory markers were observed following exposure to LA and amosite, including increased neutrophils and inflammatory gene expression, with the greatest increase in amosite-exposed rats.	Padilla-Carlin et al., 2011

^aWhen available, results are shown as number of animals with tumors/total number of animals examined.

Table 4-16. In vivo data following exposure to tremolite asbestos

Species (sex)	Exposure route	Fiber type	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 (Gouverneur Talc Co., Gouverneur, NY)	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 day, 5 days per week, total of 224 days)	South Korean tremolite and brucite	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)	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 Shinness: 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)	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
Sprague-Dawley and Wistar rats (n = 32 Wistar rats (Sample A); 48 Sprague-Dawley rats [Samples B and C])	Intrapleural injection 20 mg/rat	Tremolite (Three samples)	No tumors following exposure to Samples A and B; Sample C: 14/47	Wagner et al., 1982

Table 4-16. In vivo data following exposure to tremolite asbestos (continued)

Species (sex)	Exposure route	Fiber type	Effects ^a	Reference
Osborne-Mendel rats (n = 28/group)	Hardened gelatin technique 40 mg	Tremolite (Two samples)	Sample 1: 21/28 pleural sarcomas Sample 2: 22/28 pleural sarcomas	Stanton et al., 1981
Wistar rats (F) (n = 40/group)	Intraperitoneal injection 1 × 3.3 and 1 × 15 mg, lifetime observation	Tremolite	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., 1996, 1997
Wistar rats (M) (n = 56)	Inhalation (flow-past nose only) 100 fibers/cm ³ longer than 20 μm, 5 days, follow-up 1 year later	Tremolite	Tremolite had a pronounced inflammatory response with rapid granuloma development (1 day post exposure); Slight interstitial fibrosis observed at 90 and 180 days postexposure.	Bernstein et al., 2003, 2005
C57Bl/6 mice (F) (n = 10/group)	Intratracheal instillation Two doses of 60 μg each given 1 week apart in the first and second week of a 7-month experiment	Tremolite and wollastonite	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

^aWhen available, results are shown as number of animals with tumors/total number of animals examined.

^bAsbestiform types led to mesothelioma in most if not all exposed animals in this study.

1 **4.2.2. Inhalation**

2 There are no laboratory animal studies following inhalation exposure to Libby
3 Amphibole asbestos; however two studies have examined the effect of inhalation exposure to
4 tremolite in Wistar rats (Bernstein et al., 2005; 2003; Davis et al. 1985). Davis et al., (1985)
5 performed a chronic inhalation study examining response in male Wistar rats exposed in a
6 chamber to 10 mg/m³ (~1,600 fibers/mL, >5 µm) of commercially mined tremolite over a
7 12-month period. Bernstein et al. (2003; 2005) exposed Wistar rats to tremolite (100 fibers/cm³)
8 and chrysotile for 13 consecutive weeks (6 hours per day, 5 days per week) with 1-year
9 follow-up. The results of these inhalation studies produced pronounced inflammation and very
10 high levels of pulmonary fibrosis. Davis et al (1985) also demonstrated an increase in
11 carcinomas and mesotheliomas following exposure to tremolite, with no pulmonary tumors
12 observed in the controls. These results show that Wistar rats exposed to tremolite exhibited
13 increased numbers of pulmonary lesions and possibly tumors.

15 **4.2.3. Intratracheal Instillation Studies**

16 Intratracheal instillation has been used to examine the effect of exposure to Libby
17 Amphibole (Putnam et al., 2008; Smartt et al., 2009; Shannahan et al., 2011a; 2011b;
18 Padilla-Carlin et al., 2011) and tremolite asbestos (Sahu et al., 1975; Blake et al., 2008; Pfau et
19 al., 2008). These studies exposed C57Bl/6 mice (100 µg/mouse), Wistar Kyoto (WKY) rats
20 (0.25 or 1 mg/rat) or Fisher 344 rats (0.65 or 6.5 mg/rat) once to Libby Amphibole asbestos and
21 analyzed the results up to 3 month postexposure. Putnam et al. (2008) observed nonstatistically
22 significant increases in collagen following exposure to Libby Amphibole asbestos, as well as
23 gene expression alterations related to membrane transport, signal transduction, epidermal growth
24 factor signaling, and calcium regulation. Smartt et al. (2009) followed up this study by analyzing
25 specific genes by quantitative RT-PCR for genes involved in collagen accumulation and scar
26 formation (Col1A1, Col1A2, Col3A1). Libby Amphibole asbestos exposure led to increased
27 gene expression of Col1A2 at 1 week postinstillation and Col3A1 at 1 month post exposure.
28 Both studies observed increased inflammation, however, Libby Amphibole asbestos exposure
29 demonstrated minimal inflammation that did not progress in the time points examined. These
30 studies demonstrate that exposure to Libby Amphibole asbestos may lead to inflammation and
31 fibrosis. Shannahan et al. (2011a) exposed two rat models of human cardiovascular disease to
32 Libby Amphibole asbestos to determine if the preexisting cardiovascular disease in these models
33 would impact the lung injury and inflammation following exposure. Healthy WKY rats were
34 compared to spontaneously hypertensive (SH) and spontaneously hypertensive heart failure rats
35 following exposure. All rats (male only) were exposed to 0, 0.25, or 1.0 mg/rat via intratracheal

1 instillation and were examined at 1 day, 1 week and 1 month postexposure. No changes were
2 observed histopathologically, however, changes were observed in markers of homeostasis,
3 inflammation and oxidative stress. While inflammation and cell injury were observed in all
4 strains, no strain-related differences were observed following exposure to Libby Amphibole
5 asbestos (Shannahan et al., 2011a). In a follow-up study to further examine the role of iron in
6 the inflammatory response to Libby Amphibole asbestos exposure, Shannahan et al. (2011b)
7 exposed SH rats to Libby Amphibole asbestos alone and with bound Fe as well as with an iron
8 chelator (deferrioxamine, DEF). Exposure to Libby Amphibole asbestos led to statistically
9 significant increases in inflammatory markers (e.g., neutrophils, *IL-8*) with the greatest increase
10 occurring in the presence of DEF. Iron bound to Libby Amphibole asbestos was not released
11 following instillation except in the presence of DEF as supported by the lack of increase in
12 BALF iron. These results suggest that chelation of iron bound to Libby Amphibole asbestos as
13 well as endogenous proteins increases the toxicity of Libby Amphibole asbestos in vivo.

14 Padilla-Carlin et al. (2011) exposed Fisher 344 rats (male only) to Libby Amphibole
15 asbestos (0.65 or 6.5 mg/rat) or amosite (0.65 mg/rat; positive control) by intratracheal
16 instillation to examine inflammatory response for 3 months post-exposure. Libby Amphibole
17 asbestos exposure led to statistically significant increases of neutrophils in BALF as early 1 day
18 post-exposure, with other inflammatory markers (e.g., protein, LDH, GGT) increased statistically
19 significantly at different timepoints during the 3 month period post-exposure. However, on a
20 mass basis, amosite produced a greater inflammatory response as measured by inflammatory
21 markers (e.g., neutrophil influx, gene expression changes) and histopathological analysis
22 demonstrating interstitial fibrosis. These studies demonstrate a statistically significant increase
23 in inflammatory response to Libby Amphibole asbestos in mice and rats as measured in BALF
24 by cytology, histopathology and gene expression analysis. Follow-up studies are needed to
25 inform the chronic effects of exposure to Libby Amphibole asbestos.

26 Laboratory animal studies of tremolite intratracheal instillation exposure have been
27 performed in mice in doses ranging from 60 µg to 5 mg. Male Swiss albino mice exposed to
28 tremolite (5 mg) via intratracheal instillation demonstrated histological changes (Sahu et al.,
29 1975). Microscopic results following exposure to tremolite showed acute inflammation of the
30 lungs at 7 days post exposure, including macrophage proliferation and phagocytosis similar to
31 that observed with amosite and anthophyllite. Limited progression of fibrotic response was
32 observed at 60 and 90 days post exposure, with no further progression of fibrotic response.
33 Blake et al. (2008) and Pfau et al. (2008) examined the role of asbestos in autoimmunity. Blake
34 et al. (2008) performed in vitro assays with Libby Amphibole asbestos (see Section 4.4), and
35 both studies performed the in vivo assays with tremolite. C57BL/6 mice were instilled

1 intratracheally for a total of two doses each of 60- μ g saline and wollastonite or Korean tremolite
2 sonicated in sterile phosphate buffer saline (PBS,) given 1 week apart in the first 2 weeks of a
3 7-month experiment. Sera from mice exposed to tremolite showed antibody binding colocalized
4 with SSA/Ro52 on the surface of apoptotic blebs (Blake et al., 2008). In Pfau et al. (2008), by
5 26 weeks, the tremolite-exposed animals had a significantly higher frequency of positive
6 antinuclear antibody tests compared to wollastinate and saline. Most of the tests were positive
7 for dsDNA and SSA/Ro52. Serum isotyping showed no major changes in immunoglobulin
8 subclasses (IgG, IgA, IgM), but serum IgG in tremolite-exposed mice decreased overall.
9 Further, IgG immune complex deposition in the kidneys increased, with abnormalities suggestive
10 of glomerulonephritis. No increased proteinuria was observed during the course of the study.
11 Local immunologic response was further studied on the cervical lymph nodes. Although total
12 cell numbers and lymph-node size were significantly increased following exposure to tremolite,
13 percentages of T- and B-cells did not significantly change.
14

15 **4.2.4. Injection/Implantation Studies**

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

21 Studies by Smith and colleagues (1978; Smith et al. 1979), Wagner et al. (1982), Davis
22 et al. (1991) and Roller et al. (1996; 1997) demonstrated that intrapleural injections of tremolite
23 asbestos⁹ is associated with an increase in pleural fibrosis and mesothelioma in hamsters and rats
24 compared to controls or animals injected with less fibrous materials. Doses ranged from
25 10–25 mg/animal for each study, and although carcinogenesis was observed in these studies
26 there was a variable level of response to the different tremolite forms examined. Although these
27 studies clearly show the carcinogenic potential of Libby Amphibole or tremolite asbestos fibers,
28 intrapleural injections bypass the clearance and dissolution of fibers from the lung after
29 inhalation exposures. Further, limited information was provided confirming the presence or
30 absence of particles or fibers less than 5 μ m in length in these studies, limiting the interpretation
31 of results.

32 There is one laboratory animal study that examined the effect of tremolite exposure
33 following implantation of fibers in the pleural cavity. Stanton et al. (1981) also examined

⁹ Smith (1978) used tremolite from Libby, MT; Smith et al. (1979) may also have used tremolite from Libby, MT (i.e., Libby Amphibole asbestos).

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1 tremolite and describe a series of studies on various forms of asbestos. Fibers, embedded in
2 hardened gelatin, were placed against the lung pleura. As an intrapleural exposure, results might
3 not be comparable to inhalation exposures, as the dynamics of fiber deposition and pulmonary
4 clearance mechanisms are not accounted for in the study design. Studies using two tremolite
5 asbestos samples from the same lot were described as being in the optimal size range for
6 carcinogenesis; the fibers were distinctly smaller in diameter than the tremolite fibers Smith et al.
7 (1979) used. These samples both had a high number of fibers in the size range (>8- μm long and
8 <0.25- μm diameter; i.e., “Stanton fibers”). Exposure to both tremolite samples led to
9 mesotheliomas in 21 and 22 of 28 rats exposed. The Stanton et al. (1981) study also used talc
10 that did not lead to mesothelioma production.

11 There are no studies currently available in laboratory animals exposed to Libby
12 Amphibole asbestos by inhalation. However, the chronic intraperitoneal injection study in
13 hamsters (Smith 1978; Smith et al., 1979) demonstrated tumor formation following exposure to
14 tremolite obtained from the Libby, MT mine. No other chronic studies of Libby Amphibole
15 asbestos are available. A recent study in rats examining the impact of preexisting cardiovascular
16 disease on pulmonary inflammation demonstrated an increase in inflammatory markers
17 following exposure to Libby Amphibole asbestos via intratracheal instillation in SH rats as
18 compared to normal healthy controls exposed to the same dose (Shannahan et al., 2011). More
19 recent studies examined gene expression changes (Putnam et al., 2008; Hillegass et al., 2010)
20 and early protein markers of fibrosis (Smartt et al., 2009) in mice exposed to Libby Amphibole
21 asbestos via intraperitoneal injection. These studies demonstrated an increase in gene and
22 protein expression related to fibrosis following exposure to Libby Amphibole asbestos.
23 Tremolite fibers, although obtained from different locations throughout the world, consistently
24 led to pulmonary lesions and/or tumor formation with various routes of exposure (inhalation,
25 injection, instillation) and in multiple species (rats, hamsters, and mice) (Bernstein et al., 2003;
26 2005; Davis et al., 1985; Wagner et al., 1982; Roller et al., 1996; 1997; Stanton et al., 1981).
27 Although comparing potency of the various forms of tremolite is difficult given the limited
28 information on fiber characteristics and study limitations (e.g., length of follow-up
29 postexposure), these results show potential increased risk for cancer (lung and mesothelioma)
30 following exposure to tremolite asbestos.

31 The results of the studies described above show the fibrogenic and carcinogenic potential
32 of Libby Amphibole and tremolite asbestos. Further, the more recent studies by Blake et al.
33 (2008) and Pfau et al. (2008) support human studies demonstrating potential autoimmune effects
34 of asbestos exposure (see Section 4.3.1).

35

1 **4.2.5. Summary of Animal Studies for Libby Amphibole and Tremolite Asbestos**

2 Tables 4-15 and 4-16 summarize the studies described in this section, with full study
3 details available in Appendix D. Limited in vivo studies have been performed exposing
4 laboratory animals to Libby Amphibole asbestos. One intrapleural injection study using
5 tremolite from the Libby, MT area is included in this section under Libby Amphibole asbestos
6 since earlier terminology for Libby Amphibole asbestos was often tremolite (Smith, 1978).
7 Hamsters in this study exposed to Libby Amphibole asbestos developed fibrosis and
8 mesothelioma following exposure. Subchronic studies in mice (Putnam et al., 2008; Smartt et
9 al., 2008) demonstrated gene and protein expression changes related to fibrosis production
10 following exposure to Libby Amphibole asbestos. Finally, short-term studies in rats
11 demonstrated an increase in inflammatory markers following exposure to Libby Amphibole
12 asbestos (Shannahan et al., 2011a,b; Padilla-Carlin et al., 2011).

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

21 Chronic inflammation is hypothesized to lead to a carcinogenic response through the
22 production of reactive oxygen species and increased cellular proliferation (Hannahan and
23 Weinberg, 2011). Although limited, the data described in Section 4.2 suggest an increase in
24 inflammatory response following exposure to Libby Amphibole asbestos and tremolite asbestos
25 similar to that observed for other durable mineral fibers (reviewed in Mossman et al., 2007).
26 Whether this inflammatory response then leads to cancer is unknown. Studies examining other
27 types of asbestos (e.g., crocidolite, chrysotile, and amosite) have demonstrated an increase in
28 chronic inflammation as well as respiratory cancer related to exposure (reviewed in Kamp and
29 Weitzman, 1999). Chronic inflammation has also been linked to genotoxicity and mutagenicity
30 following exposure to some particles and fibers (Driscoll et al., 1995, 1996, 1997). The evidence
31 described above suggests chronic inflammation is observed following Libby Amphibole asbestos
32 and tremolite asbestos exposure; however, the role of inflammation and whether it leads to lung
33 cancer or mesothelioma following exposure to Libby Amphibole asbestos is unknown.

34 ROS production has been measured in response to both Libby Amphibole asbestos and
35 tremolite asbestos exposure. Blake et al. (2007) demonstrated an increase in the production of

1 superoxide anion following exposure to Libby Amphibole asbestos. Blake et al. (2007) also
2 demonstrated that total superoxide dismutase was inhibited, along with a decrease in intracellular
3 glutathione, both of which are associated with increased levels of ROS. These results are
4 supported by a recent study in human mesothelial cells (Hillegass et al., 2010; described in
5 Section 4.4 and Appendix D). Increased ROS production was also observed in human airway
6 epithelial cells following exposure to Libby Amphibole asbestos (Duncan et al., 2010; described
7 in Section 4.4 and Appendix D). This increase in ROS and decrease in glutathione are common
8 effects following exposure to asbestos fibers and particulate matter. Although ROS production is
9 relevant to humans, based on similar human responses as compared to animals, information on
10 the specifics of ROS production following exposure to Libby Amphibole asbestos is limited to
11 the available data described here. Therefore, the role of ROS production in lung cancer and
12 mesothelioma following exposure to Libby Amphibole asbestos is unknown.

13

14 **4.3. OTHER DURATION OR ENDPOINT-SPECIFIC STUDIES**

15 **4.3.1. Immunological**

16 Two epidemiology studies have examined the potential role of Libby Amphibole asbestos
17 and autoimmunity. Noonan et al. (2006) used the data from the community health screening to
18 examine self-reported history of autoimmune diseases (rheumatoid arthritis, scleroderma, or
19 lupus) in relation to the asbestos exposure pathways described above (see Table 4-17). To
20 provide more specificity in the self-reported history of these diseases, a follow-up questionnaire
21 was mailed to participants to confirm the initial report and obtain clarifying information
22 regarding the type of disease, whether the condition had been diagnosed by a physician, and
23 whether the participant was currently taking medication for the disease. Responses were
24 obtained from 208 (42%) of the 494 individuals who had reported these conditions. Of these
25 208 responses, 129 repeated the initial report of the diagnosis of rheumatoid arthritis, and
26 161 repeated the initial report of the diagnosis of one of the three diseases (rheumatoid arthritis,
27 scleroderma, or lupus). Among people aged 65 and over ($n = 34$ rheumatoid arthritis cases,
28 determined using responses from the follow-up questionnaire), a two- to threefold increase in
29 risk was observed in association with several measures reflecting potential exposure to asbestos
30 (e.g., asbestos exposure in the military) or specifically to Libby Amphibole asbestos (e.g., past
31 work in mining and milling operations, use of vermiculite in gardening, and frequent playing on
32 vermiculite piles when young). Restricted forced vital capacity, presence of parenchymal
33 abnormalities, playing on vermiculite piles, and other dust or vermiculite exposures were also
34 associated with rheumatoid arthritis in the group younger than 65 ($n = 95$ cases). Restricted
35 forced vital capacity was defined as FVC <80% predicted and a ratio of FEV1 to

1 FVC \geq 70% predicted. For all participants, an increased risk of rheumatoid arthritis was observed
 2 with increasing number of exposure pathways. RRs of 1.0, 1.02, 1.79, 2.51, and 3.98 were
 3 observed for 0 (referent), 1, 2–3, 4–5, and 6 or more pathways, respectively (trend $p < 0.001$,
 4 adjusting for restrictive spirometry, parenchymal abnormalities, and smoking history). Although
 5 the information gathered in the follow-up questionnaire and repeated reports of certain diagnoses
 6 decreased the false-positive reports of disease, considerable misclassification (over-reporting and
 7 under-reporting) is likely, given the relatively low confirmation rate of self-reports of
 8 physician-diagnosed rheumatoid arthritis (and other autoimmune diseases) seen in other studies
 9 (Rasch, 2003; Karlson, 2003; Ling, 2000).

10
 11 **Table 4-17. 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.	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.
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 sex-matched to Libby participants. Serum samples obtained; IgA levels, prevalence of antinuclear, anti-dsDNA antibodies, anti-RF antibodies, and anti-Sm, RNP, SS-A, SS-B, and Scl-70 antibodies determined.	Increased prevalence of high titer ($\geq 1:320$) 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.

13
 14
 15 Another study examined serological measures of autoantibodies in 50 residents of Libby,
 16 MT, and a comparison group of residents of Missoula, Montana (Pfau et al., 2005; see
 17 Table 4-17). The Libby residents were recruited for a study of genetic susceptibility to
 18 asbestos-related lung disease, and the Missoula residents were participants in a study of immune
 19 function. The Libby sample exhibited an increased prevalence (22%) of high-titer ($\geq 1:320$)
 20 antinuclear antibodies when compared to the Missoula sample (6%), and similar increases were
 21 seen in the Libby sample for rheumatoid factor, anti-RNP, anti-Scl-60, anti-Sm, anti-R_o (SSA),

1 and anti-La (SSB) antibodies. Although neither sample was randomly selected from the
2 community residents, an individual's interest in participating in a gene and lung disease study
3 likely would not be influenced by the presence of autoimmune disease or autoantibodies in that
4 individual.

5 Hamilton et al. (2004), Blake et al. (2008), and Pfau et al. (2008) examined the role of
6 asbestos in autoimmunity in laboratory animal or in vitro studies. Blake et al. (2008) performed
7 in vitro assays with Libby Amphibole asbestos (see Section 4.4), and both studies performed the
8 in vivo assays with tremolite. C57BL/6 mice were instilled intratracheally for a total of two
9 doses each of 60- μ g saline and wollastonite or Korean tremolite sonicated in sterile PBS, given
10 1 week apart in the first 2 weeks of a 7-month experiment. Sera from mice exposed to tremolite
11 showed antibody binding colocalized with SSA/Ro52 on the surface of apoptotic blebs (Blake
12 et al., 2008). In Pfau et al. (2008), by 26 weeks, the tremolite-exposed animals had a
13 significantly higher frequency of positive antinuclear antibody tests compared to wollastinate
14 and saline. Most of the tests were positive for dsDNA and SSA/Ro52. Serum isotyping showed
15 no major changes in immunoglobulin subclasses (IgG, IgA, IgM), but serum IgG in
16 tremolite-exposed mice decreased overall. Further, IgG immune complex deposition in the
17 kidneys increased, with abnormalities suggestive of glomerulonephritis. No increased
18 proteinuria was observed during the course of the study. Local immunologic response was
19 further studied on the cervical lymph nodes. Although total cell numbers and lymph-node sizes
20 were significantly increased following exposure to tremolite, percentages of T- and B-cells did
21 not significantly change. Hamilton et al. (2004) investigated the ability of Libby Amphibole,
22 crocidolite, and PM_{2.5} (collected over a 6 month period in Houston, TX, from EPA
23 site 48-201-1035) to alter the antigen-presenting cell (APC) function was altered in cultured
24 human alveolar macrophages. Asbestos exposure (regardless of type) and PM_{2.5} up-regulated a
25 T_{H1} lymphocyte derived cytokine, interferon gamma (IFN γ), and the T_{H2} lymphocyte-derived
26 cytokines interleukin-4 (IL-4) and interleukin-13 (IL-13). There was, however, extreme
27 variation among subjects in the amount of response. In addition, there was no correlation
28 between an individual's cells' response to asbestos versus PM, suggesting that more than one
29 possible mechanism exists for a particle-induced APC effect and individual differential
30 sensitivities to inhaled bioactive particles.

31 Although limited number of studies, these results suggest a possible effect on
32 autoimmunity following exposure to Libby Amphibole asbestos. Further studies are needed to
33 increase understanding of this potential effect.

1 **4.4. MECHANISTIC DATA AND OTHER STUDIES IN SUPPORT OF THE MODE OF**
2 **ACTION**

3 In vitro analysis of fibers depends on the characteristics of the fibers and cell types used
4 for the studies. Therefore, in reviewing the literature it is important to pay attention to cell types
5 used, particularly related to the ability to internalize fibers and produce an oxidative stress
6 response. Results from in vitro studies have demonstrated potential biological mechanisms of
7 oxidative stress and inflammation in response to exposure to Libby Amphibole and tremolite
8 asbestos. These studies are summarized below and in Tables 4-18 and 4-19, with detailed study
9 descriptions available in Appendix D.

10 Limited in vitro studies have been conducted with Libby Amphibole asbestos from the
11 Zonolite Mountain mine. These studies demonstrated an effect of Libby Amphibole asbestos on
12 inflammation and immune function (Blake et al., 2007; 2008; Hamilton et al., 2004; Duncan et
13 al., 2010), oxidative stress (Hillegass et al., 2010), and genotoxicity (Pietruska et al., 2010).
14 Similar endpoints have been examined in vitro following exposure to tremolite asbestos (Wagner
15 et al., 1982; Athanasiou et al., 1992; Suzuki and Hei 1996; Wylie et al., 1997; Okayasu et al.,
16 1999).

17
18 **4.4.1. Inflammation and Immune Function**

19 Hamilton et al., (2004) showed an increase in TH1 and TH2 cytokines following
20 exposure to both asbestos and particulate matter, suggesting a similar effect of exposure to both
21 materials on immune function. Analysis of these results is limited, as the use of primary cells in
22 culture that led to an extremely variable response. Two studies by Blake et al. (2007, 2008)
23 further examined the effect of Libby Amphibole asbestos on immune response in murine
24 macrophages. These studies demonstrated that Libby Amphibole asbestos was internalized, and
25 this internalization resulted in an increase in reactive oxygen species (ROS.) These studies also
26 showed a variable cytotoxic response, as Libby Amphibole asbestos exposure did not result in a
27 statistically significant increase in cytotoxicity, while crocidolite did. DNA damage also was
28 increased in crocidolite-exposed cells—but not in Libby Amphibole asbestos exposed-cells. An
29 increase (relative to controls) in autoantibody formation following exposure to Libby Amphibole
30 asbestos also was observed. Studies that examined cellular response to tremolite also found that
31 fiber characteristics (length and width) play a role in determining ROS production, toxicity, and
32 mutagenicity (Wagner et al., 1982; Okayasu et al., 1999).

Table 4-18. In vitro data following exposure to Libby Amphibole asbestos

Test system	Fiber type	Dose/exposure duration	Effects	Reference
Primary human alveolar macrophages and lymphocytes	Libby Amphibole asbestos 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	Libby Amphibole asbestos and crocidolite	Internalization: 0, 5, 62.5 µg/cm ² 3–24 h	Internalized Libby Amphibole asbestos 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 24 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)	Libby Amphibole asbestos 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)	Libby Amphibole asbestos 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 cells (LP9/TERT-1 and HKNM-2)	Libby Amphibole asbestos 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, particularly SOD2	Hillegass et al., 2010
Primary human airway epithelial cells (HAECs)	Libby Amphibole asbestos (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 pro-inflammatory gene expression and ROS production	Duncan et al., 2010

^aAll results for RAW264.7. Data not shown for primary cells though authors state similar response to RAW264.7.

PBS = phosphate buffer saline, ROS = reactive oxygen species, GSH = glutathione, DNA = deoxyribonucleic acid, LDH = lactic dehydrogenase, BGL = β-glucuronidase, SHE = Syrian hamster ovary, HTE = hamster tracheal epithelial, RPM = rat pleural mesothelial, NIEHS = National Institute of Environmental Health Sciences, HPRT = hypoxanthine-guanine phosphoribosyltransferase.

Table 4-19. 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 and cytotoxicity of samples tested. Sample B also led to some increased cytotoxicity.	Wagner et al., 1982
TA98, TA100, TA102 <i>S. typhimurium</i>	Metsovo tremolite	TA98, TA100, and TA102: 0–500 µg/per plate 2 days	No significant revertants were observed in any of the three Salmonella strains tested.	Athanasίου 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
A[L] cells (hamster hybrid cells containing human chromosome 11)	Tremolite, erionite, RCF-1	0–400 µg/mL 24 h	No significant increase in HPRT mutations for these three fibers; Dose-dependent induction of mutations in CD59 did occur for erionite and tremolite.	Okayasu et al., 1999

PBS = phosphate buffer saline, ROS = reactive oxygen species, GSH = glutathione, DNA = deoxyribonucleic acid, LDH = lactic dehydrogenase, BGL = β-glucuronidase, SHE = Syrian hamster ovary, HTE = hamster tracheal epithelial, RPM = rat pleural mesothelial, NIEHS = National Institute of Environmental Health Sciences, HPRT = hypoxanthine-guanine phosphoribosyltransferase.

1 Mechanisms of oxidative stress following exposure to Libby Amphibole asbestos were
2 also studied in human mesothelial cells (Hillegass et al., 2010). Gene expression changes
3 following exposure to $15 \times 10^6 \mu\text{m}^2/\text{cm}^2$ Libby Amphibole asbestos¹⁰ as compared to the
4 nonpathogenic control ($75 \times 10^6 \mu\text{m}^2/\text{cm}^2$ glass beads) in the human mesothelial cell line
5 LP9/TERT-1 for 8 and 24 hours. Gene ontology of these results demonstrated alterations in
6 genes related to signal transduction, immune response, apoptosis, cellular proliferation,
7 extracellular matrix, cell adhesion and motility, and only in one gene related to reactive oxygen
8 species processing. Oxidative stress was observed as both dose- and time-dependent in cells
9 exposed to Libby Amphibole asbestos but was increased following exposure to the higher dose
10 of Libby Amphibole asbestos (statistical analysis not possible). Glutathione (GSH) levels were
11 transiently depleted following 2–8 hours exposure to the higher dose of Libby Amphibole
12 asbestos, with a gradual recovery up to 48 hours in LP9/TERT-1 cells (HKNM-2 not analyzed).
13 These studies demonstrate that Libby Amphibole asbestos exposure leads to increases in
14 oxidative stress as measured by ROS production, gene expression, protein and functional
15 changes in oxidative stress proteins (SOD), and GSH level alterations in human mesothelial
16 cells.

17 Gene expression alterations of interleukin-8 (IL-8), cyclooxygenase-2 (COX-2), heme
18 oxygenase (HO)-1 as well as other stress-responsive genes as compared to amosite (Research
19 Triangle Institute) was observed in primary human airway epithelial cells (HAEC) following
20 exposure to Libby Amphibole asbestos. Comparisons were made with both fractionated
21 (aerodynamic diameter $\leq 2.5 \mu\text{m}$) and unfractionated fiber samples (Duncan et al., 2010).
22 Crocidolite fibers (UICC) were also included in some portions of this study for comparison.
23 Primary HAECs were exposed to 0, 2.64, 13.2, and 26.4 $\mu\text{g}/\text{cm}^2$ of crocidolite, amosite (AM),
24 amosite 2.5 (fractionated), Libby Amphibole asbestos, or Libby Amphibole asbestos
25 2.5 (fractionated) for 2 or 24 hours in cell culture. Cytotoxicity was determined by measurement
26 of lactate dehydrogenase (LDH) from the maximum dose ($26.4 \mu\text{g}/\text{cm}^2$) of both amosite and
27 Libby Amphibole asbestos samples, with less than 10% LDH present following exposure to all
28 four samples. Minimal increases in gene expression of IL-8, COX-2, or HO-1 were observed at
29 2 hours postexposure to all five fiber types; at 24 hour postexposure, however, a dose response
30 was observed following exposure to all fiber types with the results showing a pro-inflammatory
31 gene expression response (Duncan et al., 2010). These results support a limited cytotoxicity of
32 both amosite and Libby Amphibole asbestos under these concentrations and time frames.

33

¹⁰ 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 ($15 \times 10^6 \mu\text{m}^2/\text{cm}^2$) or the toxic dose ($75 \times 10^6 \mu\text{m}^2/\text{cm}^2$).

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1 4.4.2. Genotoxicity

2 Genotoxicity and, more specifically, mutagenicity, are associated with tumor formation
3 through alterations in genetic material.¹¹ Mutagenicity refers to a permanent effect on the
4 structure and/or amount of genetic material that can lead to heritable changes in function, while
5 genotoxicity is a broader term including all adverse effects on the genetic information (Eastmond
6 et al., 2009). Results of standard mutation assays like the Ames test, which analyze for point
7 mutations, have found asbestos and other mineral fibers to be negative or only marginally
8 positive (Walker et al., 1992). Several other studies, however, have shown that asbestos
9 exposure can result in a variety of chromosomal alterations, which are briefly discussed below.
10 Genotoxicity following exposure to asbestos fibers has been described as the result of
11 two distinct mechanisms, either ROS production leading to direct DNA damage, or physical
12 interference of mitosis by the fibers. For both DNA damage and mitotic interference, the fibers
13 must first enter the cell. Some studies have shown that a direct interaction between fibers and
14 cellular receptors might also lead to increased ROS production. ROS production is likely to be a
15 key event in fiber-induced direct DNA damage, as observed following exposure to other forms
16 of asbestos, while the indirect DNA damage requires fiber interaction with cellular components
17 (e.g., mitotic spindle, chromosomes).

18 ROS production and genotoxicity (micronuclei induction) following exposure to Libby
19 Amphibole asbestos has been demonstrated in XRCC1-deficient human lung epithelial
20 H460 cells (Pietruska et al., 2010). XRCC1 is involved in the repair mechanisms for oxidative
21 DNA damage, particularly single strand breaks. Micronuclei induction was measured following
22 treatment of cells by controls (positive, hydrogen peroxide; negative, paclitaxel) and by
23 5 µg/cm² fibers or TiO₂ particles for 24 hours. Spontaneous micronuclei induction was increased
24 in XRCC1-deficient cells in a dose-dependent manner following exposure to crocidolite and
25 Libby Amphibole asbestos as compared to control. These results support a potential genotoxic
26 effect of exposure to both crocidolite and Libby Amphibole asbestos.

27 Athanasiou et al. (1992) performed a series of experiments to measure genotoxicity
28 following exposure to tremolite, including the Ames mutagenicity assay, micronuclei induction,
29 chromosomal aberrations, and gap-junction intercellular communication. Although a useful test

¹¹ *Genotoxicity*: a broad term and 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 which 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 (1996).

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1 system for mutagenicity screening for many agents, the Ames assay is not the most effective test
2 to detect mutations induced by mineral fibers. Mineral fibers can cause mutation through
3 generation of ROS or direct disruption of the spindle apparatus during chromatid segregation.
4 Fibers do not induce ROS in the Ames system, however, and the *Salmonella typhimurium* strains
5 do not endocytose the fibers. Only one study was found in the published literature that used the
6 Ames assay to measure mutagenicity of tremolite. Metsovo tremolite asbestos has been shown
7 to be the causative agent of endemic pleural calcification and an increased level of malignant
8 pleural mesothelioma (see Section 4.1). To measure the mutagenicity of Metsovo tremolite,
9 *S. typhimurium* strains (TA98, TA100, and TA102) were exposed to 0–500 µg/plate of asbestos
10 (Athanasίου et al., 1992). Metsovo tremolite did not yield a statistically significant increase in
11 revertants in the Ames assay, including in the TA102 *Salmonella* strain, which is generally
12 sensitive to oxidative damage. This study demonstrated clastogenic effects of tremolite,
13 including chromosomal aberrations and micronuclei induction. Tremolite exposure in Syrian
14 hamster embryo (SHE) cells did lead to a dose-dependent increase in chromosome aberrations
15 that was statistically significant at the highest doses tested (1.0–3.0 µg/cm²) ($p < 0.01$)
16 (Athanasίου et al., 1992). A statistically significant dose-dependent increase in levels of
17 micronuclei was demonstrated following tremolite exposure at concentrations as low as
18 0.5 µg/cm² ($p < 0.01$) in BPNi cells after 24-hour exposure. Literatures searches did not find
19 tremolite tested for clastogenicity in other cell types, but the results of this study suggest
20 interference with the spindle apparatus by these fibers. No analysis was performed to determine
21 if fiber interference of the spindle apparatus could be observed, which would have supported
22 these results. No effect on the gap-junctional intercellular communication following tremolite
23 exposure was observed in both Chinese hamster lung fibroblasts (V79) and Syrian hamster
24 embryo BPNi cells, which are sensitive to transformation (Athanasίου et al., 1992).

25 Okayasu et al. (1999) analyzed the mutagenicity of Metsovo tremolite, erionite, and the
26 man-made ceramic (RCF-1) fiber. Human-hamster hybrid A(L) cells contain a full set of
27 hamster chromosomes and a single copy of human chromosome 11. Mutagenesis of the CD59
28 locus on this chromosome is quantifiable by antibody complement-mediated cytotoxicity assay.
29 The authors state that this is a highly sensitive mutagenicity assay, and previous studies have
30 demonstrated mutagenicity of both crocidolite and chrysotile (Hei et al., 1992). The cytotoxicity
31 analysis for mutagenicity was performed by exposing 1×10^5 A(L) cells to a range of
32 concentrations of fibers as measured by weight (0–400 µg/mL or 0–80 µg/cm²) for 24 hours at
33 37°C. CD59 mutant induction showed a dose-dependent increase in mutation induction for
34 erionite and tremolite, but RCF-1 did not.

1 In summary, one in vitro study examined genotoxicity of Libby Amphibole asbestos by
2 measuring DNA adduct formation following exposure via murine macrophages (primary and
3 immortalized) (Blake et al., 2007). The data showed no increase in adduct formation as
4 compared to unexposed controls. A second study observed increases in micronuclei induction in
5 both normal human lung epithelial cells and XRCC1-deficient cells for both Libby Amphibole
6 and crocidolite asbestos (Pietruska et al., 2010). Two studies of tremolite examined
7 genotoxicity. The first found no significant increase in revertants in the Ames assay (Athanasίου
8 et al., 1992), which is similar to results obtained for other forms of asbestos. This study did find,
9 however, that tremolite exposure led to a dose-dependent increase in chromosome number and
10 micronuclei formation, which has also been described for other asbestos fibers (as reviewed in
11 Hei et al., 2007; Jaurand, 1999). Hei and colleagues (Okayasu et al., 1999) performed mutation
12 analysis with tremolite and found a dose-dependent increase in mutations in CD59 in hamster
13 hybrid cells. Genotoxicity analysis in humans, following exposure to Libby Amphibole asbestos
14 or tremolite, has not been measured, although other types of asbestos fibers have led to increases
15 in genotoxicity in primary cultures and lymphocytes (Dopp et al., 2005; Poser et al., 2004). In
16 general, these studies have examined genotoxicity with a focus on ROS production as a key
17 event. Although Libby Amphibole asbestos- and tremolite-specific data are limited to in vitro
18 studies, given the similarities in response to other forms of asbestos, there is some evidence to
19 suggest genotoxicity following exposure to Libby Amphibole and tremolite asbestos. However,
20 the potential role of this genotoxicity in lung cancer or mesothelioma following exposure to
21 Libby Amphibole asbestos is unknown.

22 23 **4.4.3. Cytotoxicity and Cellular Proliferation**

24 The initial stages of tumorigenicity may be an increased cellular proliferation at the site
25 of fiber deposition, which can increase the chance of cancer by increasing the population of
26 spontaneous mutations, thereby affording genotoxic effects an opportunity to multiply.
27 Increased cell proliferative regeneration is also a hallmark of tumor clonal expansion and
28 generally occurs in response to increased apoptosis.

29 Wagner et al. (1982) examined the in vitro cytotoxicity of three forms of tremolite used
30 in their in vivo studies. LDH and β -glucuronidase were measured in the medium following
31 incubation of unactivated primary murine macrophages to 50, 100, and 150 $\mu\text{g}/\text{mL}$ of each
32 sample for 18 hours. The Korean tremolite (Sample C) produced results similar to the positive
33 control: increased toxicity of primary murine macrophages, increased cytotoxicity of Chinese
34 hamster ovary (CHO) cells, and increased formation of giant cells from the A549 cell line. The
35 tremolite sample from Greenland (Sample B) did result in increased toxicity over controls;

1 although to a lesser degree (statistics are not given). Although differential toxicity of these
2 samples was noted on a mass basis, data were not normalized for fiber content or size. The
3 inference is that differential results may be due, at least in part, to differential fiber counts.

4 Wylie et al. (1997) examined the mineralogical features associated with cytotoxic and
5 proliferative effects of asbestos in hamster tracheal epithelial (HTE) and rat pleural mesothelial
6 (RPM) cells with a colony-forming efficiency assay. HTE cells are used because they give rise
7 to tracheobronchial carcinoma, while RPM cells give rise to mesotheliomas. The results of the
8 analysis with fiber exposure by mass ($\mu\text{g}/\text{cm}^2$) show elevated colonies in HTE cells following
9 exposures to both asbestos fibers ($p < 0.05$) at the lowest concentrations, while significant
10 decreases were observed for both asbestos fibers at the higher concentrations ($0.5 \mu\text{g}/\text{cm}^2$,
11 $p < 0.05$) (Wylie et al., 1997). No proliferation was observed for either chrysotile or crocidolite
12 asbestos fibers in RPM cells, but cytotoxicity was observed at concentrations greater than
13 $0.05 \mu\text{g}/\text{cm}^2$ ($p < 0.05$). All talc samples were less cytotoxic in both cell types. Analyzing the
14 data for cytotoxicity and proliferation based on the exposure measurement demonstrated
15 differences in response depending solely on how the fibers were measured: by mass, number, or
16 surface area. These results show variability in interpreting the results of the same assay based on
17 the defined unit of exposure. Most early studies used mass as the measurement for exposure,
18 which can impact how the results are interpreted. When possible, further analysis of fiber
19 number and surface area would help elucidate the role of these metrics, particularly for in vivo
20 studies.

21 Tremolite and Libby Amphibole asbestos exposure led to increases in both fibrosis and
22 tumorigenicity in all but one animal study, supporting a possible role for proliferation in
23 response to these fibers. However, there are limited data to demonstrate that increased
24 cytotoxicity and cellular proliferation following exposure to Libby Amphibole asbestos leads to
25 lung cancer or mesothelioma.

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

1 4.5. SYNTHESIS OF MAJOR NONCANCER EFFECTS

2 The predominant noncancer health effects observed following inhalation exposure to
3 Libby Amphibole asbestos are effects on the lungs and pleural lining surrounding the lungs.
4 Recent studies have also examined noncancer health effects following exposure to Libby
5 Amphibole asbestos in other systems, including autoimmune effects and cardiovascular disease.
6 These effects have been observed primarily in studies of exposed workers and community
7 members and are supported by laboratory animal studies.

8 9 4.5.1. Pulmonary Effects

10 4.5.1.1. *Pulmonary Fibrosis (Asbestosis)*

11 Asbestosis is the interstitial pneumonitis and fibrosis caused by inhalation of asbestos
12 fibers and is characterized by a diffuse increase of collagen in the alveolar walls (fibrosis) and
13 the presence of asbestos fibers, either free or coated with a proteinaceous material and iron
14 (asbestos bodies). Fibrosis results from a sequence of events following lung injury, which
15 includes inflammatory cell migration, edema, cellular proliferation, and accumulation of
16 collagen. Asbestosis is associated with dyspnea, bibasilar rales, and changes in pulmonary
17 function: a restrictive pattern, mixed restrictive-obstructive pattern, and/or decreased diffusing
18 capacity (ATS, 2004). Radiographic evidence of small opacities in the lung is direct evidence of
19 scarring of the lung tissue and as the fibrotic scarring of lung tissue consistent with mineral dust
20 and mineral fiber toxicity. The scarring of the parenchymal tissue of the lung contributes to
21 measured changes in pulmonary function, including obstructive pulmonary deficits from
22 narrowing airways, restrictive pulmonary deficits from impacting the elasticity of the lung as
23 well as decrements in gas exchange.

24 Workers exposed to Libby Amphibole asbestos from vermiculite mining and processing
25 facilities in Libby, MT, as well as plant workers in Marysville, OH, where vermiculite ore was
26 exfoliated and processed, have an increased prevalence of small opacities on chest X-rays, which
27 is indicative of fibrotic damage to the parenchymal tissue of the lung (Rohs et al., 2008;
28 Amandus et al., 1987c; McDonald et al., 1986a; Lockey et al., 1984). These findings are
29 consistent with a diagnosis of asbestosis, and the studies are described in detail in
30 Section 4.1.1.4.2. Significant increases in asbestosis as the primary cause-of-death have been
31 documented in studies of the Libby worker cohort report (see Table 4.6 for details) (Larson et al.,
32 2010; Sullivan, 2007; Amandus et al., 1987b; McDonald et al., 1986a). For both asbestosis
33 mortality and radiographic signs of asbestos (small opacities), positive exposure-response
34 relationships are described where these effects are greater with greater cumulative exposure to
35 Libby Amphibole asbestos.

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1 Deficits in pulmonary function consistent with pulmonary fibrosis have been reported in
2 individuals exposed to Libby Amphibole asbestos. The initial study of the Marysville, OH
3 cohort measured but reported no change in pulmonary function (Lockey et al., 1984).
4 Pulmonary function was not reported for the cohort follow-up, although prevalence of pleural
5 and parenchymal abnormalities was increased (Rohs et al., 2008). Although studies of the
6 occupational Libby worker cohort do not include assessment of pulmonary function (Amandus
7 et al., 1987c; McDonald et al 1986b) data from the ATSDR community screening, which
8 included workers, provide support for functional effects from parenchymal changes. The
9 original report of the health screening data indicated moderate-to-severe pulmonary restriction in
10 2.2% of men (Peipins et al., 2003, ATSDR 2001). A recent reanalysis of these data show that for
11 study participants with small opacities viewed on the radiographs (grade 1/0 or greater), and
12 DPT the mean FVC is reduced to 78.76 (± 3.64), 82.16 (± 3.34), respectively of the expected
13 value (Weill et al., 2010). A mean FVC of 95.63 (± 0.76) was reported for those with other
14 pleural abnormalities versus 103.15 (± 0.25) in participants with no radiographic abnormalities.
15 The strongest effects of diffuse pleural thickening and/or costophrenic angle obliteration on FVC
16 were seen among men who had never smoked (-23.77 , $p < 0.05$), with smaller effects seen
17 among men who had smoked (-9.77 , $p < 0.05$) and women who had smoked (-6.73 , $p < 0.05$).
18 Laboratory animal and mechanistic studies of Libby Amphibole asbestos are consistent with the
19 noncancer health effects observed in both Libby workers and community members. Pleural
20 fibrosis was increased in hamsters after intrapleural injections of Libby Amphibole asbestos
21 (Smith, 1978). More recent studies have demonstrated increased collagen deposition consistent
22 with fibrosis following intratracheal instillation of Libby Amphibole asbestos fibers in mice
23 (Putnam et al., 2008; Smartt et al., 2009; Shannahan et al., 2011a; 2011b; Padilla-Carlin et al.,
24 2011). Pulmonary fibrosis, inflammation, and granulomas were observed after tremolite
25 inhalation exposure in Wistar rats (Bernstein et al., 2003, 2005) and intratracheal instillation in
26 albino Swiss mice (Sahu et al., 1975). Davis et al. (1985) also reported pulmonary effects after
27 inhalation exposure in Wistar rats including increases in peribronchiolar fibrosis, alveolar wall
28 thickening, and interstitial fibrosis.

29

30 **4.5.1.2. Other Nonmalignant Respiratory Diseases**

31 Mortality studies of the Libby workers indicate that there is increased mortality, not only
32 from asbestosis, but other respiratory diseases. Deaths attributed to chronic obstructive
33 respiratory disease and deaths attributed to “other” nonmalignant respiratory disease were
34 elevated more than twofold (see Table 4-6) (Larson et al., 2010; Sullivan 2001). These diseases

1 are consistent with asbestos toxicity, and the evidence of a positive exposure-response
2 relationship for mortality from all nonmalignant respiratory diseases, supports this association.

3 4 **4.5.2. Pleural Effects**

5 Pleural thickening that is caused by mineral fiber exposure includes two distinct
6 biological lesions: discrete pleural plaques in the parietal pleura and diffuse pleural thickening of
7 the visceral pleura. Both forms of pleural thickening can be viewed on standard radiographs.
8 However, the two are not always clearly distinguishable on X-rays, and smaller lesions may not
9 be detected. High resolution computed tomography is a method that can distinguish between the
10 lesions, as well as detect smaller lesions than are visible on X-rays. Pleural thickening may
11 restrict lung function, increase breathlessness with exercise, and contribute to chronic chest pain.
12 The potential for health effects and severity of health effects are increased with the extent and
13 thickness of the pleural lesions.

14 Data from the ATSDR community health screening study indicate that the prevalence of
15 pleural abnormalities, identified by radiographic examination, increases substantially with
16 increasing number of exposure pathways (Peipins et al., 2003). A reanalysis of these data also
17 considered age, smoking history, and types of exposures. Increased pleural thickening is
18 reported for Libby workers, those with other vermiculite work and those in “dusty trades.”
19 Increased LPT is reported in both those exposed only as household contacts or through
20 environmental exposure pathways, with greater incidence by age (38.3 and 12.7% respectively in
21 the 61–90 age group) (Weill et al., 2011). DPT is reported at lower rates with 5.9 and 2.2 %
22 respectively in these exposure groups in the highest age bracket evaluated (age 61–90.)

23 Increased pleural thickening is reported for both of the studied worker cohorts, with
24 evidence of positive exposure response relationships (Larson et al., 2010, Lockey et al., 1984;
25 Rohs et al., 2008; Amandus et al., 1987a, c; McDonald et al., 1986a, b; Lockey et al., 1984).
26 Both McDonald et al. (1986b) and Amandus et al. (1987c) indicate age is also a predictor of
27 pleural thickening in exposed individuals, which may reflect the effects of time from first
28 exposure. Smoking data were limited on the Libby workers and analyses do not indicate clear
29 relationships between smoking and pleural thickening (Amandus et al., 1987c; McDonal et al.,
30 1986b). Pleural thickening in workers at the Scott Plant (Marysville, OH) was associated with
31 hire on or before 1973 and age at time of interview but was not associated with BMI or smoking
32 history (ever smoked) (Rohs et al., 2008).

33 34 **4.5.3. Other Noncancer Health Effects (Cardiovascular Toxicity, Autoimmune Effects)**

35 There is limited research available on noncancer health effects occurring outside the
36 respiratory system. Larson et al. (2010) examined cardiovascular disease-related mortality in the

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1 cohort of exposed workers from Libby (see Section 4.1.1.4.3). Mechanistic studies have
2 examined the potential role of iron and the associated inflammation for both the respiratory and
3 cardiovascular disease (Shannahan et al., 2011). Two studies examined the association between
4 asbestos exposure and autoimmune disease (Noonan et al., 2006) or autoantibodies and other
5 immune markers (Pfau et al., 2005) (see Table 4-17). Limitations in the number, scope, and
6 design of these studies make it difficult to reach conclusions as to the role of asbestos exposure
7 in either cardiovascular disease or autoimmune disease.
8

9 **4.5.4. Libby Amphibole Asbestos Summary of Noncancer Health Effects**

10 The studies in humans summarized in Section 4.1 have documented an increase in
11 mortality from nonmalignant respiratory disease, including asbestosis, in workers exposed to
12 Libby Amphibole asbestos (Larson et al., 2010a; Sullivan, 2007; McDonald et al., 2004; Wheeler
13 1987). Radiographic evidence of pleural thickening and interstitial damage (small opacities) are
14 also well documented among employees of the Libby vermiculite mining operations (i.e.,
15 Amandus et al., 1987a, c; McDonald et al., 1986a, b; Larson et al., 2010a). Additional studies
16 (i.e., Lockey et al., 1984; Rohs et al., 2008) have documented an increase in radiographic
17 changes in the pleura and parenchyma among employees of a manufacturing facility in
18 Marysville, OH that used Libby vermiculite ore contaminated with Libby Amphibole asbestos.
19 Positive exposure-response relationships for these health effects for both occupational cohorts
20 studied, as well as the observed latency, support an association between exposure to Libby
21 Amphibole asbestos and these pleuro-pulmonary effects. Studies of community members
22 exposed to Libby Amphibole asbestos have documented similar pleural abnormalities and
23 pulmonary deficits consistent with parenchymal damage (Weill et al., 2010; Whitehouse, 2004;
24 Peipens et al., 2003). Although limited, animal studies support the toxicity of Libby Amphibole
25 asbestos to pleural and pulmonary tissues. Developing research supports a role of inflammatory
26 processes in the toxic action of Libby Amphibole asbestos, consistent with the observed health
27 effects (Hamilton et al., 2004; Duncan et al., 2010). Taken together, the strong evidence in
28 human studies, defined exposure response relationships, and supportive animal studies provide
29 compelling evidence that exposure to Libby Amphibole asbestos causes nonmalignant
30 respiratory disease, including asbestosis, pleural thickening, and deficits in pulmonary function
31 associated with mineral fiber exposures. Existing data regarding cardiovascular effects and the
32 potential for autoimmune disease are limited.
33

1 **4.5.5. Mode-of-Action Information (Noncancer)**

2 The precise mechanisms causing toxic injury from inhalation exposure to Libby
3 Amphibole asbestos have not been established. However, nearly all-durable mineral fibers with
4 dimensional characteristics that allow penetration to the terminal bronchioles and alveoli of the
5 lung have the capacity to induce pathologic response in the lung and pleural cavity (ATSDR,
6 2001; Witschi and Last, 1996). The physical-chemical attributes of mineral fibers are important
7 in determining the type of toxicity observed. Fiber dimension (width and length), density, and
8 other characteristics such as chemical composition, surface area, solubility in physiological
9 fluids, and durability all play important roles in both the type of toxicity observed and the
10 biologically significant dose. Fibrosis results from a sequence of events following lung injury,
11 which includes inflammatory cell migration, edema, cellular proliferation, and accumulation of
12 collagen. Fibers do migrate to the pleural space, and it has been hypothesized that a similar
13 cascade of inflammatory events may contribute to fibrotic lesions in the visceral pleura.
14 Thickening of the visceral pleura is more often localized to lobes of the lung with pronounced
15 parenchymal changes, and it has also been hypothesized that the inflammatory and fibrogenic
16 processes within the lung parenchyma in response to asbestos fibers may influence the fibrogenic
17 process in the visceral pleura. The etiology of parietal plaques is largely unknown with respect
18 to mineral fiber exposure.

19 There is currently insufficient evidence to establish the noncancer mode of action for
20 Libby Amphibole asbestos. Limited in vitro studies have demonstrated oxidative stress
21 following Libby Amphibole asbestos exposures in various cell types (Blake et al., 2007;
22 Pietruska et al., 2010; Hillegass et al., 2010; Duncan et al. 2010). Libby Amphibole asbestos
23 fibers increased intracellular ROS in both murine macrophages and human epithelial cells (Blake
24 et al., 2007; Duncan et al., 2010). Surface iron, inflammatory marker gene expression was
25 increased following exposure to Libby Amphibole asbestos in human epithelial cells (Duncan
26 et al., 2010; Pietruska et al., 2010; Shannahan et al., 2011; see Table 4-18). Tremolite studies
27 demonstrate cytotoxicity in various cell culture systems (see Table 4-19).

28 The initial stages of any fibrotic response involve cellular proliferation, which may be
29 compensatory for cell death due to cytotoxicity. Analysis of cellular proliferation has
30 demonstrated both increases and decreases following exposure to asbestos fibers in vitro and in
31 vivo depending on the specific fiber or cell type (Mossman et al., 1985; Topping and Nettesheim,
32 1980). Other studies have focused on the activation of cell-signaling pathways that lead to
33 cellular proliferation following exposure to asbestos (e.g., Zanella et al., 1996; Scapoli et al.,
34 2004; Shukla et al., 2003; Ding et al., 1999).

1 Although slightly increased compared to controls, cytotoxicity in murine macrophage
2 cells exposed to Libby Amphibole asbestos was decreased compared to other fiber types (Blake
3 et al., 2008). Cytotoxicity was slightly, but statistically significantly, increased compared to an
4 unexposed control at 24 hours post exposure to Libby Amphibole asbestos, while crocidolite
5 exposure resulted in even higher levels of cytotoxicity. No other in vitro study examined
6 cytotoxicity following exposure to Libby Amphibole asbestos, although an increase in apoptosis
7 was demonstrated in this same cell system (Blake et al., 2008). Recent studies in mice exposed
8 to Libby Amphibole asbestos demonstrated increased collagen deposition and collagen gene
9 expression, markers of fibrosis (Putnam et al., 2008; Smartt et al., 2009). Short-term studies in
10 rats also demonstrated an increased inflammatory response (Shannahan et al., 2011a,b;
11 Padilla-Carlin et al., 2011). Tremolite and Libby Amphibole asbestos exposure led to increases
12 in both fibrosis in all but one animal study, supporting a role for proliferation in response to these
13 fibers. Taken together with studies on other asbestos fibers, these data suggest that a cytotoxicity
14 and cell proliferation may play a role in the noncancer health effects following exposure to Libby
15 Amphibole asbestos.

16 Although continued research demonstrates that the Libby Amphibole asbestos has
17 biologic activity consistent with the inflammatory action and cytotoxic effects seen with other
18 forms of asbestos, the data are not sufficient to establish a mode of action for the
19 pleura-pulmonary effects of exposure to Libby Amphibole asbestos.

21 **4.6. EVALUATION OF CARCINOGENICITY**

22 **4.6.1. Summary of Overall Weight of Evidence**

23 Under the EPA *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a), Libby
24 Amphibole asbestos is “carcinogenic to humans” following inhalation exposure based on
25 epidemiologic evidence that shows a convincing association between exposure to Libby
26 Amphibole asbestos fibers and increased lung cancer and mesothelioma mortality (McDonald et
27 al., 1986a, 2004; Amandus and Wheeler, 1987; Sullivan, 2007, Larson et al., 2010b, Moolgavkar
28 et al., 2010). These results are further supported by animal studies that demonstrate the
29 carcinogenic potential of Libby Amphibole asbestos fibers and tremolite fibers in rodent
30 bioassays. As a durable mineral fiber of respirable size, this conclusion is consistent with the
31 extensive published literature that documents the carcinogenicity of amphibole fibers.

32 U.S. EPA’s *Guidelines for Carcinogenic Risk Assessment* (U.S. EPA, 2005a) indicate
33 that for tumors occurring at a site other than the initial point of contact, the weight of evidence
34 for carcinogenic potential may apply to all routes of exposure that have not been adequately
35 tested at sufficient doses. An exception occurs when there is convincing information (e.g.,

1 toxicokinetic data) that absorption does not occur by other routes. Information on the
2 carcinogenic effects of Libby Amphibole asbestos via the oral and dermal routes in humans or
3 animals is absent. The increased risk of lung cancer and mesothelioma following inhalation
4 exposure to Libby Amphibole asbestos has been established by studies in humans, but these
5 studies do not provide a basis for determining the risk from other routes of exposure.
6 Mesothelioma occurs in the pleural and peritoneal cavities and, therefore, is not considered a
7 portal-of-entry effect. However, the role of indirect or direct interaction of asbestos fibers in
8 disease at these extrapulmonary sites is still unknown. There is no information on the
9 translocation of Libby Amphibole asbestos to extrapulmonary tissues following either oral or
10 dermal exposure, and limited studies have examined the role of these routes of exposure in
11 cancer. Therefore, Libby Amphibole asbestos is considered “*carcinogenic to humans*” by the
12 inhalation route of exposure.

14 **4.6.1.1. *Synthesis of Human, Animal, and Other Supporting Evidence***

15 Libby, MT workers have been the subject of multiple mortality studies demonstrating an
16 increased cancer mortality in relation to estimated fiber exposure. Occupational studies
17 conducted in the 1980s (i.e., Amandus and Wheeler, 1987; McDonald et al., 1986a) as well as
18 the extended follow-up studies published in more recent years (Sullivan et al., 2007; McDonald
19 et al., 2004; Larson et al., 2010b) and additional analyses of the extended follow-up (Moolgavkar
20 et al., 2010) provide evidence of an increased risk of lung-cancer mortality and of mesothelioma
21 mortality among the workers exposed to Libby Amphibole asbestos in the Libby vermiculite
22 mining and processing operations. This pattern is seen in the lung cancer analyses using an
23 internal referent group in the larger follow-up studies (Larson et al., 2010; Sullivan, 2007;
24 McDonald et al., 2004), with cumulative exposure analyzed using quartiles or as a continuous
25 measure, and in the studies reporting analyses using an external referent group (i.e., standardized
26 mortality ratios (Sullivan, 2007; Amandus and Wheeler, 1987; McDonald et al., 1986a).
27 McDonald et al. (2004) also reported increasing risk of mesothelioma across categories of
28 exposure; the more limited number of cases available in earlier studies precluded this type of
29 exposure-response analysis. This association is also supported by the case series of
30 11 mesothelioma patients among residents in or around Libby, MT, and among family members
31 of workers in the mining operations (Whitehouse et al., 2008).

32 Although experimental data in animals and data on toxicity mechanisms are limited for
33 Libby Amphibole asbestos, tumors were observed in tissues similar to those in humans (e.g.,
34 mesotheliomas, lung cancer) indicating the existing data are consistent with the cancer effects
35 observed in humans exposed to Libby Amphibole asbestos. Smith (1978) reported increased

1 incidence of mesotheliomas in hamsters after intrapleural injections of Libby Amphibole
2 asbestos. Additionally, studies in laboratory animals (rats and hamsters) exposed to tremolite via
3 inhalation (Bernstein et al., 2005, 2003; Davis et al., 1985), intrapleural injection (Smith et al.,
4 1979; Wagner et al., 1982; Davis et al., 1991, Roller et al., 1997, 1996) or implantation (Stanton
5 et al., 1981) have shown increases in mesotheliomas and lung cancers. Tremolite from various
6 sources was used and varied in fiber content and in potency (see Section 4.2, Appendix D).
7 Although McConnell et al. (1983a) observed no increase in carcinogenicity following oral
8 exposure to nonfibrous tremolite, the ability of this study to inform the carcinogenic potential of
9 fibrous tremolite through inhalation is unclear, and these study results contribute little weight to
10 the evaluation of the carcinogenicity of fibrous Libby Amphibole asbestos.

11 The available mechanistic information suggests Libby Amphibole asbestos induces
12 effects that may play a role in carcinogenicity (see Section 4.3.4, Appendix D). Several in vitro
13 studies have demonstrated oxidative stress and genotoxicity following Libby Amphibole
14 asbestos exposures in various cell types (Blake et al., 2007; Pietruska et al., 2010; Hillegass et
15 al., 2010; Duncan et al. 2010). Libby Amphibole asbestos increased intracellular ROS in both
16 murine macrophages and human epithelial cells (Blake et al., 2007; Duncan et al., 2010).
17 Additionally, surface iron, inflammatory marker gene expression and aneugenic micronuclei
18 were increased following exposure to Libby Amphibole asbestos in human epithelial cells
19 (Duncan et al., 2010; Pietruska et al., 2010). Tremolite studies demonstrate cytotoxic and
20 clastogenic effects (e.g., micronucleus induction and chromosomal aberrations) of the fibers in
21 various cell culture systems.

22 In summary, the epidemiologic data demonstrate an association between exposure to
23 Libby Amphibole asbestos and increased cancer risk. Supporting evidence of carcinogenic
24 potential was observed in the limited number of laboratory animal studies exposed to Libby
25 Amphibole asbestos or tremolite (see Tables 4-15 and 4-16 summarizing in vivo studies).
26 Overall, the available evidence supports the conclusion that Libby Amphibole asbestos is
27 carcinogenic to humans.

28 29 **4.6.2. Mode-of-Action Information**

30 **4.6.2.1. Description of the Mode-of-Action Information**

31 EPA guidance provides a framework for analyzing the potential mode(s) of action by
32 which physical, chemical, and biological information is evaluated to identify key events in an
33 agent's carcinogenicity (U.S. EPA, 2005). Agents can work through more than one mode of
34 action (MOA), and MOA can differ for various endpoints (e.g., lung cancer versus
35 mesothelioma). Reasonably, the analysis of a MOA would start with some knowledge of an

1 agent's biological activity that leads to cellular transformation resulting in carcinogenicity.
2 Although early steps in the process often can be identified, carcinogenicity is a complex process
3 resulting from multiple changes in cell function. Due to the limited data available specific to
4 Libby Amphibole asbestos, the mode of action of Libby Amphibole asbestos for lung cancer and
5 mesothelioma following inhalation exposure cannot be established.

6 Research on various types of mineral fibers supports the role of multiple biologic
7 responses following exposure to asbestos in general (i.e., chronic inflammation, generation of
8 ROS, direct genotoxicity, and cytotoxicity and cellular proliferation) in the carcinogenic
9 response to mineral fibers. However, the complexities of fiber toxicity make it difficult to define
10 modes of action for asbestos, in general (as reviewed in Aust et al., 2011; Mossman et al., 2011;
11 Huang et al., 2011; Bunderson-Schelvan et al., 2011; Broaddus et al., 2011). Further, limitations
12 in early study design and presentation of the results hinder understanding of mode and
13 mechanism of action for specific fiber types. Most studies lack information on the
14 characterization of fibers and cell types used, hindering understanding of the mode(s) of action.
15 Particularly of importance is the route of exposure utilized in the in vivo studies, as results
16 obtained from nonphysiologically relevant routes of exposure (i.e., intraperitoneal injection,
17 gelatin implant) may not accurately reflect the response in occupational inhalation exposures.

18 Occupational studies demonstrate human health effects (e.g., lung cancer, mesothelioma)
19 following exposure to Libby Amphibole asbestos. Although the limited mechanistic data
20 demonstrate biological effects similar to those of other mineral fibers following exposure to
21 Libby Amphibole asbestos, the existing literature are insufficient to establish a mode of action
22 for Libby Amphibole asbestos for lung cancer or mesothelioma. These biological effects
23 following exposure to Libby Amphibole asbestos and/or tremolite are demonstrated in a limited
24 number of laboratory animal and in vitro studies. Multiple key events for one particular MOA
25 have not been identified; therefore, the mode of action for Libby Amphibole asbestos
26 carcinogenicity cannot be established.

27 28 **4.6.2.2. Application of the Age-Dependent Adjustment Factors**

29 As described above, the mode of action for Libby Amphibole asbestos is unknown. The
30 weight of evidence does not support a mutagenic mode of action for Libby Amphibole asbestos
31 carcinogenicity. Therefore, according to EPA's *Supplemental Guidance for Assessing*
32 *Susceptibility from Early-Life Exposure to Carcinogens* (U.S. EPA, 2005b), the application of
33 the Age-Dependent Adjustment Factors is not recommended.

1 4.7. SUSCEPTIBLE POPULATIONS

2 Certain populations may be more susceptible to adverse health effects from exposure to
3 Libby Amphibole asbestos. Because the adverse health effects resulting from exposure to Libby
4 Amphibole asbestos have been, for the most part, studied in occupational cohorts of adult white
5 men (see Sections 4.1.1 and 4.1.3), there is limited information on the effects to a broader
6 population. A few studies, however, have examined health effects resulting from
7 nonoccupational exposure in other age groups, in other genders (i.e., females), and in different
8 race or ethnicity groups. The data from these studies could inform whether any differential risk
9 exists for these groups (see Sections 4.1.2 and 4.1.4). However, it should be noted that the
10 ability to distinguish true differences from chance variation in effect estimates is related to the
11 sample size and statistical power, which, in most cases, is quite limited in these studies. In
12 addition, genetic polymorphisms, preexisting health conditions, and differences in nutritional
13 status may alter an individual's response to Libby Amphibole asbestos. Finally, coexposures to
14 other substances (e.g., tobacco smoke or particulate matter) may increase an individual's risk of
15 adverse health effects from exposure to Libby Amphibole asbestos. Where data are available,
16 each of these factors is discussed below with respect to increased susceptibility to noncancer
17 effects and cancer from exposure to Libby Amphibole asbestos, and where information specific
18 to Libby Amphibole asbestos is not available, the general literature on the toxicity of mineral
19 fibers is briefly referenced.

20 There are also factors that may influence one's exposure potential to asbestos based on
21 lifestage or other defined population. For example, children spend more hours outside and may
22 engage in activities which impact exposure level compared to adults (NRC, 1993; U.S. EPA
23 2006). Because lifestage and activity patterns can increase the potential for health effects from
24 exposure, these factors define those who may be more susceptible to health effects due to greater
25 exposure. Section 2.3 discusses this exposure potential, including how children workers,
26 household contacts and residents may be exposed to Libby Amphibole asbestos.

27 28 4.7.1. Influence of Different Lifestages on Susceptibility

29 Individuals at different lifestages differ from one another physiologically, anatomically,
30 and biochemically. Individuals in early and later lifestages differ markedly from adulthood in
31 terms of body composition, organ function, and many other physiological parameters, which can
32 influence the toxicokinetics and toxicodynamics of chemicals and their metabolites in the body
33 (ILSI, 1992). This also holds true for mineral fibers, including asbestos fibers (see Section 3).
34 This section presents and evaluates the literature on how individuals in early or later lifestages

1 might respond differently and thus potentially be more susceptible to adverse health effects of
2 Libby Amphibole asbestos exposure.

4 **4.7.1.1. *Lifestage Susceptibility***

5 Humans in early lifestages (i.e., conception through adolescence) can have unique
6 susceptibilities compared to those in later lifestages because they undergo rapid physiological
7 changes during critical periods of development (Selevan et al., 2000). Furthermore, they are
8 often exposed to xenobiotics via unique exposure pathways (i.e., transplacental transfer and
9 breast milk ingestion) (NRC, 1993; U.S. EPA, 2006, 2008). Although no data exist for Libby
10 Amphibole asbestos, limited observations in stillborn infants indicate occurrence of
11 transplacental transfer of tremolite (Haque et al., 1996, 1998) and other asbestos and nonasbestos
12 fibers (Haque et al., 1991, 1992, 1996, 1998). Haque et al. (1992) hypothesized that maternal
13 health conditions might influence the translocation of fibers, as some of the mothers had
14 preexisting health conditions. Transplacental transfer of asbestos also has been demonstrated in
15 animals following maternal exposure by gavage (Haque et al., 2001) or injection (Cunningham
16 and Pontefract, 1974; Haque and Vrazel, 1998) (see Section 3). These studies did not evaluate
17 sources or levels of exposure, and injection studies are a less relevant route of exposure than
18 inhalation. Based on these studies, Libby Amphibole asbestos fibers may be transferred through
19 the placenta, resulting in prenatal exposure at any stage of fetal development.

20 Increased lung deposition of fibers in children compared with adults has been observed
21 (Asgharian et al., 2004; Bennett et al., 2008; Isaacs and Martonen, 2005; Oldham et al., 1997;
22 Phalen and Oldham, 2001; Phalen et al., 1985; Schiller-Scotland et al., 1994). Nasal deposition
23 of particles was shown to be lower in children compared to adults—particularly during exercise
24 (Becquemin et al., 1991). The lung and nasal depositional differences are due in part to
25 structural differences across lifestages, which can change the depositional pattern of different
26 fiber sizes and possibly alter the site of action and result in differential clearance and subsequent
27 health effects. It is unclear, however, whether the lung surface, body weight, inhalation volume,
28 or exposure patterns are most determinative of dose. One study reported that the ratio of lung
29 surface area to body weight does not differ considerably for a 10-month old, a 9-year old, and an
30 adult (Short, 1952). Another study suggested that deposition of fine particles (2- μ m mass
31 median aerodynamic diameter, which is in the size range of those for Libby Amphibole asbestos
32 reported in Table 2-2) in the lung is increased for overweight ($\geq 95^{\text{th}}$ percentile BMI) children
33 who breathe more at rest compared to underweight children ($< 25^{\text{th}}$ percentile BMI) (Bennett and
34 Zeman, 2004).

1 There are few studies analyzing noncancer outcomes in children exposed to Libby
2 Amphibole. A Libby medical screening program collected data on 7,307 participants, including
3 600 children aged 10–17 years old, representing 8.2% of the cohort (Peipins et al., 2003).
4 Pulmonary function tests showed that none of these children had moderate or severely restricted
5 lung function (ATSDR, 2001, 2002). This study also studied chest radiographs for those
6 18 years old or older (ATSDR, 2001; Noonan et al., 2006; Peipins et al., 2003), but X-rays were
7 not conducted on children. In addition, the prevalence of some self-reported respiratory
8 symptoms among 10–29-year-old adolescents and young adults was associated with certain
9 exposure pathways. These participants were ≤ age 18 in 1990 when the mining/milling
10 operations closed (Vinikoor et al., 2010). Understanding of the community health effects and the
11 examination of the potential progression of adverse health effect in this community would
12 benefit from additional research to establish the clinical significance of these findings. No other
13 studies of noncancer outcomes in early lifestages of humans or experimental animals exposed to
14 Libby Amphibole asbestos have been reported.

15 For exposure to other types of asbestos, studies have reported noncancer outcomes in
16 early lifestages. Those in the very young include reports of stillbirth (Haque et al., 1996, 1998)
17 and death among infants (age 1–27 months) due to sudden infant death syndrome and
18 bronchopulmonary dysplasia (Haque and Kanz, 1988). These studies found higher levels of
19 asbestos in the lungs of those who died compared to controls. In the infant study, the authors
20 speculate that either there was a preexisting abnormal lung physiology in these children that may
21 contribute to a reduced ability to clear fibers from the lung, or that the children could have an
22 increased exposure to asbestos (Haque and Kanz, 1988). Those in older children include reports
23 of pleural and diaphragmatic calcifications (Epler et al., 1980) and altered immune and
24 respiratory conditions (Shtol et al., 2000).

25 In experimental animals, offspring of rats exposed to tremolite had decreased body
26 weight gain at weaning and 8-weeks-old compared to controls (McConnell et al., 1983a; NTP,
27 1990b). This was also observed in some similar studies of other forms of asbestos (McConnell
28 et al., 1983a; NTP, 1985, 1988, 1990a, 1990b) but not in others (McConnell et al., 1983b; NTP,
29 1983). Embryonic toxicity was observed in a few experimental animal studies. Crocidolite
30 injected into pregnant mice resulted in altered limb differentiation in cultured embryos (Krowke
31 et al., 1983, abstract), and chrysotile in drinking water given to pregnant mice resulted in
32 decreased postimplantation survival in cultured embryos (Schneider and Maurer, 1977);
33 however, pregnant mice exposed to chrysotile in drinking water did not affect in vivo embryonic
34 survival (Schneider and Maurer, 1977).

1 It is possible that early lifestage exposure may increase the risk of noncancer outcomes in
2 adulthood compared to adult exposure. After tremolite exposure during childhood, one study
3 reported altered immunity in adulthood (Zerva et al., 1989), and one study described a case
4 report of asbestosis in adulthood (Voisin et al., 1994). Another study also reported an increased
5 risk of asbestosis after childhood exposure to asbestos from parental occupational exposure to
6 asbestos (Kilburn et al., 1985). To address the potential for increased susceptibility to cancer
7 from early lifetime exposures, one needs to consider if there is evidence of differential health
8 effects such as increased potency from early lifetime exposure, decreased latency based on the
9 age of exposure, or cancers observed with early lifetime exposures not seen with adult exposures.
10 There are no published reports that can directly answer these questions for exposure to Libby
11 Amphibole asbestos.

12 While cancers in adults have been documented following exposure to Libby Amphibole
13 asbestos, similar reports describing childhood cancers resulting from this exposure have not been
14 identified. Few cancers occurring in children have been documented in children exposed to any
15 form of asbestos. Examples of cases include a 17-year old exposed to chrysotile and tremolite
16 (Andrion et al., 1994) and a 3-year old exposed to chrysotile (Lieben and Pistawka, 1967), both
17 of whom developed mesothelioma. However, childhood mesothelioma, in particular, may have
18 an etiology that is different from that of the disease that is seen in adults (Cooper et al., 1989).
19 No cancer bioassays have been performed in juvenile animals exposed to Libby Amphibole
20 asbestos.

21 Of the 11 Libby Amphibole asbestos-related mesothelioma cases described by
22 Whitehouse et al. (2008), 2 reported potential exposure scenarios that were limited to childhood,
23 and both of these were diagnosed at a relatively young age at diagnosis (48, compared with 52 to
24 82 years of age for the other nine cases). Although these case studies support the link between
25 exposure to Libby Amphibole asbestos and mesothelioma, it is unclear if children are more
26 susceptible than adults.

27 Case reports of exposure to tremolite during childhood, and subsequent diagnosis of
28 mesothelioma in adulthood (Magee et al., 1986; Rey et al., 1993; Sakellariou et al., 1996;
29 Schneider et al., 1998; Senyigit et al., 2000), support the limited data summarized above for
30 Libby Amphibole asbestos. Additional case studies of mesothelioma after childhood exposure to
31 other types of asbestos are available (Anderson et al., 1976; Ascoli et al., 2003; Cazzadori et al.,
32 1992; Inase et al., 1991; Kane et al., 1990; Li et al., 1978, 1989; Magnani et al., 2001;
33 Martensson et al., 1984; Roguin et al., 1994; Rom et al., 2001; Schneider et al., 1995, 1996a, b;
34 Wagner et al., 1960; Wassermann et al., 1980; Yano et al., 2009). These studies, however, do

1 not clarify whether exposure during childhood yields different adverse health effects compared
2 with exposure during adulthood.

3 In experimental studies, the offspring of rats orally exposed to nonfibrous tremolite did
4 not demonstrate an increase in tumors compared to controls (McConnell et al., 1983a; NTP,
5 1990b). Similar studies of other forms of asbestos did report an increase of various neoplasms in
6 the offspring (McConnell et al., 1983a, 1983b; NTP, 1985, 1988, 1990a), but another study
7 reported none (NTP, 1983).

8 Studies of exposure to other types of asbestos have attempted to determine if exposure to
9 asbestos in early life results in an increased risk of developing cancer. An early study in the
10 United Kingdom described occupational exposure to chrysotile, crocidolite, and amosite for a
11 group of 900 women. First exposure from ages 15–24 years led to a higher relative mortality
12 risk for lung and pleural cancer compared with women who were first exposed at older ages
13 (SMR 30 based on 12 observed and 0.4 expected, SMR 8 based on 4 observed and 0.5 expected,
14 and SMR 6.7 based on 6 observed and 0.9 expected in the first exposure at ages 15–24, 25–34,
15 and ≥ 35 years, respectively) (Newhouse et al., 1972). A study by Hansen et al. (1998) in
16 Wittenoom, Western Australia examined 27 individuals diagnosed with mesothelioma who had
17 been environmentally exposed to crocidolite (i.e., residents of the town but not directly employed
18 in the area’s crocidolite mining and milling industry); 11 of these subjects were children
19 < 15 years old at the time of exposure. One-third of all the subjects were less than 40 years old
20 when diagnosed, but the authors found no increase in mesothelioma mortality rates when
21 analyzed by age at first exposure. However, risk was significantly increased based on time from
22 first exposure, duration of exposure, and cumulative exposure (Hansen et al., 1998). Additional
23 studies of this cohort found that the mesothelioma mortality rate was lower for those first
24 exposed (based on age residence in the area began) to crocidolite at ages < 15 years ($n = 24$;
25 mesothelioma mortality rate 47 per 100,000 person-years) compared with those first exposed at
26 ages ≥ 15 years ($n = 43$; mesothelioma mortality rate 112 per 100,000 person-years) (Reid et al.,
27 2007). The hazard ratio for age at first residential exposure of ≥ 15 years compared with
28 < 15 years was 3.83 (95% CI: 2.19, 6.71), adjusting for cumulative exposure, gender, and an
29 interaction term for gender and cumulative exposure.

30 Based on these very limited and inconclusive studies on other forms of asbestos, no
31 conclusions can be drawn about differential risk of adverse health effects after early lifestage
32 exposure to Libby Amphibole asbestos compared to exposure during adulthood. It is unknown
33 whether early lifestage exposure compared to adult exposure increases susceptibility for adult
34 cancers, as measured by increased incidence, severity, or disease progression, or by decreased
35 latency.

1 Later lifestage is generally defined as ≥ 65 years old. Because pulmonary function
2 (volume and rate of breathing) decreases with age (Weiss, 2010), increased deposition of fibers
3 in the lung from exposures in later lifestages is unlikely. Clearance of fibers from the lung might
4 be reduced, however, as older adults have a less effective cough reflex and strength and the cilia
5 are less able to move mucus up and out of the airway (U.S. EPA, 2005). Older adults could be
6 more susceptible to the effects of Libby Amphibole asbestos due to the gradual age-related
7 decline in physiological processes. Additionally, decreased immune function, increased genetic
8 damage, and decreased DNA repair capacity can result in increased susceptibility with age
9 (U.S. EPA, 2005). These age-associated alterations could decrease fiber-induced DNA damage
10 repair but might also reduce the incidence of fiber-induced DNA damage due to decreased
11 phagocytosis or inflammation. Specific data pertaining to age-varying effects of Libby
12 Amphibole asbestos on these processes are not available.

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

28 No studies assessing the carcinogenic effect of exposures occurring in older age groups
29 are available for Libby Amphibole asbestos. It should be noted that observed health effects
30 among individuals exposed to Libby Amphibole asbestos are likely to increase with increasing
31 age due to the long latency period for the exposure response for asbestos and lung cancer and
32 other chronic diseases. However this type of observation would not directly address the question
33 of whether exposures at older ages have a stronger or weaker effect compared with exposures at
34 younger ages.

35

1 **4.7.2. Influence of Gender on Susceptibility**

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

12 Most occupational studies for Libby Amphibole asbestos have examined the effects of
13 exposure only in men (Amandus and Wheeler, 1987; Amandus et al., 1987a, 1988; McDonald
14 et al., 1986a, 1986b, 2004; Sullivan, 2007; Moolkavkar et al., 2010). There is limited
15 information specifically on women exposed to Libby Amphibole asbestos. In the Libby, MT
16 community studies, no gender-related trends in mortality due to lung or digestive cancer were
17 observed (ATSDR, 2000). These limited data do not provide a basis for drawing conclusions
18 regarding gender-related differences in adverse health effects from Libby Amphibole asbestos.
19

20 **4.7.3. Influence of Race or Ethnicity on Susceptibility**

21 Race and ethnicity often are used in medical and epidemiological studies to define
22 various groups of the population. These categories could be surrogates for differences in
23 exposure (e.g., occupation, socioeconomic, behavior) or biology (e.g., physiology, genetics), in
24 which case these factors may play a role in susceptibility as well. Nasal structure and lung
25 architecture can influence the depositional patterns for both particles and fibers. One study of
26 18 Caucasians (ages 8 to 30 years) and 14 African Americans (ages 8 to 25 years) reported
27 increased ventilation rates during exercise in the African Americans (matched on sex, age,
28 height, and weight) (Cerny, 1987). Another study (11 Caucasians and 11 African Americans,
29 ages 18 to 31 years) reported decreased nasal deposition efficiency (for particle sizes of 1–2 μm ,
30 which is in the range of those for Libby Amphibole asbestos reported in Table 2-2) in African
31 Americans compared to Caucasians (Bennett and Zeman, 2005). Furthermore, nasal breathing
32 during exercise occurred less in Caucasians compared to African Americans in this study
33 (Bennett et al., 2003).

34 Of the occupational and residential studies for Libby Amphibole asbestos, the vast
35 majority of subjects with known race were white, precluding the ability to conduct an analysis of

1 racial and ethnicity-related differences in the mortality risks within the Libby worker cohort. In
2 a study of occupational exposure to chrysotile asbestos in a textile factor, lung-cancer mortality
3 risk in relation to exposure was lower in nonwhite males (0.84, 95% CI: 0.52–1.27) compared to
4 white males (2.34, 95% CI: 1.94–2.79), although a statistically significant increase in SMR was
5 observed for nonwhite males at high exposure levels (≥ 120 fiber-years/mL) (Hein et al., 2007).
6 This observed difference could be due to a lower prevalence of smoking among nonwhite
7 compared with white males (Hein et al., 2007).

9 **4.7.4. Influence of Genetic Polymorphisms on Susceptibility**

10 XRCC1 is a DNA damage repair gene. A recent study demonstrated that
11 XRCC1-deficient cells exposed to Libby Amphibole or crocidolite asbestos demonstrated
12 increased levels of micronuclei induction (Pietruska et al., 2010). Two other studies examined
13 XRCC1 polymorphisms in relation to disease risk with other types of asbestos exposure. Zhao
14 et al. (2005) found no association between XRCC1 polymorphisms and asbestosis in
15 asbestos-exposed workers. A study by Dianzani et al. (2006), however, did find an association
16 between XRCC1 and asbestos-induced lung disease in a population exposed to asbestos
17 pollution. Further work is necessary, with clear definitions of patient populations and their
18 exposure levels, so that these studies and others can be compared to determine if XRCC1
19 polymorphisms increase susceptibility to adverse health effects following exposure to Libby
20 Amphibole asbestos.

21 SODs are free radical scavengers that dismutate superoxide anion to oxygen and
22 hydrogen peroxide. SODs are expressed in most cell types exposed to oxygen. Several common
23 forms of SODs occur and are named by the protein cofactor: copper/zinc, manganese, iron, or
24 nickel. A recent study observed no significant alterations in levels of intracellular SOD
25 following a 3 hour exposure to Libby Amphibole asbestos in mice (Blake et al., 2007). Other
26 studies in humans and mice have examined SOD expression in relation to other types of asbestos
27 exposure. Manganese superoxide dismutase activity was elevated in biopsies of human
28 asbestos-associated malignant mesothelioma, although no genotypic differences were found to
29 be related to this change in activity (Hirvonen et al., 2002). Other studies have focused on the
30 role of extracellular superoxide dismutase (EcSOD) and asbestos-induced pulmonary disease
31 (Fattman et al., 2006; Gao et al., 2008; Kliment et al., 2008; Tan et al., 2004). These studies
32 have suggested a protective effect of EcSOD, with mice that lack this form of SOD having
33 increased sensitivity to asbestos-induced lung injury (Fattman et al., 2006). Familial studies
34 showing unusually high incidence of mesothelioma suggest that genetic factors might play a role
35 in the etiology of mesothelioma (Huncharek, 2002; Roushdy-Hammady et al., 2001; Ugolini

1 et al., 2007), although whether a genetic factor or a common environmental element leads to the
2 similar responses in these families is difficult to determine. Increased interest in the role of
3 genetic factors in asbestos-related health outcomes has led to several analytical studies on
4 specific genetic polymorphisms. A review of 24 published reports (19 studies) discusses the
5 current state of knowledge regarding genetic susceptibility associated with asbestos-related
6 diseases (in particular, malignant pleural mesothelioma). Results from several studies
7 demonstrated an association between asbestosis-related diseases and GSTM1-null
8 polymorphism, whereas results for other polymorphisms were conflicting (Neri et al., 2008).
9 Some polymorphisms discussed in Neri et al. (2008) are in genes for *N*-acetyl-transferase 2;
10 glutathione-s-transferases (GSTs); SOD; CYP1A1, CYP2D6; neurofibromatous 2 (Nf2); p53;
11 and XRCC1. Although occupational asbestos exposure was assessed, the type of asbestos is
12 generally unknown in these studies.

13 Limited animal studies have examined the role of genetic variations related to asbestos
14 exposure, including specific signaling pathways (Shukla et al., 2007), DNA damage repair (Lin
15 et al., 2000; Ni et al., 2000), and tumor suppressor genes (Kleymenova et al., 1997; Vaslet et al.,
16 2002; Marsella et al., 1997). Genetic alterations of particular interest for mesothelioma include
17 those involved in tumor suppression (p53, Nf2) and oxidative stress (SOD, GSTs). Nf2 and p53
18 are frequently altered in mesotheliomas, but no consistent mutations have been found (Bianchi
19 et al., 1995; Cheng et al., 1999; Mayall et al., 1999). Alterations in expression of antioxidant
20 enzymes like SOD and GST in mesothelioma can yield cells more resistant to oxidative stress as
21 compared to normal cells due to increased antioxidant activity (Ramos-Nino et al., 2002;
22 Rahman et al., 1999). No studies that examine the role of cell-cycle control genes were found
23 following exposure to Libby Amphibole asbestos. Additionally, no information on other genetic
24 polymorphisms in relation to disease risk among those exposed to Libby Amphibole asbestos
25 was identified in the available literature.

26

27 **4.7.5. Influence of Health Status on Susceptibility**

28 Preexisting health conditions could potentially alter the biological response to asbestos
29 exposure. Mesothelioma risk has been hypothesized to be related to immune impairment
30 (Bianchi and Bianchi, 2008) and simian virus 40 exposure in humans (Bocchetta et al., 2000;
31 Carbone et al., 2007; Cristaudo et al., 2005; Foddiss et al., 2002; Mayall et al., 1999; Kroczyńska
32 et al., 2006). Coexposure to asbestos and SV40 has been associated with p53-related effects in
33 vitro (Mayall et al., 1999; Bocchetta et al., 2000; Foddiss et al. 2002), and cell signaling
34 aberrations in vivo (Kroczyńska et al., 2006; Cristaudo et al. 2005). However, the influence on

1 cancer risk is unknown, as these lines of research are not fully developed and have not been
2 applied specifically to Libby Amphibole asbestos.

3 Obesity can compromise inhalation exposure, as increased particle deposition in the lungs
4 of overweight children (Bennett and Zeman, 2004) and adults (Graham et al., 1990) has been
5 observed. Individuals with respiratory diseases could have compromised lung function that
6 alters inhalation exposure to Libby Amphibole asbestos. For example, individuals with chronic
7 obstructive pulmonary disease have increased inhalation volume (Phalen et al., 2006) and
8 increased fine particle deposition (Bennett et al., 1997; Kim and Kang, 1997; Phalen et al., 2006)
9 and retention (Regnis et al., 2000). Similarly, studies have reported an increase in coarse particle
10 (aerodynamic diameter >5 µm) deposition in individuals with cystic fibrosis (Brown et al., 2001;
11 Brown and Bennett, 2004). For people exposed to Libby Amphibole asbestos, an increased risk
12 for interstitial lung abnormalities was observed for those with a history of pneumonia (Peipins
13 et al., 2003). In another study, bronchial asthma was examined as a potential confounding
14 variable for asbestos-related effects on pulmonary function, although no confounding was
15 observed (Whitehouse, 2004).

16 17 **4.7.6. Influence of Lifestyle Factors on Susceptibility**

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

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

1 **4.7.7. Susceptible Populations Summary**

2 A very limited amount of information is available on exposure to Libby Amphibole
3 asbestos early in life that could lead to increased risk of asbestos-induced disease later in life.
4 Due to the long latency period of some diseases in relation to asbestos exposure in general,
5 adverse effects may be more likely to be observed with an increase in age. This assumption
6 requires further investigation. The number of women who have been occupationally exposed to
7 Libby Amphibole asbestos is very small, and health risks have not been evaluated specifically
8 for this group. Differences between men and women in residential sources and types of exposure
9 (e.g., types of activities done in the household) also preclude the possibility of drawing
10 conclusions regarding the relative susceptibility of women compared with men to health effects
11 of exposure to Libby Amphibole asbestos. Similarly, sufficient data are not available to draw
12 conclusions regarding racial or ethnic variation in susceptibility to diseases caused by exposure
13 to Libby Amphibole asbestos. In addition, the potential modifying effects of genetic
14 polymorphisms, preexisting health conditions, nutritional status, and other lifestyle factors have
15 not been studied, specifically as related to exposure of Libby Amphibole asbestos and health
16 outcomes.

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5. EXPOSURE-RESPONSE ASSESSMENT

5.1. ORAL REFERENCE DOSE (RfD)

Data are unavailable to characterize the toxic effects of Libby Amphibole asbestos¹ following oral exposure. Thus, an oral reference dose is not derived.

5.2. INHALATION REFERENCE CONCENTRATION (RfC)

5.2.1. Choice of Principal Study and Critical Effect

Studies in humans have shown radiographic evidence of health effects on the lung and pleura (a thin tissue surrounding the lung and lining the chest cavity) such as pleural thickening and fibrosis of the lung and pleura in exposed workers (Rohs et al., 2008; Amandus et al., 1987b; McDonald et al., 1986b; Lockey et al., 1984) as well as community studies (Weill et al., 2010; Peipins et al., 2003; Peipins et al., 2004; Whitehouse, 2004; Muravov et al., 2005) (see Sections 4.1.1.4 and 4.1.2). Five cohort mortality studies of workers who mined, milled, and processed Libby vermiculite (henceforth described as the Libby workers) identified increased risk of mortality from noncancer causes including nonmalignant respiratory disease—especially asbestosis, chronic obstructive pulmonary disease, and silicosis (McDonald et al., 1986a; Amandus et al., 1987b; McDonald et al., 2004; Sullivan, 2007; Larson et al., 2010a) as well as cardiovascular disease (Larson et al., 2010a). Additionally, there is a potential for autoimmune effects following inhalation exposure to Libby Amphibole asbestos (Noonan et al., 2006; Pfau et al., 2005; see Section 4.3). The overall noncancer hazard identification for exposure to Libby Amphibole asbestos is summarized in Section 4.5. A reference concentration (RfC) is intended to define an exposure level that is likely to be without an appreciable risk of adverse health effects; studies that relate these health effects to exposure levels are necessary for RfC derivation². Quantitatively, study characteristics preferred for RfC derivation include adequate exposure-response information, ideally with analyses based on estimates including assignment of quantitative exposure estimates to distinguish exposure levels in the study subjects.

Of the available human studies, only the worker mortality and morbidity studies provide exposure estimates suitable for quantitative analysis to derive benchmark concentration estimates or NOAELs/LOAELs and, thus, would allow for consideration for use in RfC derivation (Rohs

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.

² An RfC is defined as “An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime.”

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1 et al., 2008; Amandus et al., 1987b; McDonald et al., 1986a,b, 2004; Amandus and Wheeler,
2 1987; Sullivan, 2007; Larson et al., 2010a; Lockey et al., 1984). Although there are data that
3 define exposures from some activities in the community (see Section 2.3), these data do not
4 address all potential exposures nor are data available on activity patterns, which would be needed
5 to provide individual exposure measurements. There are no studies in laboratory animals on the
6 inhalation route of exposure suitable for derivation of an RfC because available animal studies
7 lack adequate exposure-response information and are of a short-term duration. Therefore, only
8 the worker studies that include adequate exposure assessment and identify health effects are
9 considered for RfC derivation.

10 Five cohort mortality studies of Libby workers identified increased risk of mortality from
11 noncancer causes (McDonald et al., 1986a, 2004; Amandus and Wheeler, 1987; Sullivan, 2007;
12 Larson et al., 2010a). These studies were not considered as candidates for RfC derivation
13 because the radiographic parenchymal and pleural abnormalities are more sensitive than the
14 corresponding mortality causes. An RfC is intended to be a level at which no category of
15 adverse health outcome would occur.

16 Although one study (i.e., Larson et al., 2010a) has reported an increase in mortality from
17 various cardiovascular diseases, no studies have been conducted in a population exposed to
18 Libby Amphibole asbestos on cardiovascular endpoints other than mortality. The reported
19 excess mortality specific to vascular effects is unique, and further substantiation of this finding is
20 needed. Thus, the mortality represents a more severe health effect from related pulmonary and
21 pleural endpoints. The less severe indicator of the first radiographic changes is the preferred
22 endpoint for RfC derivation.

23 Several morbidity studies examined the quantitative association between exposure to
24 Libby Amphibole asbestos and lesions in the lung or surrounding pleura in exposed human
25 populations; two are studies in Libby workers (Amandus et al., 1987b; McDonald et al., 1986b),
26 and two are studies in workers from the Marysville, OH facility (Lockey et al., 1984; Rohs et al.,
27 2008). Rohs et al. (2008) was a follow-up study to Lockey et al. (1984) on a subset of the same
28 cohort and reported a higher prevalence of adverse effects following the longer time from first
29 exposure. These four studies, all of which demonstrate an association between Libby Amphibole
30 asbestos exposure and increased risk of effects on the lung and pleura, were considered for
31 selection as the principal study to serve as the basis for the derivation of the RfC.

32 All four candidate principal studies (Rohs et al., 2008; Amandus et al., 1987b; McDonald
33 et al., 1986b; Lockey et al., 1984) have adequate reporting of the studied populations, methods of
34 analysis, statistical analyses, and results. Each of the four candidate studies reports radiographic
35 signs of nonmalignant respiratory effects, which may be considered as endpoints for an RfC

1 derivation, specifically pleural thickening (localized and/or diffuse) and small opacities
2 (indicative of parenchymal damage) (ILO, 1971, 1980, 2000). Table 5-1 summarizes the four
3 candidate principal studies. See Sections 4.1.1.4 and 4.1.3 for detailed study information.
4

5 **5.2.1.1. *Evaluation of Candidate Studies and Selection of Critical Study***

6 The candidate studies were evaluated in terms of quality attributes that would support
7 their use as a principal study in the derivation of an RfC. When selecting among candidate
8 principal studies, there were several factors, summarized in Table 5-2, that were generally
9 considered.
10

11 **5.2.1.2. *Evaluation of Exposure Paradigm in Candidate Studies***

12 Each of the studies provided estimates of cumulative Libby Amphibole asbestos exposure
13 (in fibers/cc-year), rather than mean or peak exposure. However, there were differences in
14 exposure intensity. In contrast to vermiculite facility workers in Libby, MT, the workers at the
15 O.M. Scott Plant in Marysville, OH, were generally exposed at lower levels (see Table 5-1), and
16 were primarily exposed in the workplace. Because of showering and changing into civilian
17 clothes at the end of the work shift for most employees, nonoccupational exposure in the
18 Marysville workers was minimal. Despite the uncertainty in the magnitude of pre-1972
19 exposures (discussed below), the available data indicate worker exposures in the Marysville
20 plant did not generally include the high intensity exposures observed for the Libby worker
21 cohort, with Rohs et al. (2008) reporting a mean exposure of 2.48 fibers/cc-year. The lower
22 intensity exposures for the Marysville cohort and corresponding lower cumulative exposures are
23 advantages of this study, considering there are uncertainties inherent in exposure-response data
24 and extrapolating from the high intensity occupation exposures to lower level exposures often
25 seen in community and environmental exposures.
26

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

Cohort and reference	Study population	Outcome assessment	Radiographic endpoints evaluated	Exposure assessment	Exposure characteristics												
<i>Libby Worker Cohort</i>																	
McDonald et al., 1986b	244 employees, comprising 164 “current” workers (as of July 1, 1983) and 80 “past” workers Age at exam (years): <table border="1" data-bbox="388 600 697 722"> <thead> <tr> <th></th> <th>“current”</th> <th>“past”</th> </tr> </thead> <tbody> <tr> <td><39</td> <td>80</td> <td>1</td> </tr> <tr> <td>40–59</td> <td>69</td> <td>30</td> </tr> <tr> <td>>60</td> <td>15</td> <td>49</td> </tr> </tbody> </table> No job tenure information; (10.7 years as reported by Armstrong et al., 1988)		“current”	“past”	<39	80	1	40–59	69	30	>60	15	49	Radiographs taken at time of cohort assembly (1983) Films independently read by three experienced readers using 1980 ILO standards Film quality: Good: 56% Fair: 36% Poor: 7% Unreadable: 0.4%	1) Parenchymal changes (small opacities $\geq 1/0$) 2) Pleural changes (pleural thickening on chest wall, pleural calcification)	Individual work histories and exposure levels for specific work locations were used to estimate cumulative exposures for cohort members. 1935–1967: Exposure estimated based on professional judgment. For mill locations only (1950–1967), exposure estimated using dust-to-fiber conversion and interviews with plant employees. 1968–1982: Air samples analyzed for fibers by PCM analysis.	Mean cumulative exposure “current” 40.1 fibers/cc-yr “past” 118.9 fibers/cc-yr Exposure categories: <10 fibers/cc-yr ($n = 92$) 10–<20 fibers/cc-yr ($n = 64$) 20–<100 fibers/cc-yr ($n = 53$) 100–<200 fibers/cc-yr ($n = 16$) ≥ 200 fibers/cc-yr ($n = 19$)
	“current”	“past”															
<39	80	1															
40–59	69	30															
>60	15	49															

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

Cohort and reference	Study population	Outcome assessment	Radiographic endpoints evaluated	Exposure assessment	Exposure characteristics
Amandus et al., 1987b	<p>184 men employed 1975–1982, with at least 5 years job tenure</p> <p>Mean (SD), years: Age at exam: 44 (12) Job tenure: 14 (8)</p>	<p>Company radiographs Source year: 1981–1982 (72.8%) 1976–1980 (26.6%) <1975 (1 worker)</p> <p>Films independently read by three readers using 1980 ILO standards</p> <p>Film quality (by reader): Excellent: 22.8, 24.4, 47.9% Acceptable: 60.9, 60.9, 29.3% Poor: 16.3, 14.7, 22.8% Unreadable: None</p>	<p>1) Parenchymal changes (small opacities $\geq 1/0$)</p> <p>2) Pleural changes (“any pleural change”^a, pleural calcification, pleural thickening on chest wall only)</p>	<p>Individual work histories and exposure levels for specific work locations were used to estimate cumulative exposures for cohort members.</p> <p>1935–1967: Exposure estimated based on professional judgment. For mill locations only (1950–1967), exposure estimated using dust-to-fiber conversion and interviews with plant employees.</p> <p>1968–1982: Air samples analyzed for fibers by PCM analysis.</p>	<p>Exposure categories: 0–15 fibers/cc-year ($n = 63$) 16–30 fibers/cc-year ($n = 29$) 31–85 fibers/cc-year ($n = 44$) >86 fibers/cc-year ($n = 48$)</p>

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

Cohort and reference	Study population	Outcome assessment	Radiographic endpoints evaluated	Exposure assessment	Exposure characteristics
O.M. Scott Plant Cohort, Marysville, OH^b					
Lockey et al., 1984	512 plant employees Mean (range), years: Age at exam: 37.5 (19–66) Mean (SE), years: Job tenure by exposure group and smoking status (NS=nonsmoker, EX=former smoker, CS=current smoker) Low, NS: 6.6 (1.1) Low, EX: 11.3 (1.6) Low, CS: 10.5 (1.2) Medium, NS: 8.4 (1.0) Medium, EX: 13.3 (1.3) Medium, CS: 8.9 (0.7) High, NS: 12.2 (0.9) High, EX: 13.0 (1.1) High, CS: 10.7 (0.9)	Posterior-anterior chest radiographs taken in 1980 Films independently read by 2 board-certified radiologists (B-readers) using modification of 1971 ILO standards. A third B-reader was used to resolve any difference in diagnosis.	1) Parenchymal changes (only one small opacity recorded [grade 1/1], unclear if opacities graded 1/0 or 0/1 would have been reported) 2) Pleural changes (pleural plaque, pleural thickening, pleural calcification) 3) Costophrenic angle blunting only	Self-reported individual work histories and exposure levels for specific work locations were used to estimate cumulative exposures for cohort members. 1957–1971: Exposure estimated based on interviews with plant employees and post-1972 air measurements. Some workplace exposure control measures were taken prior to 1972. 1972–1980: Air samples analyzed for fibers by PCM analysis. The exposure reconstruction in the original study was based on limited data, and air sampling data from 1972 on were not available for all jobs. Where data were not available, the earliest available sampling data informed early exposures (Lockey, 1985).	Exposure categories: <1 fibers/cc-year (<i>n</i> = 253) 1–10 fibers/cc-year (<i>n</i> = 200) >10 fibers/cc-year (<i>n</i> = 48)

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

Cohort and reference	Study population	Outcome assessment	Radiographic endpoints evaluated	Exposure assessment	Exposure characteristics
Rohs et al., 2008	280 plant employees (follow-up of cohort described in Lockey et al., 1984) Mean (SD), range (years): Age: 59.1 (10.5), 44–87 Mean (SD), median (years): Years since first exposure No pleural changes (n = 200): 32.1 (5.5), 31.0 Pleural changes present (n = 80): 36.8 (4.9), 37.9	Posterior-anterior chest radiographs taken 2002–2005 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	1) Parenchymal changes (small opacities, profusion score >1/0) 2) Pleural changes (localized pleural thickening [any pleural thickening excluding costophrenic angle blunting], diffuse pleural thickening [any pleural thickening with costophrenic angle blunting], pleural calcification)	Exposure assessment from Lockey et al. (1984) with change in start date to 1963.	Exposure categories: 0.01–0.28 fibers/cc-year (n = 70) 0.29–0.85 fibers/cc-year (n = 72) 0.86–2.20 fibers/cc-year (n = 68) 2.21–19.03 fibers/cc-year (n = 70)

^aAmandus et al. (1987c, p. 28) define “any pleural change” as “...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...”

^bIn addition to the exposure information used by Lockey et al. (1984) and Rohs et al. (2008), the University of Cincinnati augmented and refined these exposure estimates using additional exposure data, which included industrial hygiene measurements not previously available and measurements using industrial hygiene data from the facility to determine estimates of exposure after 1980.

Table 5-2. Summary of rationale for identifying candidate principal studies on Libby Amphibole asbestos for RfC development

Attribute	Preferred characteristics for candidate principal studies for the Libby Amphibole Asbestos RfC
Relevance of exposure paradigm	<p>Studies of subchronic or chronic duration are preferred over studies of acute exposure duration because most relevant environmental exposure scenarios are expected to address chronic exposure scenarios (potentially including both continuous exposure from ambient conditions and episodic activity-related exposures).</p> <p>Measures of cumulative exposure are a widely used metric to address asbestos risk. It is consistent with the expectation that toxic responses will reflect an accumulative effect of asbestos inhaled and deposited in tissues over time. Additionally, mean exposure, exposure duration, and time from first exposure (TSFE) have all been reported as predictors of health effects from asbestos exposure. Cumulative exposure has the advantage that it reflects both duration and intensity (e.g., mean level) of asbestos exposure.</p> <p>Relatively lower 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.</p> <p>Results from studies with high exposure intensity or cumulative exposure are, other things being comparable, judged less relevant for environmental risk assessment compared to studies defining effects at lower levels of exposure. Some biological processes (e.g., potential decrease in effectiveness of particle clearance processes) may more strongly influence responses at very high levels of exposure and be less relevant at lower levels. Thus, exposure conditions with lower level exposures may remove some of the uncertainty in estimating health effects from environmental exposures.</p>
Study design characteristics	<p>Sufficient follow-up time for outcomes to develop (which can depend on the health outcome being addressed).</p> <p>Study size and participation rates that are adequate to detect and quantify health outcomes being studied are preferred, with no indications of bias in study population selection.</p> <p>Use of a study design or analytic approach, which adequately addresses the relevant sources of potential confounding, including age, sex, smoking, and exposure to other risk factors (such as non-Libby asbestos).</p>

1

Table 5-2. Summary of rationale for identifying candidate principal studies on Libby Amphibole asbestos for RfC development (continued)

Measurement of exposure	<p>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 appropriate exposure information, and individual, rather than area samples are preferred where available. 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, 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 do not confirm the mineral nature of the counted fibers. Total dust measurements are the least informative of those available.</p> <p>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.</p> <p>Exposure reconstruction and estimating exposures based on air sampling from other time periods and/or operations are less preferred methods of exposure estimation.</p>
Measurement of effect(s)	<p>Emphasis is placed on the more sensitive health outcome endpoints that are available. For 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.</p> <p>Pleural and parenchymal abnormalities assessed using good quality radiographs or high-resolution computed tomography (HRCT) and independently evaluated multiple qualified readers according to ILO standards.</p> <p>Evaluation of radiographs should not be influenced by knowledge of exposure status.</p>

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5.2.1.2.1. Evaluation of study design in candidate studies

The candidate principal studies differed in the study populations, in terms of follow-up time, study size and participation, and available information (see Table 5-1). The study sizes are similar for the two Libby worker studies ($n = 184$ and $n = 244$, respectively) (Amandus et al., 1987b; McDonald et al., 1986b) and the Marysville update ($n = 280$) (Rohs et al., 2008).

Adequate follow-up time allows for the health effect to manifest prior to sampling. In the case of pleural abnormalities, there is some variability with latency based on intensity of exposure as well as the nature of the pleural lesion where discrete pleural plaques have a shorter latency than diffuse thickening of the visceral pleura. Larson et al. (2010b) studied the latency for individuals in the Libby worker cohort, reporting a median latency of 8.6 years for localized pleural thickening versus 27 years for diffuse pleural thickening and 19 years for minimal signs

1 of small opacities (parenchymal changes).³ Lockey et al. (1984) report the mean employment
2 duration for their exposure groups from 6.6 to 13.3 years at the time of their study (but do not
3 assess time since first exposure (TSFE); thus, it is unclear whether in the first examination these
4 workers had sufficient follow-up to assess the radiographic changes, especially diffuse pleural
5 thickening and small opacities. The Rohs et al. (2008) report includes 24 more years of
6 follow-up time and is preferred over the early Lockey et al. (1984) study on this basis.

7 Both studies of the Libby workers report duration of employment and average age of the
8 participants, but not TSFE. The McDonald et al. (1986b) study included both current and former
9 workers—these former workers likely have longer time from first exposure compared with
10 current workers. The study included all current plant employees (164 men, 9 women).
11 However, there was a lower participation rate in former employees (80 of 110 eligible former
12 employees agreed to provide chest radiographs). Additionally, X-rays for all study participants
13 were taken in the same year, providing similar quality X-rays between past and current
14 employees. In contrast, Amandus et al. (1987b) only considered workers employed during 1975
15 to 1982 and relied on available radiographs regardless of year (radiographs were available for
16 93% of employees). Because workers terminated prior to 1975 were excluded from the study,
17 older individuals, and individuals with longer TSFE were less likely to be included than in the
18 study by McDonald et al. (1986b), which included former workers. Both Libby worker studies
19 do report radiographic abnormalities, so the follow-up is adequate for some effects to be
20 documented; however, compared with the Rohs et al. (2008) study, the Libby worker studies
21 have shorter follow-up times.

22 Among Marysville workers, there were very few employees who declined to participate
23 in the earlier study by Lockey et al. (1984), where 512 out of 530 employees were included, but
24 there is potential for selection bias in the follow-up by Rohs et al. (2008), where only
25 280 employees out of the original cohort were evaluated. Rohs et al. (2008) state that employees
26 hired in 1973 or earlier (when exposure estimates were more uncertain) were more likely to
27 participate compared to employees hired after 1973, and while the range of cumulative Libby
28 Amphibole asbestos exposure was similar between participants and nonparticipants, participants
29 did have higher mean cumulative exposure estimates. While it is accurate that exposure levels

³ Individual latency for visible LPT in Libby exposed workers was evaluated in 84 workers with radiographic evidence of pleural and/or parenchymal changes (Larson et al., 2010b). By examining historical radiographs, researchers were able to identify the first appearance of the lesions, although it is recognized that retrospective design of this study likely identified lesions at earlier time points, as the readers were aware of the later -X-rays (Larson et al., 2010b). It is acknowledged that some of the workers at Libby may have been exposed through the community prior to working, and in fact, one individual had the first pleural change noted at 9 years of age, prior to occupational exposure (Larson et al., 2010b). Where data on prior exposures were available, workers with no prior exposure had an average latency of 9.4 years versus 5.1 years for workers with potential exposures prior to hire ($N = 63$ and 31 , respectively).

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1 were uncertain before sampling began at Marysville in 1972, it is also accurate that exposures
2 were much lower beginning in 1974, when additional industrial hygiene controls were
3 implemented. Thus, persons hired ≤ 1973 had higher exposure (if less perfectly measured), while
4 those hired ≥ 1974 had lower exposure, and likely less disease (under an assumption of an
5 exposure-response effect). Thus, we might assume that the prevalence rates in nonparticipants
6 are likely lower than in participants. The self-selection to participate in the study is dependent
7 on the exposure, thus leading to dependent censoring and potential selection bias (see
8 Section 4.1.3 for a discussion of this potential selection bias). However, Rohs et al. (2008)
9 conducted a sensitivity analysis assuming that all living nonparticipants had no pleural changes
10 and report a similar significant trend of increased pleural changes by exposure quartile. In
11 contrast, participation rates for the Libby worker studies were much higher (see above), and there
12 is no indication of potential bias in selection of these study participants (Amandus et al., 1987b;
13 McDonald et al., 1986b).

14 Both studies of Libby workers also evaluated age and smoking as potential confounders
15 of the association between Libby Amphibole asbestos exposure and radiographic abnormalities.
16 McDonald et al. (1986b) report that both age and cumulative exposure are significant predictors
17 of small opacities and pleural abnormalities in the study of current and former workers,
18 providing regression coefficients for cumulative exposure, age, and smoking status. Amandus et
19 al. (1987b) report that although cumulative exposure and age are both significant predictors for
20 small opacities, cumulative exposure was not significantly related to pleural abnormalities when
21 age is included in the model, thus limiting the usefulness of these data for RfC derivation based
22 on pleural abnormalities. Neither study of Libby workers addressed gender, body mass index
23 (BMI), or time from first exposure, although both studies excluded workers with other
24 asbestos/dusty trade occupations.

25 With respect to the Marysville, OH worker cohort, Lockey et al. (1984) only matched on
26 age in their analysis. The follow-up examination by Rohs et al. (2008) included information on
27 several important covariates, including age, gender, hire date, prior exposure to asbestos, BMI,
28 and smoking history. Hire date and age were significantly associated with the prevalence of
29 pleural abnormalities, and results are presented considering these covariates.

30

31 **5.2.1.3. Evaluation of Exposure Assessment in Candidate Studies**

32 For both the O.M. Scott facility in Marysville, OH and the Libby, MT facilities, exposure
33 estimates rely primarily on fiber counts using phase contrast microscopy (PCM) and
34 reconstruction of earlier exposures from company records, employee interviews, and the
35 professional judgment of the researchers estimating historical exposures (McDonald et al.,

1 1986b; Amandus et al., 1987a; Lockey et al., 1984). Work histories for the Libby worker cohort
2 were extracted from company employment records, while work histories for the Marysville
3 cohort were self-reported.

4 The two studies of workers in Libby, MT (McDonald et al., 1986b; Amandus et al.,
5 1987b) used similar exposure estimation, based on the same fiber measurements and work
6 records. As discussed in Section 4.1.1.2, exposures prior to 1968 are not based on fiber
7 measurements by PCM and, thus, are more uncertain than later exposure estimates.⁴ The study
8 population of McDonald et al. (1986b) included current and former workers, with 26% of
9 participants over 60 and 40% of participants between 40–59 years of age at the time of their
10 X-ray in 1983. Although tenure and dates of employment are not reported, exposure estimates
11 for this study group would include the less-certain exposure estimates prior to 1968. However,
12 Amandus et al. (1987b) studied workers still employed during 1975–1982 (i.e., excluding those
13 terminated prior to 1975) who had at least 5 years of employment. The average tenure of the
14 study participants was 14 years. Although both studies have the limitation of less-certain
15 exposure estimates prior to 1968, based on study design, the Amandus et al. (1987b) study group
16 includes a greater proportion of more recent workers. However, neither researcher assessed
17 these uncertainties nor the impact of early exposure estimates on the apparent exposure-response
18 relationship.

19 Another source of uncertainty in exposure estimates for this cohort is possible
20 community/nonoccupational exposures. Members of the Libby worker cohort may have lived in
21 Libby prior to/after employment and resided in Libby and surrounding areas during employment.
22 In both cases, there may have been community exposures to Libby Amphibole asbestos that are
23 not captured in occupational-based cumulative exposure metrics. This unmeasured
24 nonoccupational exposure may be low relative to the estimated occupational exposures, but is,
25 nevertheless, a source of uncertainty in estimating the exposure-response relationship.

26 The quality of the exposure assessment also changed over time in the Marysville cohort
27 (Lockey, 1985; Rohs et al., 2008). Industrial hygiene measurements based on PCM analysis are
28 available for the O.M. Scott facility beginning in 1972, although personal breathing zone
29 samples were not available until 1976 (Rohs et al., 2008). Thus, exposure levels for all job tasks
30 prior to 1972 are estimates from later sampling events. Additionally, air sampling data were not
31 available for several job tasks until the late 1970s. For example, air-sampling data were only
32 available for two of seven job tasks in the trionizing department beginning in 1973 (expander
33 and dryer). All others have dates of 1976 or later (see Table 10, Lockey, 1985). The installation

⁴ Exposures in the dry mill at Libby, MT, prior to 1967 were estimated from total dust measurements based on site-specific conversion ratios. Exposures for all other location operations prior to 1968 were estimated because no air sampling data were available (Amandus et al, 1987a; McDonald et al., 1986b).

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1 of exposure control equipment in 1974 adds to the uncertainty in early exposures estimated from
2 sampling in later years. There is uncertainty when the Libby ore was first used in the facility.
3 Company records indicated that the date was between 1957 and 1960, and the University of
4 Cincinnati used the best-available information from focus group interviews to assign the first
5 usage of Libby ore in 1959 (see Appendix F).

6 EPA has collaborated with the University of Cincinnati research team to better evaluate
7 historical exposures at the O.M. Scott facility in Marysville, OH (see Appendix F). Although no
8 air-sampling results were found prior to 1972, additional information on plant processes from
9 other records and employee interviews has resulted in updated exposure estimates (see
10 Section 5.2.3.1). These refined estimates of the historical exposure improve exposure
11 characterization for the Marysville worker cohort over previous publications.
12

13 **5.2.1.3.1. Evaluation of outcome assessment in candidate studies**

14 In all four candidate studies, outcomes were assessed using chest radiographs
15 independently evaluated by multiple readers. However, there were differences in the standards
16 used for evaluation of radiographic changes, as well as timing and quality of the radiographs.
17 The two studies in Libby workers (McDonald et al., 1986b; Amandus et al., 1987b) used similar
18 outcome-assessment procedures, with radiographs evaluated by three readers according to 1980
19 ILO standards. Two different sets of standards were used to evaluate radiographs in the
20 Marysville cohort. The first study used modified 1971 ILO standards (modifications not
21 stipulated) (Lockey et al., 1984), while the follow-up study used the updated 2000 ILO standards
22 (Rohs et al., 2008).

23 Radiograph quality may also impact outcome assessment. In McDonald et al. (1986b),
24 which used radiographs taken in 1983 specifically for the study, 7% of films were classed as
25 “poor quality” (some technical defect impairing the pneumoconiosis classification) and 0.4% as
26 “unreadable.” Amandus et al. (1987b), which used available radiographs taken over a wide time
27 period (1975 to 1982), report that the proportion of films rated as “poor quality” ranged from
28 14.7% to 22.8% depending on the reader. In the Marysville cohort, Lockey et al. (1984) state
29 that “...radiographs that could not be interpreted because of poor quality were repeated” (p. 953).
30 Rohs et al. (2008) do not report the percentage of films rated as “poor quality” but do note that
31 7 out of 298 (2.3%) radiographs taken were considered unreadable.
32

33 **5.2.1.3.2. Selection of principal cohort**

34 Based on the criteria set out in Table 5-2 and the above evaluation, the update of the
35 Marysville, OH worker cohort (Rohs et al., 2008) is the preferred cohort. The main advantages

1 of the Marysville, OH worker cohort over the two studies of pleural and lung abnormalities in
2 the workers in Libby, MT are:

- 3
- 4 1) Adequate follow-up time and the availability of time from first exposure data for
5 evaluation,
- 6 2) Minimal exposure to Libby Amphibole asbestos outside of the workplace,
- 7 3) Better quality radiographs, and use of the most recent ILO reading guidelines in the
8 cohort update,
- 9 4) Data are more appropriate for low-dose extrapolation—a lower range of cumulative
10 exposures for the study participants ($n = 280$), compared to Libby workers,
- 11 5) The data allow consideration of more covariates and potential confounders (e.g.,
12 BMI, smoking status, age),
- 13 6) The presence of a demonstrated exposure-response relationship for Libby amphibole
14 asbestos exposure and radiographic abnormalities—in contrast to the study by
15 Amandus et al. (1987b), which does not support an exposure-response relationship
16 for pleural abnormalities based on the cumulative exposure metric (when age is
17 included as a covariate).
- 18
- 19

20 The disadvantages of the Marysville, OH cohort compared to the two studies of pleural
21 and lung abnormalities in the workers in Libby, MT are:

- 22
- 23
- 24 1) Approximately 70% of the Marysville, OH cohort were hired before 1972 when there
25 were no measured exposure data, (Rohs et al., 2008, and Lockey et al. 1984) study.
- 26 2) Participants in Rohs et al. (2008) were self-selected, with greater participation among
27 older employees and those who began work prior to 1973 when exposures were
28 relatively higher. This is a potential source of bias in study population selection
29 analyzed by Rohs et al. (see Section 4.1.3).
- 30 3) Exposure estimates are based on self-reported work histories. In this case, there is
31 some uncertainty in the employment history, and some individuals had extensive
32 overtime work. Employment history was self-reported during interviews with each
33 individual for the original study (i.e. Lockey et al., 1984), and errors in this process
34 could affect assigned Libby Amphibole asbestos exposure estimates for this cohort.
- 35

1 5.2.1.4. *Selection of Critical Effect*

2 There are several endpoints that are suitable for consideration for the derivation of an
3 RfC for Libby Amphibole asbestos where health effects data and exposure information are
4 available in the principal study (Rohs et al., 2008; Lockey et al., 1984): (1) parenchymal changes
5 viewed as small opacities in the lung; (2) blunting of the costophrenic angle (measured between
6 the rib cage and the diaphragm); or (3) pleural thickening (both localized and diffuse). Each of
7 these effects is an irreversible pathological lesion (ATS, 2004). As the available epidemiologic
8 studies describe these endpoints as viewed on standard X-rays (see Text Box 5-1), it is important
9 to understand the distinction between what is viewed on the radiograph versus the underlying
10 biologic lesion. The following discussion reviews the health effects associated with each of
11 these radiographic abnormalities observed in workers exposed to Libby Amphibole asbestos.
12

Text Box 5-1. Radiographic Abnormalities of the Lung and Pleura

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 standards 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 of the lung (ILO, 2000).

Obliteration of the costophrenic angle: The costophrenic angle (CPA) is measured as the angle between the ribcage and the diaphragm on a posterior anterior-viewed radiograph (the costophrenic recess). When CPA blunting or obliteration is noted on a radiograph, it is recorded as present or absent (ILO, 2000). Obliteration of the CPA 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” (ILO, 2000). Localized pleural thickening may also be viewed in-profile or face-on and is generally a pleural plaque (parietal). Calcification is noted where present (ILO, 2000).

13 14 15 5.2.2. Evaluation of Radiographic Lesions as Potential Critical Effects

16 5.2.2.1. *Health Effects of Parenchymal Changes as Small Opacities Viewed on Standard* 17 *Radiographs*

18 Radiographic evidence of small opacities in the lung is evidence of fibrotic scarring of
19 lung tissue consistent with mineral dust and mineral fiber toxicity. The scarring of the
20 parenchymal tissue of the lung contributes to measured changes in pulmonary function,

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1 including obstructive pulmonary deficits from narrowing airways, restrictive pulmonary deficits
2 from impacting the elasticity of the lung as well as decrements in gas exchange. However,
3 although data across the mineral fiber literature strongly support a finding of functional deficits
4 where small opacities are visible on radiographs, the data also indicate that deficits in pulmonary
5 function (consistent with interstitial fibrosis) are seen before these changes are detected by
6 radiographic examination. Thus, changes in lung function may occur before the fibrotic lesions
7 can be detected on standard radiographs (ATS, 2004; Brodikin et al., 1994). For example,
8 decreased Carbon monoxide (CO) diffusion is a sign of reduced gas exchange in the pulmonary
9 region of the lung and is observed in workers exposed to other types of asbestos even when small
10 opacities are absent on radiographs. Similarly, obstructive deficits in lung function may be
11 observed without radiographic signs for fibrotic lesions of small opacities. As decreased
12 diffusion and obstructive deficits are mechanistically linked to changes in the parenchymal tissue
13 these data suggest radiographs may not be sensitive enough to detect and protect against small
14 localized lesions in parenchymal tissue of the lung. Radiographic evidence of small opacities
15 indicates interstitial damage of the lung parenchyma, is associated with decreased pulmonary
16 function and considered evidence of an adverse health effect. Thus, small opacities are an
17 appropriate endpoint for RfC derivation. However, as there is evidence of functional changes in
18 lung function from lesions not detectable on conventional radiographs, more sensitive endpoints
19 should be considered.

20

21 **5.2.2.2. Health Effects of Diffuse Pleural Thickening (DPT) Viewed on Standard** 22 **Radiographs**

23 DPT is a fibrotic lesion (often described as a basket weave of collagen) in the visceral
24 pleura that encases each lobe of the lungs. The fibrotic lesion restricts the ability of the lung to
25 expand mechanically, as well as by reducing the available volume (where thickening has
26 progressed) (Jones, 1988) and DPT is strongly associated with reduced lung function (ATS,
27 2004). There are consistent reports of impaired lung function associated with DPT in
28 asbestos-exposed populations (Borderick et al., 1992; Kilburn et al., 1991; Bourbeau et al.,
29 1990). A cross-sectional study of men ($n = 1,298$) exposed to asbestos through various trades
30 (e.g., boiler makers, welders, plumbers/pipefitters) included chest radiographs and spirometry
31 (Kilburn et al., 1991). When considering the effect of DPT (with costophrenic angle [CPA]
32 blunting) on radiographic function, FVC, FEV1, and FEF25-75⁵ were all significantly reduced
33 (85, 79, and 66% of predicted values, respectively) as compared with individuals with

⁵ Forced Vital Capacity (FVC); Forced Expiratory Volume in 1 second (FEV1) and Percent FVC
($FEV\% = [(100 \times FEV1) \div FVC]$, FEF25-75, is the expiratory flow between 25% and 75% of the FEV.)

1 calcification or plaques only in men with no signs of small opacities (ILO profusion score of 0/0
2 or 0/1) ($p < 0.0001$). The relationship between pleural fibrosis and FVC was studied in
3 asbestos-exposed sheet metal workers ($N = 1,211$) where not only the type of thickening
4 (discrete versus diffuse [ILO, 1980]) but also CPA involvement and the location of the
5 thickening were taken into consideration (Broderick et al., 1992). Univariate analysis indicated
6 FVC was decreased by both DPT (with CPA blunting) and circumscribed thickening, diaphragm
7 involvement, CPA involvement, and the extent of the thickening (Broderick et al., 1992).
8 Multivariate linear regression, allowing for control of potential confounders, found decreased
9 FVC was significantly related to DPT, plaques, CPA involvement, and extent of the thickening,
10 but not diaphragmatic involvement (Broderick et al., 1992).

11 The mechanisms for reduced lung volume in individuals with asbestos-related DPT have
12 been examined by measuring lung function and changes in diaphragm length, rib-cage
13 dimensions, and subphrenic volume in 26 patients during breathing (Singh et al., 1999). DPT
14 reduced both total lung capacity and FVC with corresponding decreases in rib-cage expansion
15 and movement of the diaphragm, consistent with the restrictive nature of these lesions, which
16 may encase part of the lung (Singh et al., 1999). These direct measurements of the effect of DPT
17 chest wall and diaphragmatic motion illustrate the role of DPT in reducing lung volume,
18 contributing to restrictive deficits in pulmonary function. Taken together, the epidemiologic
19 evidence and the mechanistic information that support a restrictive effect of fibrotic lesion in the
20 visceral pleura, substantiate the associations between DPT and decreased pulmonary function.
21 As such, the observation of DPT on standard radiographs is representative of pathological
22 changes directly related to reduced lung function and is, therefore, an indication of adversity,
23 and, can serve as an appropriate health endpoint for consideration in RfC derivation.

24

25 **5.2.2.3. Health Effects of Localized Pleural Thickening (LPT) Viewed on Standard** 26 **Radiographs**

27 Localized pleural thickening (LPT) viewed on a standard radiograph may include both
28 pleural plaques and pleural thickening that does not involve blunting of the costophrenic angle
29 (ILO, 2000). Thus, both parietal plaques and localized thickening of the visceral pleura may be
30 designated as LPT. Thickening of the parietal pleura is due to an acellular collagen plaque
31 (basket weave of collagen fibers) between the parietal pleura and the ribcage (or along the
32 diaphragm) often described as discrete or circumscribed pleural plaques (ATS, 2004; Jones,
33 2002). Thickening of the visceral pleural is a fibrosis with diffuse borders and may extend into
34 the lung parenchyma (ATS, 2004; Jones et al., 2002). The pathology and health effects of the
35 different lesions are evaluated here in the characterization of the health significance of LPT.

1 Costal parietal plaques occur between the thoracic cage and parietal pleura, which is
2 normally adherent to the thoracic cage (ATS, 2004; Jones, 2002). Costal parietal plaques have
3 been described as collagen deposits with ragged irregular edges and up to 1 cm in depth and may
4 be calcified. These parietal plaques have been associated with constricting pain in the thoracic
5 cavity (Mukherjee et al., 2000; Bourbeau et al., 1990). The parietal pleura is well innervated by
6 the intercostal and phrenic nerves and is considered very sensitive to painful stimuli (Jones,
7 2002). With respect to parietal plaques, pain during exertion or exercise could result in
8 restrained chest wall motion during exertion or exercise (Bourbeau et al., 1990). Thus, Bourbeau
9 et al. (1990) hypothesized that the dyspnea and changes in pulmonary function noted in
10 individuals with pleural plaques may be due to physical irritation and perhaps a constricting
11 action where parietal plaques are well progressed or numerous and impact a large proportion of
12 the parietal surface.

13 Kouris et al (1991) examined the presence of dyspnea, and measures of pulmonary
14 function (i.e., FVC, FEV1, and FEV%⁶) in asbestos-exposed workers ($n = 913$) in relation to
15 radiographic signs of lung and pleural anomalies. Radiographs were contemporary to the study
16 and read in accordance with ILO (1980) guidelines. Pleural plaques were associated with
17 reduced FVC and FEV1.0 (87.6% and 84.1% of predicted, respectively, $p < 0.0005$), although
18 deficits associated with diffuse thickening were greater (76.4% and 73.9%, $p < 0.0005$) (Kouris
19 et al., 1991). Correspondingly odds ratios for decreased FVC and FEV1.0 (80% decrement)
20 were increased by the presence of both plaques and diffuse thickening (1.5 for plaques and
21 4.2 and 4.7 for diffuse thickening, respectively). Interestingly, when history of lung disease was
22 considered, pleural plaques had a greater effect in individuals without previous lung disease
23 (OR of 2.1 for FVC and 1.7 for FEV1.0).

24 Pleural thickening in general is associated with decreased pulmonary function (Miller et
25 al., 1994; Wang et al., 2001; Petrovic et al., 2004) and this association is strengthened as the
26 severity of the pleural thickening increases (Lilis et al., 1991). Few available studies have
27 examined the relationship between pleural plaques identified on standard radiographs (ILO,
28 1980) and pulmonary function without including DPT in the analysis and adequately controlling
29 for the presence of small opacities (indicative of parenchymal damage)⁷.

⁶ Forced Vital Capacity (FVC); Forced Expiratory Volume in 1 second (FEV1) and Percent FVC
($FEV\% = [(100 \times FEV1) \div FVC]$).

⁷ It is difficult to control for effects subradiographic parenchymal fibrosis on lung function, where it may not have progressed to visible small opacities, and it has been suggested that reduced lung function, which has been associated with circumscribed plaques in some studies, may be reflecting the effects of subradiographic parenchymal changes, rather than a direct effect of DPP (ATS, 2004, Broderick et al., 1992, Erdinc et al., 2003, and Miller et al., 1996).

1 Lilis et al. (1991) examined pulmonary function in long-term asbestos insulation workers,
2 and found that one measure (FVC) decreased significantly as the severity of pleural fibrosis (all
3 types, as indicated by a pleural index) increased. This decrease was more dramatic when
4 including parenchymal changes (small opacities) or if DPT was viewed separately. A second
5 analysis focusing on participants with pleural plaques found an inverse relationship between
6 severity of the pleural plaques and FVC ($p < 0.0001$), when adjusting for the independent effects
7 of duration, smoking and presence of small opacities (Lilis et al., 1991). This finding supports a
8 view that pleural plaques, when extensive, may contribute to restrictive lung deficits, but the
9 analysis included individuals with known small opacities (e.g. lung fibrosis). The authors do not
10 address the potential that the pleural index may also correspond to increased severity of
11 parenchymal changes, potentially confounding the analysis where accounting for small opacities
12 (profusion scores of 1/0 or greater) may not adequately control for asbestos-related parenchymal
13 damage.

14 Oliver et al. (1988) studied the relationship between pulmonary function and pleural
15 plaques in asbestos-exposed railway workers ($n = 383$). Case selection included exclusion of
16 workers with DPT (ILO, 1980) and exclusion of any indication of small opacities (only
17 profusion scores of 0/0 were included). Standard spirometry was conducted to evaluate
18 restrictive and obstructive pulmonary deficits. Additionally, single-breath diffusing capacity
19 (DLCO) was measured which would indicate parenchymal defects. The DLCO was similar in
20 subjects with and without circumscribed plaques, suggesting little or no subradiographic
21 parenchymal damage, which corresponded to the presence of pleural plaques. Pleural plaques
22 were associated with both decreased FVC and pulmonary restriction ($p = 0.03$ and 0.04 ,
23 respectively) where the diagnostic certainty for the plaques was considered ‘definite’, and there
24 was an association between level of diagnostic certainty and these pulmonary deficits ($p = 0.02$)
25 (Oliver et al., 1988). Quantitative pleural score, based on the number and extent of plaques, was
26 also associated with decreased FVC and pulmonary restriction ($p = 0.0135$ and 0.0126 ,
27 respectively) (Oliver et al., 1988). Of the available studies that assess pleural thickening with
28 standard radiographs, this study best controls for the possibility of subradiographic parenchymal
29 damage and is, therefore, strong evidence that circumscribed pleural plaques independently
30 impact pulmonary function. The observed restrictive pulmonary deficit is consistent with the
31 potential for pleural plaques to restrict chest wall motion or the elasticity of the diaphragm.

32 Three high-resolution computed tomography (HRCT) studies were conducted specifically
33 to assess the potential for parietal plaques to impact lung function. Staples et al. (1989) report no
34 difference in lung function or diffusing capacity between participants ($n = 76$) with and without
35 pleural plaques. Soulat et al. (1999) found no difference in FEV1 or FVC between

1 asbestos-exposed insulators with ($n = 84$) and without ($n = 51$) pleural plaques in the absence of
2 any parenchymal changes. As severity of pleural thickening has been shown to be positively
3 associated with decrease measures of pulmonary function, Van Cleemput et al. (2001) not only
4 examined the effect of HRCT defined pleural plaques on pulmonary function, but also assessed
5 the extent of the pleural plaques. Neither the presence nor extent of pleural plaques were
6 associated with lung function parameters (diffusing capacity or normalized spirometric values)
7 (Van Cleemput et al., 2001). Where pleural plaques and diffuse thickening (visceral pleura)
8 were both identified by HRCT and correlated to pulmonary function, diffuse visceral
9 thickening—but not plaques—were associated with decreased lung volume and FVC (Copley et
10 al., 2001). Although CPA involvement was not independently assessed, several scoring systems
11 for severity were compared which included CPA involvement, and as in other studies, increased
12 severity correlated to greater decrements.

13 The mechanisms for reduced lung volume in individuals with asbestos-related pleural
14 plaques and DPT have been examined by measuring lung function and changes in diaphragm
15 length, rib-cage dimensions and subphrenic volume in 26 patients during breathing (Singh et al.,
16 1999). Pleural plaques alone did not reduce any of the measures of lung function in this study,
17 but there were indications of reduced diaphragm movement (Singh et al., 1999). This may be an
18 indication that diaphragmatic plaques in the parietal pleura have the potential to attenuate the
19 movement of the diaphragm during breathing. Because this study is relatively small ($N = 26$)
20 and a distinction was not made between costal and diaphragmatic plaques by the study authors,
21 additional work is needed to better understand the direct effects of pleural plaques on lung
22 function.

23 Although some researchers have questioned that pleural plaques alone directly impact
24 pulmonary function, a critical review of the literature from 1965-1999 concludes: “1)
25 Individuals with asbestos-induced pleural plaques may have alterations in pulmonary function
26 and /or clinical symptoms that are independent of smoking and radiographic parenchymal
27 fibrosis and, 2) the respiratory changes due to asbestos-induced pleural plaques are generally
28 less severe than those caused by pleural thickening” (Rockoff et al., 2002, p. 113). Therefore,
29 although the evidence is mixed, pleural plaques may be independently associated with reduced
30 pulmonary function.

31 No studies correlating pulmonary function to radiographic signs of localized pleural
32 thickening (LPT) using the ILO 2000 guidelines could be located. However, several researchers
33 employed similar classification schemes, modifying earlier ILO classification systems, such that
34 DPT was diagnosed only in conjunction with blunting of the CPA. This modification potentially
35 includes cases of diffuse pleural thickening (without CPA blunting) in their analysis of pleural

1 plaques, making their findings somewhat applicable to the current classification of LPT
2 (Broderick et al., 1992; Garcia-Closas et al., 1995). Pleural thickening (without CPA blunting)
3 was associated with mixed respiratory impairment in a study of asbestos-exposed construction
4 carpenters ($n = 631$) (OR of 3.7 [95% Confidence Interval (CI): 1.4–12.3]) but was only weakly
5 associated when the outcome was restrictive deficit specifically (1.3 [95% CI: 0.4–3.9])
6 (Garcia-Closas et al., 1995). Broderick et al. (1992) found decreased FVC was not only
7 significantly associated with “diffuse thickening” (with CPA blunting) but also with “pleural
8 plaques” (which included all pleural thickening without CPA blunting). The severity of pleural
9 thickening (both as width or percentage of lateral wall) and calcification was associated with
10 reduced FVC as well (Broderick et al., 1992). Kilburn and Warshaw (1991) assessed pulmonary
11 function in individuals with “plaques only,” “diffuse thickening only,” and “diffuse thickening
12 with CPA blunting,” showing progressive deficits across these categories in FVC, FEV1, and
13 mid-expiratory flow (e.g., FEV1: 90.5, 86.2, and 49.4% [$p < 0.05$], respectively). Again, there is
14 a trend that diffuse thickening has a greater impact on lung function parameters, although an
15 independent effect of plaques cannot be ruled out by these data.

16 In summary, the radiographic classification of localized pleural thickening (LPT) under
17 current ILO guidelines may include both parietal plaques (in the pleura lining the interior of the
18 ribcage) and diffuse visceral thickening (without CPA obliteration) (ILO, 2000). The two
19 lesions (parietal plaques and localized visceral thickening) are distinct and may contribute
20 independently to observed health effects. Parietal plaques are known to induce chronic
21 constricting chest pain that increases in severity as the extent of the plaques increases. Pleural
22 thickening in general is associated with reduced lung function parameters with increased effect
23 correlating with increased severity of the pleural thickening (Lilis et al., 1991; Miller et al., 1994;
24 Wang et al., 2001; Petrovic et al., 2004). There is clear evidence from HRCT studies that the
25 presence and extent of visceral thickening does impair lung function, although, when evaluated
26 independently, parietal plaques were not statistically correlated with decreased pulmonary
27 function (Swartz et al., 1993; Copley et al., 2001). Specifically considering the designation of
28 LPT, lung function impairment has been demonstrated in several studies where pleural
29 thickening without CPA involvement has been studied (Broderick et al., 1992; Kilburn and
30 Warshaw, 1991; Garcia-Closas et al., 1995). Thus, the radiographic classification of localized
31 pleural thickening (LPT) (ILO, 2000) includes pleural lesions associated with chronic chest pain,
32 decreased lung volume, and decreased measures of lung function. Therefore, EPA considers
33 LPT an adverse effect and an appropriate endpoint for RfC derivation.

34

1 **5.2.3. Methods of Analysis**

2 **5.2.3.1. Exposure Data and Choice of Exposure Metric**

3 EPA collaborated with a research team at the University of Cincinnati to update the
4 exposure reconstruction for use in the job-exposure matrix (JEM) for all workers in the
5 Marysville, OH cohort, taking into account additional industrial hygiene data that were not
6 available for previous studies conducted in this cohort. As discussed in detail in Appendix F,
7 exposure estimates for each worker in the O.M. Scott Marysville, OH plant were developed
8 based on available industrial hygiene data from the plant. Figure 5-1 shows the average
9 exposure concentrations of fibers in air (PCM fibers/cc)⁸ of each department from 1957 to 2000,
10 indicating the time periods when fiber measurements were not available ('Estimated') and were
11 available ('Measured').
12
13

⁸ PCM, where fibers are viewed and counted by light microscopy, does not identify the composition of the fiber. Thus, the mineralogy of fibers identified under PCM cannot be determined.

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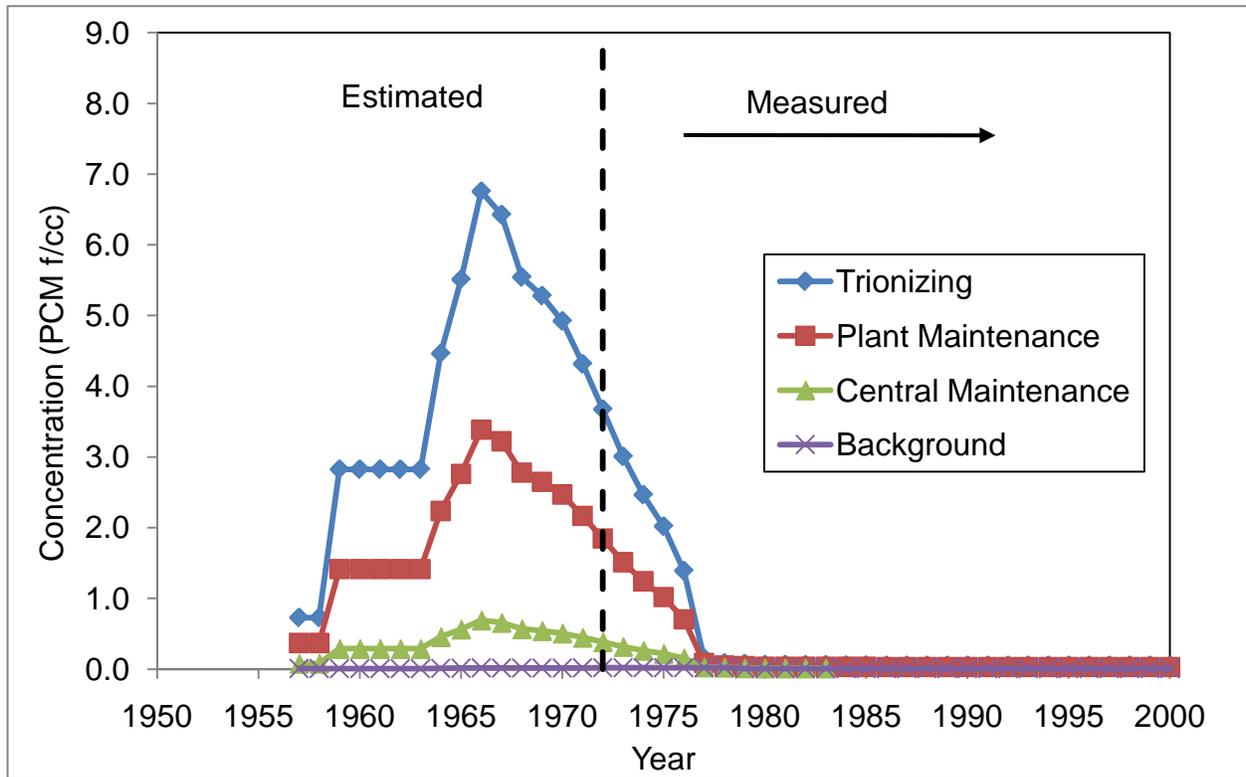


Figure 5-1. Estimated and measured exposure concentrations in Marysville, OH facility^a

^aTrionizing is a term used in the Marysville, OH facility and includes unloading of rail cars containing vermiculite ore (track), using conveyers to move the vermiculite ore into the expander furnaces, separation of the expanded vermiculite from sand, blending in of lawn care chemicals, and drying and packaging of the final product. As no unexpanded ore was used in pilot plant, research, polyform, office, packaging, or warehouse, jobs in these categories were assigned as background. Workers assigned to plant maintenance activities spent 50% of their time in trionizing areas and 50% of their time in areas assigned as plant background. Workers assigned to central maintenance spend 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).

1 In brief, the starting point for the JEM was the measured or estimated concentration of
2 fibers in air (fibers/cc) of each department from 1957–2000. The distribution of exposure by
3 department is summarized in Figure 5-1. Using available data on the year of hire and the
4 departments in which each person worked, the cumulative exposure (fibers/cc-year) for each
5 worker for each year since the date of hire was estimated. Each worker’s cumulative exposure
6 was then adjusted to a cumulative human equivalent exposure for continuous exposure (CHEEC;
7 fibers/cc-year) to represent exposure 24 hours/day and 365 days/year (assuming that any
8 exposure off site was zero) for the full duration of employment. Adjustments for different
9 inhalation rates in working versus nonworking time periods were incorporated in this analysis.
10 The calculated value is similar to what EPA usually refers to as continuous human equivalent
11 exposure (U.S. EPA, 1994b). These calculations are somewhat more complex than the usual
12 conversions to equivalent continuous exposure concentrations that EPA makes in the analysis of
13 occupational studies. Conversions for noncancer effects are usually made using an adjustment
14 factor of $240 \text{ days} \div 365 \text{ days} \times 10 \text{ m}^3 \div 20 \text{ m}^3$ (U.S. EPA, 1994). However, the adjustment
15 factor in this current assessment takes into account the extensive seasonal overtime for some job
16 codes at the Marysville facility, as well as other annual periods when work hours were reduced
17 (see Appendix F). The estimated CHEEC was used to represent Libby Amphibole asbestos
18 exposure in all subsequent analyses because it combines aspects of both intensity of exposure
19 and duration of exposure.⁹ For Libby Amphibole asbestos, the exposure metric is calculated as
20 cumulative exposure (fibers/cc-year). Cumulative exposure is a commonly evaluated exposure
21 metric in occupational studies, especially for mineral fibers, where fiber retention may be
22 relevant to toxicity. It should be noted that discrete parietal plaques have often been associated
23 with other exposure metrics (e.g., mean exposure, TSFE) (Paris et al., 2008; Jakobsson et al.,
24 1995; Ehrlich et al., 1992 and Copes et al., 1985). Paris et al. (2008) show significant
25 exposure-response relationships for both mean and cumulative exposure metrics for pleural
26 plaques (identified by HRCT) among workers with mixed fiber exposures, when accounting for
27 age, smoking, and TSFE. Mean exposure provided a better overall fit (Paris et al., 2009). Thus,
28 EPA has conducted an uncertainty assessment for the RfC derivation from the sub-cohort by also
29 exploring alternative methods to weight the BMCL_{10} in units of cumulative exposure, to
30 represent the average exposure needed for RfC derivation (see Section 5.3.7).

31 Because localized pleural thickening does not generally occur immediately after exposure
32 and requires some time to develop to the state that it can be detected on a conventional chest
33 X-ray, exposures that occur close to the time of X-ray may not contribute to the occurrence of
34 observable disease and may obscure the exposure-response relationship. Accordingly, a lagged

⁹ The University of Cincinnati used the term CHEEC in its report (see Appendix F).

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1 exposure (i.e., cumulative exposure discounting the most recent time period) may be the most
2 appropriate measure to use. Therefore, exposure estimates with various lags were investigated
3 (lags of 0, 5, 10, 15, and 20 years). For example, a CHEEC value based on a lag of 5 years
4 excludes all exposures that occurred within 5 years of the date of X-ray. Looking at the
5 occurrence of the outcome for various categories of time elapsed since first exposure, the first
6 localized pleural thickening was detected ~10 years after the first exposure.

8 **5.2.3.2. Data Sets for Modeling Analyses**

9 The individual health outcome data for all workers who participated in the Lockey et al.
10 (1984) study and the follow-up study by Rohs et al. (2008) were used for exposure-response
11 modeling. To avoid any bias from previous occupational exposure to asbestos, only the data
12 from those who did not report any previous occupational exposure to asbestos were used. The
13 data from Lockey et al. (1984) and Rohs et al. (2008) were combined for the full cohort to
14 provide a greater range in time from first exposure (described below). Outcome assessments,
15 i.e., chest X-rays, were performed at two different time points, 1980 and 2002–2005. While the
16 evaluation approaches were generally similar (independent readings by three certified
17 B-readers), it is important to note that X-ray readings were performed by different individuals,
18 under a different reading protocol in 1980 (modified 1971 ILO standards) compared to 2000s
19 (2000 ILO standards), leading to some uncertainty in statistical analyses that combine these data
20 sets. An additional consideration is human body composition—in some cases, difficulty in
21 distinguishing fat pads from true pleural thickening may lead to misclassification of the outcome.
22 BMI measurements are available for the latter study but not for the 1980 evaluation; the effect of
23 BMI was investigated and is discussed below.

24 Radiographs were evaluated by two B-readers with a consensus evaluation by a third
25 reader in the case of disagreement in the original study by Lockey et al. (1984). In the follow-up
26 by Rohs et al. (2008), a radiographic reading was considered positive “when the median
27 classification from the three independent B readings was consistent with pleural and/or
28 interstitial changes” (p. 631). Because the ILO criteria were updated in 2000, the reader forms
29 from Lockey et al. (1984) showing pleural changes were evaluated for consistency with the ILO
30 2000 criteria. This reevaluation did not result in any change in the diagnosis for any individual
31 from the 1980 reading.¹⁰ In addition, no difference in reported X-ray quality was noted between
32 the Lockey et al. (1984) data and the follow-up by Rohs (2008).

¹⁰ Personal communication (e-mail) from Dr. James Lockey, University of Cincinnati, to Dr. Robert Benson in March 2011 reports that a review of the 1980 B-reader forms using the ILO 2000 guidelines would not result in changes in individual diagnosis for study participants.

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1 The full data set of the exposure-response relationship for localized pleural thickening
2 was as follows. The radiographic data from Lockey et al. (1984; $n = 513$) and Rohs et al. (2008;
3 $n = 280$), were combined for a total of 793 X-ray evaluations (this includes repeated X-rays on
4 the same individual). X-rays obtained from workers who reported exposure to asbestos at other
5 locations were excluded from consideration ($n = 793 - 105 = 688$ X-ray evaluations).

6 For workers who were X-rayed in both Lockey et al. (1984) and Rohs et al. (2008), one
7 of the observations was excluded so that there were no repeat observations for individual
8 workers in the data set used for modeling. For workers who were negative for localized pleural
9 thickening in Lockey et al., the 1984 study data were excluded, and the Rohs et al. (2008) data
10 were retained. For workers who were positive for localized pleural thickening in Lockey et al.
11 and also in Rohs et al., the 1984 study data were retained. One worker was positive in 1984 and
12 negative in 2008 (removing this worker from the analysis did not change results). The 2008
13 study data were retained for this worker. This procedure resulted in $n = 688$
14 X-rays – 252 duplicates = 436 X-rays, representing 436 individual workers.

15 Two workers from Lockey et al. (1984) were excluded because the start day and the
16 X-ray date were the same ($n = 436 - 2 = 434$). For each worker, the estimated cumulative
17 exposure corresponded to the date of the X-ray retained for analysis—if the 1980 X-ray was
18 used, the individual’s cumulative exposure estimate covered the period from start of work
19 through the X-ray date in 1980. If the 2002–2005 X-ray was used, cumulative exposure covered
20 the period from start of work through the date of job stop or 2000, whichever occurred earlier.

21 The Marysville cohort data comprise 434 workers who were not previously exposed to
22 asbestos and had at least one X-ray observation. Because the concentration of Libby Amphibole
23 asbestos in workplace air was estimated rather than measured for all years prior to 1972, this data
24 set was stratified into two subsets: (1) workers hired in 1972 or after (for whom all exposure
25 values are measured), and (2) workers hired before 1972 (for whom some of the exposure values
26 are estimated). Distributions of cases and TSFE (T) at each outcome assessment are shown in
27 Table 5-3.

28

1 **Table 5-3. Distribution of cases and time from first exposure (*T*) for cohort**
 2 **of Marysville workers**
 3

	All participants ^a		First exposed before 1972		First exposed 1972 or later	
	Cases/Total	Range of <i>T</i>	Cases/Total	Range of <i>T</i>	Cases/Total	Range of <i>T</i>
Examined 1980 (Lockey et al., 1984)	5/434	0.42–23.43	4/236	8.75–23.43	1/198	0.42–8.42
Examined 2002–2005 (Rohs et al., 2008)	57/250	23.14–47.34	45/131	31.07–47.34	12/119	23.14–32.63
Marysville cohort (<i>n</i> = 434, examination in either 1980 or 2002–2005)	61/434	0.42–47.34	48/236	8.75–47.34	13/198	0.42–32.63

4
 5 ^aThe 252 individuals examined in 2002–2005 were also examined in 1980. Note that there were originally
 6 513 individuals in the Lockey et al. (1984) cohort; of these, 77 had previous asbestos exposure and were excluded
 7 (*n* = 436). Two individuals were excluded because their X-ray date was the same as their employment start date
 8 (*n* = 434). These exclusions are also reflected in the Rohs et al. (2008) cohort.
 9

10 Source: Rohs et al. (2008) and Lockey et al. (1984).
 11
 12

13 The more accurate exposure data are considered to be those from 1972 and later, as these
 14 data were based on analytical measurements. Due to the longer follow-up time and additional
 15 covariate information, the most informative outcome data come from the 2002–2005
 16 examination. Based on these considerations, a sub-cohort of the Marysville workers, which
 17 includes data from workers in the 2002–2005 examination, and who began work in 1972 or later
 18 (12 cases of localized pleural thickening and 106 unaffected individuals;¹¹ Rohs et al., 2008),
 19 was chosen as the preferred analysis to develop a point of departure (POD) for localized pleural
 20 thickening to serve as the basis for the RfC. Additionally, sample POD estimates based on
 21 statistical analyses of results from the full cohort (Lockey et al., 1984 and Rohs et al., 2008
 22 combined, as described above) were included for comparison.
 23

¹¹ There was one individual whose radiographic examination indicated diffuse pleural thickening, who was excluded from further analyses of the preferred sub-cohort. Diffuse pleural thickening represents a more severe outcome than the selected critical effect of LPT--including this individual as a case would not be appropriate given that the critical effect is selected to represent a most sensitive endpoint, and the subsequent selection of a benchmark response in modeling efforts. Diffuse pleural thickening is considered separately as an endpoint (with appropriate benchmark response) in sensitivity analyses of alternative outcomes in the larger group of workers examined in 2002--2005 (see Section 5.3.8).

1 **5.2.3.3. Statistical Modeling of the Sub-cohort**

2 EPA performed analyses of study results for the sub-cohort whose exposures began on or
3 after 1/1/1972 when workplace PCM measurements were available, reducing uncertainties
4 associated with exposure assessment. Localized pleural thickening (LPT), as diagnosed from a
5 standard radiograph (ILO, 2000), was selected as the critical effect based on the health effects
6 associated with pleural thickening specific to this diagnosis (see Section 5.2.2.3). Alternative
7 critical effects were not considered for the sub-cohort analysis given the limited number of cases
8 (one case of DPT and no cases of small opacities). Epidemiologic methods were used to analyze
9 the exposure-response data, and benchmark concentration (BMC) methodology was used to
10 estimate PODs. In this approach, the available data are fit to a set of mathematical
11 exposure-response models to determine an appropriate empirical representation of the data.
12 General model fit is evaluated to determine whether the model form appropriately represents the
13 data; here, this was done using the Hosmer-Lemeshow test (a form of the Pearson χ^2
14 goodness-of-fit statistic). Among models with adequate general fit, a recommended model form
15 is then determined; commonly, this is the model with the best fit as measured by Akaike's
16 Information Criterion (AIC) value among these model forms judged to provide an appropriate
17 and statistically adequate representation of the data. For inhalation data, the BMC is defined as
18 the exposure level, calculated from the best-fit model, which results in a specified benchmark
19 response (BMR). The RfC is derived from the lower 95% confidence limit of the BMC, referred
20 to as the BMCL, which accounts for statistical uncertainty in the model fit to the data. All
21 analyses were performed using SAS® statistical software v. 9.1. BMCLs were obtained by the
22 profile likelihood method as recommended by Crump and Howe (1985) using the NLMIXED
23 (nonlinear mixed modeling) procedure in SAS (Wheeler, 2005) (see Appendix E for details).

24 For models where a background parameter is included, a 1% risk of localized pleural
25 thickening was assumed. Establishing a background rate for LPT prevalence is problematic for
26 several reasons. Little data exist to define background rates for LPT, as this designation is more
27 recent, and the majority of the published data use earlier ILO guidelines, which define discrete
28 pleural plaques (DPP). Secondly, it is difficult to define a population without exposure to
29 asbestos in any setting. As environmental and community exposures can increase pleural
30 thickening (Weill et al., 2010; Liu et al., 2002; Hiraoka et al., 1998, and Ziting et al., 1996), the
31 question arises, Is there a true background rate? Also, in general, pleural thickening increases
32 with both age and TSFE in a population. There is a study that reports the LPT in Libby
33 community members with no reported pathways of exposure (Weill et al., 2010). LPT
34 prevalence is reported at 0.4% in participants age 25–40, and 1.4% in participants age 41–50
35 (based on X-rays taken in 2000). Older study participants (61–90) had a LPT prevalence of

1 12.7%, likely influenced by high historical exposures, as well as the increased TSFE. In two
2 studies of persons not known to be previously exposed to asbestos, Anderson et al. (1979) and
3 Castellan et al. (1985) report DPP estimated prevalence of 1.2% (4/326) and 0.2% (3/1,422),
4 respectively. In cross-sectional studies, which may include persons with occupational exposure
5 to asbestos, Rogan reported DPP prevalence estimates of 1.2% in the National Health and
6 Nutrition Examination (NHANES) I study (1971–1975; Rogan, 1987) and 3.9% in the NHANES
7 II study (Rogan, 2000). Among military populations, two studies have reported an estimated
8 DPP prevalence of 2.3% (Miller, 1996; Bohnker, 2005). Based on these reports, the
9 1% background rate was chosen as representing the prevalence among persons without
10 occupational exposure to asbestos in the age range of the Rohs et al. (2008) study population. As
11 there is some uncertainty regarding the true background rate for LPT, a sensitivity analysis was
12 performed where the model includes the background rate as an estimated parameter rather than
13 using the set value of 1%. There was little change in the resulting model fits or BMCLs (see
14 Section 5.3.4).

15 In the absence of agent-specific information to assist in identifying a BMR, a 10% extra
16 risk was judged to be a minimally biologically significant level of change, and is also
17 recommended for standard reporting purposes (US EPA, 2000b). LPT is an irreversible
18 pathological change and associated with health effects including chronic pain, dyspnea, and
19 deficits in pulmonary function (see Section 5.2.2.3). The likelihood and severity of these health
20 effects increases with increased extent and severity of the pleural thickening. However, as the
21 data from the critical study do not provide information on the severity of the lesions, we cannot
22 assess the relative likelihood of any of these health effects. Thus, the observed LPT prevalence
23 may include a range of lesions from minimally adverse to severe. The biology of more severe
24 lesions (i.e., DPT and small opacities) could justify lower BMRs; however, there are not enough
25 cases to model these endpoints in this sub-cohort. A sensitivity analysis was conducted using the
26 data set included in Rohs et al. (2008) to examine the impact of choice of BMR and critical
27 effect on the POD (see Section 5.3.8).

28

29 **5.2.3.3.1. Statistical model evaluation and selection**

30 Dichotomous statistical models describing the probability of individual response as a
31 function of cumulative exposure (represented by CHEEC in units of fibers/cc-year) were used.
32 In order to investigate the key explanatory variables for analysis, a forward-selection process was
33 used to evaluate the association of each of the potential covariates with the risk of localized
34 pleural thickening, controlling for Libby Amphibole asbestos exposure. Covariates considered
35 for inclusion in the model were TSFE (*T*), age at X-ray, gender, smoking history, and BMI. This

1 initial modeling was done using a standard logistic regression model, as is commonly applied in
2 analysis of epidemiological data. The base model was a logistic regression model with
3 cumulative Libby Amphibole asbestos exposure (natural log transformed) as the independent
4 variable. This model provided an adequate fit to the data (Hosmer-Lemeshow p -value of 0.64),
5 and the exposure variable was statistically significantly associated with the outcome
6 (beta = 0.5676, standard error, [SE] = 0.2420 increase in log odds for every unit increase in
7 CHEEC, p -value = 0.02). Covariates were evaluated according to whether inclusion of the
8 covariate improved model fit as assessed by the AIC, and statistical significance of the covariate.
9 When controlling for Libby Amphibole asbestos exposure, none of these covariates were
10 associated with odds of localized pleural thickening: T : p -value = 0.89; age at X-ray:
11 p -value = 0.77; gender: p -value = 0.78; smoking history: p -value = 0.17; BMI: p -value = 0.41.
12 The inclusion of each of the covariates with the exception of smoking increased the AIC for the
13 model, and the improvement in model fit with the addition of smoking was marginal (decrease of
14 0.1 AIC units). Therefore, only cumulative Libby Amphibole asbestos exposure (CHEEC) was
15 included in further analyses, although sensitivity analyses were performed to investigate the
16 potential impact of smoking (see Section 5.3.6 and Appendix E).

17 The candidate models (see Table 5-4 for model forms) were logistic (with CHEEC
18 considered as continuous, and continuous with a natural logarithm transformation), probit (with
19 CHEEC considered as continuous, and continuous with a natural logarithm transformation),
20 3-parameter log-logistic, dichotomous Hill, and dichotomous Michaelis-Menten models (with
21 only CHEEC for the latter three models). These are statistical models used to evaluate
22 dichotomous data that were considered appropriate here given the supralinear nature of the
23 observed relationship between Libby Amphibole asbestos exposure and prevalence of localized
24 pleural thickening. For each of the candidate models, exposure lags of 0, 5, 10, 15, and 20 years
25 were investigated. Although zero lag exposures are not likely to be biologically relevant (i.e.,
26 some lag is expected for development of LPT), these models were included for completeness and
27 for comparison of relative model fits. Similarly, although we explored models with exposure
28 lagged by 20 years, there were cases of localized pleural thickening in the full cohort with fewer
29 than 20 years since first exposure; therefore, using such a long lag (which necessitates the
30 assumption that these are background cases) was not judged to be appropriate, and the results are
31 not further considered; these models are indicated by gray shading in Table 5-4. Further details
32 of these analyses are included in Appendix E.

33 All of the candidate models had adequate fit. Models were compared using the AIC—
34 values were quite similar among the candidate models, ranging from 74.0 to 77.8 (see
35 Table 5-4). The model with the lowest AIC was the Michaelis-Menten model with 10-year

1 lagged exposure (AIC = 74.0). For this model form, the AIC values did not vary much for lags
2 of 5 to 15 years, but the 10-year lagged exposure provided the lowest AIC and was selected as
3 the preferred exposure metric. There were several models that had similar model fits (within
4 2 AIC units, a proximity that can be considered to be a range that cannot clearly differentiate
5 between models [Burnham and Anderson, 2002]) as the best-fitting model, including the logistic
6 and probit models with the natural log of CHEEC as the exposure metric (lags of 5, 10, and
7 15 years), the 3-parameter log-logistic model (lags of 5, 10, and 15 years), the Dichotomous Hill
8 model (lag of 10 years), and the Michaelis-Menten model with exposure lagged by 5 or 15 years.
9 The range was relatively narrow among these similarly fitting models (BMCLs ranging from
10 0.0441 to 0.1352), with the lowest BMCL ~2.7 times lower than the BMCL for the
11 Michaelis-Menten model, with exposure lagged by 10 years.
12

Table 5-4. Candidate models for association between cumulative Libby Amphibole asbestos exposure in the Marysville sub-cohort and localized pleural thickening

1

Model	Exposure metric	Form ^a	AIC	Hosmer-Lemeshow GOF p-value	BMC	BMCL
Logistic	CHEEC	$P(LPT) = 1/[1 + \exp(-a - b * CHEEC)]$	77.7	0.7423	--	--
CHEEC, lag 5			77.5	0.6914	1.5245	0.8836
CHEEC, lag 10			77.4	0.6751	1.4734	0.8540
CHEEC, lag 15			77.6	0.6474	1.4510	0.8242
CHEEC, lag 20			77.8	0.8800	--	--
Logistic	ln(CHEEC)	$P(LPT) = 1/[1 + \exp(-a - b * \ln(CHEEC))]$	75.5	0.6537	--	--
CHEEC, lag 5			75.2	0.5454	0.2281	0.0601
CHEEC, lag 10			74.6	0.5708	0.2028	0.0591
CHEEC, lag 15			74.7	0.6620	0.1686	0.0463
CHEEC, lag 20			75.4	0.8152	--	--
Probit model	CHEEC	$P(LPT) = \Phi(a + b * CHEEC)$	77.2	0.7698	--	--
CHEEC, lag 5			77.0	0.7146	1.3773	0.8481
CHEEC, lag 10			77.0	0.6864	1.3336	0.8048
CHEEC, lag 15			77.2	0.6645	1.3148	0.7776
CHEEC, lag 20			77.4	0.8884	--	--
Probit model	ln(CHEEC)	$P(LPT) = \Phi(a + b * \ln(CHEEC))$	76.0	0.6041	--	--
CHEEC, lag 5			75.7	0.4967	0.2066	0.0502
CHEEC, lag 10			75.2	0.5385	0.1843	0.0496
CHEEC, lag 15			75.0	0.6166	0.1544	0.0441
CHEEC, lag 20			75.7	0.7945	--	--
3-parameter log-logistic	ln(CHEEC)	$P(LPT) = bkg + (1 - bkg)/[1 + \exp(-a - b * \ln(CHEEC))]$	74.9	0.7030	--	--
CHEEC, lag 5			74.6	0.4894	0.3096	0.0979
CHEEC, lag 10			74.1	0.5853	0.2696	0.0888
CHEEC, lag 15			74.3	0.7238	0.2193	0.0693
CHEEC, lag 20			75.2	0.8277	--	--

2

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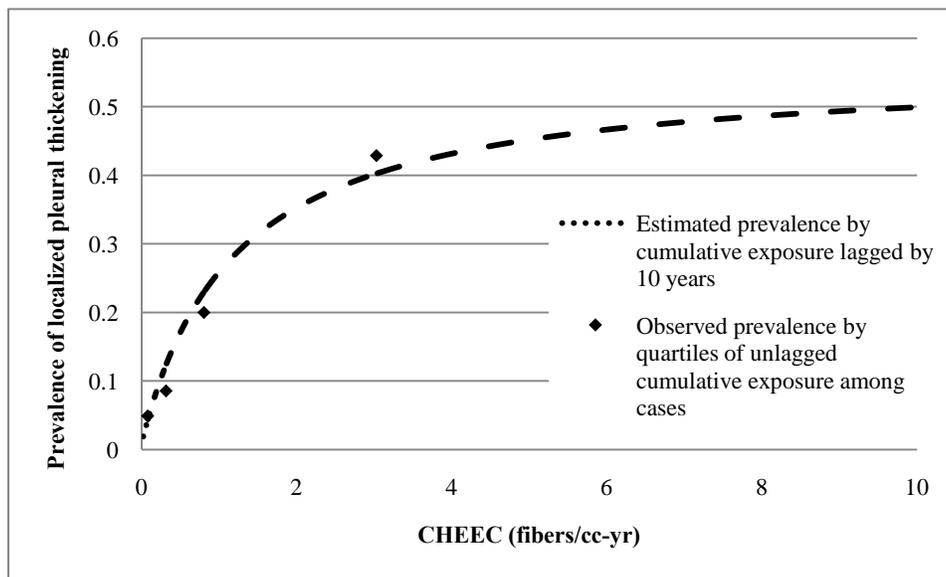
Table 5-4. Candidate models for association between cumulative Libby Amphibole asbestos exposure in the Marysville sub-cohort and localized pleural thickening (continued)

Model	Exposure Metric	Form*	AIC	Hosmer-Lemeshow GOF <i>p</i> -value	BMC	BMCL
Dichotomous Hill ^b	ln(CHEEC)	$P(LPT) = \text{bkg} + (\text{Plateau} - \text{bkg}) * \text{CHEEC}^b / [\exp(-a) + \text{CHEEC}^b]$	76.9	0.6040	--	--
CHEEC, lag 5			76.5	0.3598	0.3083	0.1015
CHEEC, lag 10			76.0	0.4244	0.2640	0.0923
CHEEC, lag 15			76.2	0.6659	0.2112	0.0724
CHEEC, lag 20			77.2	0.8277	--	--
Michaelis-Menten ^c	ln(CHEEC)	$P(LPT) = \text{bkg} + (\text{Plateau} - \text{bkg}) * \text{CHEEC} / [\exp(-a) + \text{CHEEC}]$	74.9	0.5243	--	--
CHEEC, lag 5			74.5	0.3351	0.3096	0.1352
CHEEC, lag 10^d			74.0	0.4163	0.2642	0.1177
CHEEC, lag 15			74.3	0.5664	0.2097	0.0898
CHEEC, lag 20			76.0	0.5610	--	--

1 ^abkg indicates background rate, fixed at 1%.
2 ^bFor statistical modeling, the equivalent model form was used: $P(PT) = \text{bkg} + (\text{Plateau} - \text{bkg}) / [1 + \exp(-a - \beta * \ln(\text{CHEEC}))]$.
3 ^cFor statistical modeling, the equivalent model form was used: $P(PT) = \text{bkg} + (\text{Plateau} - \text{bkg}) / [1 + \exp(-a - \ln(\text{CHEEC}))]$.
4 ^dParameter estimates for the best-fitting models are as follows:
5
6 intercept = -0.1801 (SE = 1.0178), plateau = 0.5577 (SE = 0.3568, *p*-value = 0.1207).
7
8
9

10 The potential confounding effect of covariates was reexamined in the best-fitting model.
11 As in the initial assessment, after controlling for the effect of exposure (CHEEC, lagged by
12 10 years), there was no association between risk of LPT and TSFE (*p*-value = 0.997), age at
13 X-ray (*p*-value = 0.87), gender (*p*-value = 0.55) or BMI (*p*-value = 0.38), and inclusion of each
14 of these covariates increased the AIC (with the exception of BMI, due to missing information for
15 some individuals). The variable representing smoking history did not meet the alpha = 0.05
16 criterion for statistical significance (*p*-value = 0.08), although inclusion of this variable decreased
17 the AIC from 74.0 in the best-fitting model, to 72.3. Smoking was not considered further in the
18 derivation of the RfC due to the lack of statistical significance at the alpha = 0.05 level.
19 However, because inclusion of the smoking variable did improve model fit, it is investigated
20 further as a sensitivity analysis (see Section 5.3.6 and Appendix E).

1 The Michaelis-Menten model using the 10-year lagged exposure had a p -value for fit of
2 0.42, an AIC value of 74.0, and an estimated intercept = -0.1801 (SE = 1.0178) and plateau of
3 0.5577 (SE = 0.3568) (see Figure 5-2). This model yielded a BMC_{10} of 0.2642 fibers/cc-year,
4 and corresponding $BMCL_{10}$ of 0.1177 fibers/cc-year for a 10% increase in prevalence of
5 localized pleural thickening. This $BMCL_{10}$ of 0.1177 fibers/cc-year is the preferred POD
6 estimate to support development of an RfC for Libby Amphibole asbestos.
7
8



9
10 **Figure 5-2. Graph of observed and estimated prevalence of localized pleural**
11 **thickening calculated using the Michaelis-Menten model with 10-year lagged**
12 **exposure.**
13
14

15 **5.2.4. RfC Derivation—Including Application of Uncertainty Factors (UFs)**

16 Among the available studies that could provide exposure-response data for the
17 relationship between Libby Amphibole asbestos exposure and risk of localized pleural
18 thickening (LPT), consideration of study attributes led to the selection of a study of the
19 Marysville, OH worker cohort as the primary data set for RfC derivation (Rohs et al., 2008) (see
20 Section 5.2.1). An updated job-exposure matrix is available for this follow-up of the original
21 cohort described by Lockey et al. (1984). The updated job-exposure matrix provides a more
22 refined understanding of exposure to Libby Amphibole asbestos throughout plant operation (see
23 Section 5.2.3.1 and Appendix F). However, due to remaining uncertainties in exposures prior to
24 1972, EPA elected to model a sub-cohort of plant employees that consisted of individuals who

1 began their employment in 1972 or later (see Section 5.2.3.2). It is acknowledged that although
2 this provides a sub-cohort with less potential for exposure misclassification, there is reduced
3 power due to fewer individuals and fewer observed cases. Therefore, EPA provides a supporting
4 analysis using the combined results for the Marysville plant workers as reported in both the
5 original study and in the update (Lockey et al., 1984 and Rohs et al., 2008) (Section 5.2.5).

6 LPT is an irreversible pathological change associated with constricting chest pain,
7 dyspnea, and decreased pulmonary function and, therefore, it is selected as the critical effect in
8 the sub-cohort. The Michaelis-Menten model, with a 10-year lag for exposure, provided the best
9 model fit for the sub-cohort data (AIC 74.0, see Table 5-4). Using a 10% BMR for LPT, a BMC
10 of 0.2642, and a $BMCL_{10}$ of 0.1177 (fibers/cc)-years were calculated (see Table 5-4). As this
11 POD is in units of cumulative exposure, and the RfC is given in continuous lifetime exposure,
12 the POD was adjusted to 70 years of exposure, lagged by 10 years (nonoccupational, lifetime
13 exposure). Thus the adjusted lifetime $BMCL_{10}$ is 1.96×10^{-3} fibers/cc (as derived below), and is
14 the POD for RfC derivation.

$$\begin{aligned} \text{Lifetime-}BMCL_{10} &= BMCL_{10} \div (\text{lifetime exposure duration}) \\ &= [0.1177 \text{ (fibers/cc) x year}] \div [70 - 10 \text{ years}] \\ &= 1.96 \times 10^{-3} \text{ fibers/cc} \end{aligned}$$

22 Following EPA practices and guidance (U.S. EPA, 2002; 1994b), application of the
23 following uncertainty factors was evaluated resulting in a composite UF of 100.

- 26 • An interspecies uncertainty factor, UF_A , of 1 is applied for extrapolation from animals to
27 humans because the critical effect used as the basis for the RfC was observed in humans.
- 28 • An intraspecies uncertainty factor, UF_H , of 10 was applied to account for human
29 variability and potentially susceptible individuals in the absence of quantitative
30 information to assess the toxicokinetics and toxicodynamics of Libby Amphibole
31 asbestos in humans. Only adults sufficiently healthy for full-time employment were
32 included in the principal study and the study population was primarily male.
- 33 • A LOAEL to NOAEL uncertainty factor, UF_L , of 1 was applied because the current
34 approach is to address this factor as one of the considerations in selecting a BMR for
35 BMC modeling. In this case, a BMR of 10% extra risk was considered to be minimally
36 biologically significant.

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- 1 • A subchronic-to-chronic uncertainty factor, UF_S , of 1 was applied because the selected
2 POD is from a study population including chronic exposure (Rohs et al., 2005). The
3 average employment duration for the sub-cohort corresponding for the RfC derivation is
4 18.7 years (SD = 8.6; range = 0.3–29.0).
- 5 • A database uncertainty factor, UF_D , of 10 was applied to account for database
6 deficiencies in the available literature for the health effects of Libby Amphibole asbestos.
7 Although there is a large database for asbestos in general, only three study populations
8 exist for Libby Amphibole asbestos specifically: the Marysville, OH worker cohort, the
9 Libby worker cohort and the ATSDR community screening (which includes some Libby
10 worker cohort participants). Limitations of these studies are described below.
- 11 1. Evidence exists for an association between exposure to Libby Amphibole asbestos
12 and other noncancer health effects with no exposure-response information.
13 Without additional data, it is unknown if a lower POD or RfC would be derived
14 for these effects.
- 15 a. Two studies have found a possible increased prevalence of autoimmune
16 disease and biological markers for autoimmune disease in Libby residents
17 (Pfau et al., 2005; Noonan et al., 2006), although these studies do not
18 indicate whether the autoimmune effects would be observed at exposures
19 lower than that observed for localized pleural thickening. Subsequent
20 animal studies have indicated that exposure to Libby Amphibole asbestos
21 does induce auto-antibodies in mice (Blake et al., 2008).¹²
- 22 b. A mortality analysis for the Libby worker cohort also found associations
23 between occupational exposures to Libby Amphibole asbestos and
24 mortality due to cardiovascular disease (Larson et al., 2010a).
- 25 c. Deficits in pulmonary function have been documented in those exposed to
26 Libby Amphibole asbestos occupationally or in the community. However,
27 exposure data are lacking to define an exposure response relationship on
28 this sensitive endpoint (Weill et al., 2010; Whitehouse, 2004).
- 29 2. There are no data in laboratory animals or humans on general systemic effects for
30 Libby Amphibole asbestos. However, it is known that inhaled asbestos fibers
31 migrate out of the lung and into other tissues (see Section 3.1), lending
32 uncertainty to any assumptions that other effects would not be expected.
- 33 3. Although data do exist to define an exposure-response relationship for
34 radiographic abnormalities in the Marysville, OH worker cohort, these data are
35 limited by the dates of the available radiographs. The data for the sub-cohort of

¹² It is unknown if autoimmune effects are secondary to the chronic inflammatory response expected from exposure to mineral fibers. However, one study of individuals in a community exposed to tremolite found changes in immune parameters in exposed individuals without localized pleural thickening, and that additional immune markers, including autoantibodies, increased in individuals with localized pleural thickening (Zerva et al., 1989).

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1 workers exposed post-1972 allowed for assessing prevalence of LPT up to
2 approximately 30 years after first exposure (Mean = 28.2 years,
3 range = 23.2–32.7 years). However, there is evidence to indicate that the
4 prevalence of pleural plaques and pleural thickening in general is likely to
5 continue to increase more than 30 years after first exposure (Paris, 2009, 2008;
6 Jakobsson et al., 1995; Hillerdal, 1994; Ehrlich et al., 1992; Järholm, 1992; Lillis
7 et al., 1991; Merchant, 1990; McDonald et al., 1986b). As the RfC is intended for
8 a lifetime of exposure, and pleural thickening is known to progress across the
9 lifetime (even with less-than-lifetime exposures), the lack of health data assessed
10 at end of lifetime is a data gap.

11
12
13 The derivation of the RfC from the morbidity studies of the Marysville, OH worker
14 cohort (i.e., Rohs et al., 2008) was calculated from a POD, lifetime-BMCL₁₀ of 1.96×10^{-3}
15 fibers/cc for localized pleural thickening, (adjusted to 70 years of exposure, lagged by 10 years
16 (nonoccupational, lifetime exposure), and dividing by a composite uncertainty factor (UF) of
17 100.

18 As derived below, the chronic RfC is 2×10^{-5} fibers/cc for Libby Amphibole asbestos
19 and was calculated by dividing the lifetime-POD by a total UF of 100:

$$\begin{aligned} \text{Chronic RfC} &= \text{Lifetime-BMCL}_{10} \div \text{UF} \\ &= 1.96 \times 10^{-3} \text{ fibers/cc} \div 100 \\ &= 1.96 \times 10^{-5} \text{ fibers/cc, rounded to } 2 \times 10^{-5} \text{ fibers/cc} \end{aligned}$$

27 **5.2.5. Alternative Analyses of the Full Marysville Cohort**

28 Modeling of the full cohort was also conducted utilizing the full data set for localized
29 pleural thickening from the Marysville cohort. Since the full cohort includes data combined
30 from Lockey et al. (1984) and Rohs et al. (2008), there were individuals who had more than one
31 observation. As described in Section 5.2.3.2, for those workers X-rayed in both 1980 (Lockey et
32 al., 1984) and 2004–2005 (Rohs et al., 2008), one of the observations was excluded so that there
33 are no repeat observations for individual workers in the data used for the modeling.

34 Time from first exposure to X-ray (the variable T , in this model) is an important variable
35 in understanding the full Marysville data set, as can be seen by the much higher prevalence of
36 localized pleural thickening in the 2000s compared to the 1980 assessment, an increase which
37 cannot be fully explained by the increases in cumulative exposure occurring with continued

1 exposure. Consequently, in looking at the full cohort, T is a strong predictor of localized pleural
2 thickening. Study T -values are measures of the time from first exposure to the event that an
3 X-ray was taken that detected an abnormality. As such, these values in themselves are not
4 measures of biological latency—an abnormality may be present for some time before the event
5 that an X-ray is taken. Given the occurrence of higher exposures in earlier years in this study,
6 higher T -values correspond to individuals who likely experienced the early higher intensity
7 exposures. This may lead to some uncertainty in the estimated models because uncertainty in the
8 estimated exposures can influence the apparent relationship between T and lesion prevalence. A
9 similar approach as described in Section 5.2.3.3.1 was used to evaluate candidate models for the
10 full cohort. Details are provided in Appendix E. However, as time from first exposure (T) was
11 an important covariate for these analyses, further efforts were needed to develop a model
12 incorporating T along with cumulative exposure. The logistic and probit models including
13 CHEEC as a continuous exposure had inadequate model fit as evaluated using the
14 Hosmer-Lemeshow test (p -values of 0.003 for both) and so were not considered for further
15 analysis. The remaining candidate models (logistic and probit with the natural logarithm of
16 CHEEC, 3-parameter log-logistic, dichotomous Hill, and dichotomous Michaelis-Menten) had
17 adequate fit. Among these models, the AIC values ranged from 327.9 (Michaelis-Menten)
18 to 346.8 (logistic with the natural logarithm of CHEEC) (see Appendix E). Based on these
19 results, the Michaelis-Menten model was selected for further evaluation, and different
20 approaches were investigated to represent T along with cumulative exposure to Libby Amphibole
21 asbestos using this model form.

22 The approach taken to incorporate T was through modification of the plateau term in the
23 Michaelis-Menten model to allow the plateau for the exposure-response relationship to change
24 for different values of T . After investigating various forms for the plateau (described in
25 Appendix E), the plateau term used took the form: Plateau = Background + (1-background) \times
26 $\Phi(T|m,s)$, where $\Phi(T|m,s)$ represents the cumulative normal probability distribution function.
27 Different exposure lags were then investigated for this model—as seen for the sub-cohort, the
28 AIC values were quite similar for lags of 0–15 years (AICs ranging from 277.72 to 278.04).
29 However, the 20-year lagged exposure had an increased AIC of 280.60 and was not judged an
30 appropriate choice. In order to estimate a BMC_{10} and corresponding $BMCL_{10}$ for this model
31 form, a fixed value of T must be specified.

32 To facilitate comparison of the results of the two models, the Cumulative Normal
33 Michaelis-Menten model was run with the variables consistent with the sub-cohort hired in 1972
34 or later (see Section 5.2.3.3.1). A value of $T = 30$ years and a lag time of 10 years were used.
35 For the sub-cohort, the mean time from first exposure was 28 years. For the Cumulative Normal

1 Michaelis-Menten model, the BMC_{10} was 0.1477 fibers/cc-year, and the $BMCL_{10}$ was
2 0.0580 fibers/cc-year. These values are generally similar to the results from the sub-cohort for
3 those hired in 1972 or later using the Michaelis-Menten model (BMC_{10} and $BMCL_{10}$ of 0.2642
4 and 0.1177 fibers/cc-year, respectively).

5 One alternative analysis using the full cohort model, with a TSFE value of $T = 40$ years
6 was conducted. A $BMCL_{10}$ of 0.0136 fibers/cc-year was calculated with the Cumulative Normal
7 Michaelis-Menten model. The $BMCL_{10}$ with $T = 40$ years is used because it is near the upper
8 end of the range of T values available in the data set ($T_{max} = 47.375$ years). This POD combined
9 with a lag time of 5 years (used because Larson et al. [2010b] showed that discrete pleural
10 thickening could be observed much earlier than previously thought) and a total UF of 100 was
11 used to derive an alternative RfC of 3.8×10^{-6} fibers/cc, or rounding to one significant digit,
12 4×10^{-6} fibers/cc. See Appendix E for details. This alternative RfC is a factor of 5 lower than
13 the RfC derived from the sub-cohort. This alternative RfC is an order of magnitude lower
14 compared to both the preferred sub-cohort analysis and the full cohort analysis, with a fixed T of
15 30 years.

16 Another alternative analysis is based on projection of risks using the full cohort model for
17 a “lifetime” time from first exposure of 70 years. Note that none of the workers had a
18 $T > 50$ years; therefore, this modeling represents a mathematical extrapolation beyond available
19 data. A $BMCL_{10}$ of 0.0042 fibers/cc-year was calculated using the Cumulative Normal
20 Michaelis-Menten model. This POD combined with a lag time of 5 years and a total UF
21 of 30 was used to derive an alternative RfC of 2.1×10^{-6} fibers/cc, or rounding to one significant
22 digit, 2×10^{-6} fibers/cc. See Appendix E for details.

23 Each of the candidate PODs (analyses from both the sub-cohort and full cohort) has
24 strengths and weaknesses. A major strength of the preferred analysis (Marysville sub-cohort) is
25 that by limiting the data set to those individuals hired in 1972 or later, the exposure
26 reconstruction relies only on data supported by industrial hygiene measurements in the facility.
27 The exposures were also lower after 1972 as compared to previous years. However, this
28 approach reduces the number of individuals in the data set from 434 to 119 and reduces the
29 number of cases from 61 to 12. In addition, this approach narrows the range in the time from
30 first exposure to 23.15–32.65 years (see Table 5-3). The analyses of the full cohort have the
31 strength of using all of the data available on the Marysville cohort and of using a model that
32 incorporates both cumulative exposure and time from first exposure as relevant explanatory
33 variables. One weakness of the full cohort analyses is that the exposure reconstruction relies on
34 estimates of the exposure conditions in the Marysville facility before industrial hygiene data
35 were available in 1972.

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1 **5.2.6. Previous Reference Concentration (RfC) Derivation**

2 There is no previous RfC derivation for Libby Amphibole asbestos.
3

4 **5.3. UNCERTAINTIES IN THE INHALATION REFERENCE CONCENTRATION**
5 **(RfC)**

6 **5.3.1. Uncertainty in the Exposure Reconstruction**

7 As in all epidemiologic studies, there are uncertainties in the exposure reconstruction. In
8 this case, there is some uncertainty in the employment history, and some individuals had
9 extensive overtime work. Employment history was self-reported during interviews with each
10 individual for the original study (Lockey et al., 1984), and errors in this process could affect
11 assigned Libby Amphibole asbestos exposure estimates. As stated previously, fiber
12 measurements started in the Marysville plant in 1972; exposures prior to this time were estimated
13 by University of Cincinnati scientists, based on focus group interviews with 15 long-term former
14 workers and the times when engineering changes were made to control dust in the facility (see
15 Appendix F). Exposure estimates for the period prior to 1972, can, thus, be considered as
16 semiquantitative rather than directly based on industrial hygiene data. The University of
17 Cincinnati analysis assumed that early exposure levels in the plant are twice those measured in
18 1972 (see Appendix F). The greater uncertainty of the pre-1972 exposure estimates led to EPA's
19 decision to focus the analysis on the post-1972 group of workers rather than the full cohort.
20 Although it is generally true that the use of more data is an advantage for statistical analyses
21 because it allows for the computation of more statistically precise effect estimates, this increased
22 precision may be offset by a negative impact on the accuracy of the effect estimate if an increase
23 in sample size is accompanied by greater exposure misclassification or other biases.

24 While the uncertainties related to a lack of quantitative measurements are not relevant to
25 the sub-cohort analysis, it is important to recognize that exposure assessment post-1972 also has
26 some limitations. The main sources of uncertainty are incomplete exposure measurements for
27 some of the occupations/tasks before industrial hygiene improvements that started about 1973 or
28 1974 and continued throughout the 1970s (see Appendix F, Figure F-1).

29 There is uncertainty when the Libby ore was first used in the facility. Company records
30 indicated that the date was between 1957 and 1960, and the University of Cincinnati used the
31 best-available information from focus group interviews to assign the first usage of Libby ore in
32 1959 (see Appendix F). There is also uncertainty in the data regarding asbestos content in other
33 ore sources before and after Libby ore use. In 1957 and 1958, only ore from South Carolina was
34 used. From 1959 to 1971, ores from Libby and South Carolina were used. From 1972 to 1980,
35 ores from Libby, South Carolina, South Africa, and Virginia were used with Libby being the
36 major source. Libby ore was not used in the facility after 1980. However, industrial hygiene

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1 measurements collected after 1980 showed low levels of fibers in the facility. PCM analysis
2 does not determine the mineral/chemical make-up of the fiber, and, thus, cannot distinguish
3 between different kinds of asbestos.

4 As reported in Appendix C, the EPA analysis of bulk ores from Virginia and South
5 Africa showed the presence of only a few or no Amphibole asbestos fibers; EPA could not obtain
6 a sample of ore from South Carolina. However, the South Carolina ore is known to contain
7 fibers (see Appendix F; U.S. EPA, 2000d; McDonald et al., 1988). Using the industrial hygiene
8 data, the University of Cincinnati estimated that the fiber content of the South Carolina ore was
9 about 10% of that of the Libby ore (see Appendix F). This result is consistent with data
10 comparing South Carolina and Libby ores from samples tested in 1982 (U.S. EPA, 2000d). EPA
11 believes that the overwhelming exposure to fibers in the Marysville facility is from the Libby
12 ore. Therefore, EPA has attributed all of the adverse health effects to exposure to fibers from
13 Libby ore from 1957 to 1980 and from the post-1980 exposure. However, because the
14 concentration of fibers in the workplace was near background after 1980, the post-1980 time
15 period makes only a small contribution to an individual's cumulative exposure.

16 There was potential coexposure to other chemicals in the Marysville facility (see
17 Section 4.1.3). These other chemicals were used after expansion of vermiculite ore in another
18 area of the facility. Industrial hygiene data showed very low levels of fibers in the areas where
19 the additional chemicals were added to the expanded vermiculite. In addition, none of these
20 chemicals are volatile. The most likely route of exposure to these chemicals is through dermal
21 contact. It is unlikely that any coexposure to these particular chemicals would alter the
22 exposure-response relationship of Libby Amphibole asbestos in the respiratory system (see
23 Sections 4.1.3 and 5.3.1).

24 The University of Cincinnati Research Team assumed that there was no exposure to
25 Libby Amphibole asbestos outside of the workplace. The interviews with the Marysville
26 workers revealed that about 10% of the workers reported bringing raw vermiculite home. These
27 interviews also revealed that changing to street clothes from work-supplied coveralls was
28 standard practice at the end of the shift, and approximately 64% of the workers showered before
29 leaving the workplace. For these workers, it is likely that additional exposure outside the
30 workplace was minimal. However, for the remainder of the workers, it is reasonable to assume
31 that additional exposure could have occurred at home. Additional data collected by the
32 University of Cincinnati Research Team document that no increased prevalence of pleural or
33 parenchymal change consistent with asbestos exposure has been observed in household contacts
34 of the workers from the Marysville facility (J. Lockey, University of Cincinnati, personal
35 communication to Robert Benson, U.S. EPA, 2011).

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1 **5.3.2. Uncertainty in the Radiographic Assessment of Localized Pleural Thickening**

2 The use of conventional radiographs to diagnose pleural thickening has several
3 limitations. The localized thickening must be of sufficient size and thickness to be viewed on the
4 X-ray; small lesions may exist but not be reported. More severe and larger lesions are more
5 reliably detected on radiographs. There are also potential interferences. Fat pads may be
6 mistaken as pleural plaques as they generally occur against the ribcage in a similar location
7 (Gilmartin, 1979); this is one source of uncertainty between readers. Although generally related
8 to mineral fiber exposure, pleural plaques may also be a result of trauma to the chest, and pleural
9 thickening may appear after an active TB infection. Often signs of trauma (e.g., fractured ribs)
10 and radiographic signs of past TB infection can be seen and are noted by the reader. In these
11 cases, LPT would not be diagnosed. There is a certain amount of subjectivity when viewing the
12 X-rays determining which features are representative of pleural thickening and if signs of
13 alternative etiology can be noted; thus, several certified readers are generally consulted, and a
14 consensus of opinions determines the diagnosis. Regardless, there is still potential for outcome
15 misclassification. For example, one of the workers in the Marysville cohort had a positive X-ray
16 in the 1980 evaluation but a negative X-ray at the 2002–2005 evaluation (excluding this worker
17 from the analysis did not change results). However, uncertainty in the presence or absence of
18 localized pleural thickening in each individual is considered minimal due to the use of three
19 highly qualified chest radiologists evaluating the radiographic films and the use of the majority
20 vote of the readers for the diagnosis.

21 BMI was investigated as a potential explanatory variable because fat pads can sometimes
22 be misdiagnosed as pleural thickening. BMI was not measured in the 1980 examination but was
23 available for most participants of the 2000s examination. To address whether fat deposits may
24 affect outcome classification, EPA considered the effect of adding BMI as a covariate in the
25 model. However, BMI did not display an association with odds of localized pleural thickening
26 in this population (see Appendix E). While these covariates were not associated with the risk of
27 localized pleural thickening in the sub-cohort after adjusting for exposure, it was not possible to
28 evaluate this relationship in the full cohort. In the general U.S. population, BMIs have increased
29 between 1980 and the 2000s, so one cannot necessarily assume the relationships will be the same
30 for the two examination periods.

31 32 **5.3.3. Uncertainty Due to Time From First Exposure**

33 There is some uncertainty associated with the length of follow-up of the Marysville
34 cohort. The observed range of TSFE to X-ray in the full cohort is 0.4–47 years, and 23.2–32.7
35 years in the preferred sub-cohort (see Table 5-3). It is anticipated that the prevalence of

1 localized pleural thickening in the study population—and in the post 1972 exposure cohort—
2 may continue to show some increase with passage of time. In this case, the modeling approach
3 may not accurately reflect the exposure-response relationship that would be seen with a longer
4 follow-up time. However, a recent study by Larson et al. (2010b) examined serial radiographs
5 conducted on a group of Libby vermiculite workers with pleural or parenchymal changes. They
6 found that among those workers with localized pleural thickening, all cases were identified
7 within 30 years, and that the median time from hire to the first detection of localized pleural
8 thickening was 8.6 years. Albeit the retrospective evaluation of radiographs is a different and
9 more sensitive procedure, these findings indicate that the range of follow-up time in the
10 Marysville sub-cohort is likely sufficient to support the exposure-response modeling developed
11 in this current assessment. Note that the likelihood that prevalence of localized pleural
12 thickening may further increase beyond 30 years after first exposure is a principal rationale cited
13 for the selection of a database UF of 10 in this current assessment.
14

15 **5.3.4. Uncertainty in Background Rate of Localized Pleural Thickening**

16 In the derivation of the RfC, a background rate of 1% for localized pleural thickening was
17 used. As discussed in Section 5.2.3.3, there is uncertainty in estimating the value of this
18 parameter. However, in statistical modeling of the Marysville sub-cohort, potential uncertainty
19 in the background rate of localized pleural thickening has little impact on the estimated POD.
20 The best-fitting model (Michaelis-Menten with 10-year lagged exposure) was rerun, allowing the
21 background rate to be estimated as a parameter rather than fixed, with a resulting estimated
22 background rate of 3.12% (SE = 2.84%). Both the fixed and estimated values are in the range of
23 estimates from previous studies described above, and the difference in the POD when the
24 background rate is fixed at 1% versus when it is estimated is ~15% (0.1177 compared with
25 0.1349 fibers/cc-year, and it does not affect the proposed RfC (after rounding to one significant
26 digit).
27

28 **5.3.5. Uncertainty in Model Functional Form and Lagged Exposure**

29 A number of model forms were explored in the initial stages of analysis (see Appendix E)
30 before selecting the Michaelis-Menten model. In this application, the ratio of the BMC_{10} to the
31 $BMCL_{10}$ ($0.2642 \div 0.1177 = 2.2$) was reasonable given the size of the available data set,
32 indicating acceptable statistical precision in the BMC estimate. In addition, BMCs and BMCLs
33 estimated from other candidate models for the post-1972 exposure sub-cohort were in a similar
34 range to the selected model. Finally, the complementary analysis with the full cohort (utilizing a
35 time from first exposure of 30 years, which was selected to be consistent with time since first

1 exposure values within the sub-cohort) provided similar results to the sub-cohort analysis. A
2 second model-based uncertainty is the choice of lag for cumulative exposure. The RfC
3 derivation is based on the exposure lagged by 10 years, since this lag yielded the lowest AIC.
4 However, if other lags (with similar AICs) are used, the difference in POD may fluctuate to be
5 approximately 20% higher or approximately 55% lower. Thus, the choice of lag does not affect
6 the proposed RfC (after rounding to one significant digit).

7

8 **5.3.6. Uncertainty Due to Effect of Smoking**

9 Smoking is an important variable to consider when evaluating respiratory health
10 outcomes. Although data are mixed, a few studies suggest smoking may affect risk of
11 developing pleural thickening or timing of pleural thickening development among persons
12 exposed to asbestos. However, no studies were identified that assessed the relationship between
13 LPT specifically and any measure of smoking status. Discrete pleural plaques as defined in
14 earlier ILO classification systems have not been associated with smoking in asbestos-exposed
15 workers (Mastrangelo et al., 2009; Paris et al., 2009; Koskinen et al., 1998), but there is evidence
16 that small opacities (asbestosis) and diffuse pleural thickening may be associated with smoking
17 in asbestos-exposed individuals.¹³ As the current classification of LPT includes cases of diffuse
18 pleural thickening where the CPA is not involved, investigation of the potential for smoking to
19 modify the effect of asbestos exposure on the prevalence of LPT is warranted.

20 Each of the four candidate studies considered for RfC derivation considered smoking in
21 their analytic approach. In the Libby workers cohort, McDonald et al. (1986b) assessed pleural
22 thickening of the chest wall (both discrete and diffuse regardless of CPA involvement) and found
23 smoking status (current, former, or never smoker) was of borderline statistical significance
24 ($p = 0.10$) in a regression model, controlling for Libby Amphibole asbestos exposure and age.
25 This is consistent with the broader asbestos literature, addressing all pleural thickening or all
26 pleural abnormalities. Amandus et al. (1987b) evaluated radiographic abnormalities consistent
27 with the current LPT designation; the authors took a different analytic approach to assess smoking
28 effects, constructing separate models for the full cohort and restricting to current and former

¹³ Studies among populations exposed to general 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 diffuse pleural thickening, [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—or possible—associations when examining risk of pleural changes (Baker et al., 1985; Lilis et al., 1991; Yano et al., 1993; Zittig et al., 1996; Dement et al., 2003; Paris et al., 2008) or no association with smoking (Ehrlich et al., 1985, Rosenstock et al., 1988; Delclos et al., 1990; Neri et al., 1996; Soulat et al., 1999). 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.

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1 smokers. The parameter estimates were not significant for the two models, although the
2 coefficients corresponding to Libby Amphibole asbestos exposure were slightly higher for the
3 full cohort model.

4 In the Marysville workers cohort, smoking was characterized using pack-years in the
5 original study (Lockey et al., 1984) and as ever/never smoking in the follow-up (Rohs et al.,
6 2008). Lockey et al. (1984) reported that the pack-years variable was significantly associated
7 with risk of all radiographic changes using discriminate analysis (any pleural thickening, small
8 opacities, and blunting of the CPA) but did not present results for effect of smoking controlling
9 for Libby Amphibole asbestos exposure. Rohs et al. (2008) did not find a difference in smoking
10 prevalence among those with and without any radiographic changes but also did not report
11 results controlling for Libby Amphibole asbestos exposure, or for LPT specifically.

12 Therefore, EPA explored the effect of smoking on the critical endpoint. In analyses for
13 RfC derivation, the variable representing smoking history (ever smoker vs. never smoker) was of
14 borderline significance in the best-fitting model ($p = 0.08$) and improved model fit (see
15 Appendix E). The limited sample size (only three cases were never smokers) and limited nature
16 of the smoking information precluded use of the smoking variable for RfC derivation. However,
17 the model including smoking was examined as a sensitivity analysis. In this analysis, BMCs and
18 BMCLs estimated separately for smokers and nonsmokers differed by approximately sixfold,
19 suggesting that smokers may be at a higher risk for LPT from exposure to Libby Amphibole
20 asbestos than nonsmokers. Thus, an estimated BMCL for smokers would be lower than the POD
21 used for RfC derivation (0.04 fibers/cc-year for smokers versus 0.12 fibers/cc-year for the entire
22 sub-cohort). Conversely, a BMCL for nonsmokers would be slightly higher
23 (0.25 fibers/cc-year). These sensitivity analyses indicate a need for further research on the effect
24 of smoking in relation to LPT risk among asbestos-exposed populations.

26 **5.3.7. Sensitivity Analysis: Derivation of a POD for Lifetime Exposure From the** 27 **Cumulative Exposure Metric**

28 Exposure–response modeling for LPT in the Marysville sub-cohort used the cumulative
29 exposure (CE) metric (represented as CHEEC, described in Section 5.2.2.1) providing a POD in
30 fibers/cc-years. In order to derive an RfC in the units of continuous air concentration for a
31 lifetime (i.e. fibers/cc), the POD from the CE metric was weighted across a lifetime exposure.
32 Thus, the lifetime $BMCL_{10}$ is 1.96×10^{-3} ($0.1177 \text{ fibers/cc-years} \div 60 \text{ years}^{14}$). This procedure is
33 one way to account for the duration of exposure in the occupational study being less than
34 lifetime. There is some uncertainty as to whether and how to take account for less-than-lifetime

¹⁴ Because the best-fitting model had a 10-year lag, the lag is applied to the weighting across a lifetime as well. Sixty years represent lifetime exposure of 70 years; 70 years – 10 years for the lag in exposure.

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1 exposure in the occupational cohort. The cohort participants had a wide range of exposure
2 durations, all of which are less than lifetime¹⁵. As there are other reasonable alternatives to
3 derive a lifetime RfC, a sensitivity analysis was conducted to examine if RfC derivation was
4 greatly impacted by the method chosen to convert the POD in units of cumulative exposure, to
5 an air concentration for lifetime exposure.

6 Use of the CE metric adjusted based on ventilation rates and work schedule to a
7 continuous air concentration is consistent with EPA guidance (represented as CHEEC in this
8 assessment) (U.S. EPA 2002a, 1994). Guidelines also recommend that if the human study is a
9 less-than-lifetime study, additional adjustment may be needed, depending on the nature of the
10 observed health effect for an RfC applicable to lifetime exposure U.S. EPA, 1994. Although
11 cumulative exposure is often associated with asbestosis (small opacities) and DPT, many other
12 studies have found pleural plaques are better predicted by other exposure metrics (e.g., average
13 intensity, mean exposure, duration). The use of a measure of average exposure (averaged over
14 the period of exposure) is consistent with previous studies (asbestos in general) that report
15 associations of the prevalence of pleural plaques with mean or average asbestos exposure (i.e.,
16 Ehrlich et al., 1992; Jakobsson et al., 1995; Paris et al., 2008). The first alternative method was
17 to weight the POD across duration of exposure in the sub-cohort, rather than a full lifetime. The
18 second alternative is model the exposure-response relationship for LPT against average exposure
19 (a measure of the cumulative exposure for each worker averaged over the individual worker's
20 duration of work exposure).

21 The first sensitivity analysis is calculated by dividing the modeled POD for the
22 sub-cohort (0.1177 fibers/cc-years [30-year BMCL₁₀]) by the average employment duration for
23 the sub-cohort of 18.7 years. Therefore, the POD expressed as the equivalent concentration for
24 the mean worker exposure duration for the sub-cohort is 6.3×10^{-3} (fibers/cc, continuous air
25 concentration) ($[0.1177 \text{ fibers/cc-years}] \div 18.7 \text{ years}$).

26 For the second analysis, the average exposure was calculated for each participant
27 ($\text{AvgExp} = \text{CHEEH for each worker} \div \text{duration of exposure for each worker}$). The
28 exposure-response relationship was defined using the best-fitting model for the sub-cohort
29 (Michaelis-Menten). The average exposure metric also provided an adequate fit to the data for
30 the preferred sub-cohort (Hosmer-Lemeshow GOF¹⁶; $P = 0.72$) and provided a slightly better—
31 but similar—fit to the CE metric [AIC = 72.2 versus 74.0]. The Michaelis-Menten model

¹⁵ This is especially true for the RfC derived from the sub-cohort hired after 1972, which had a more limited range of employment duration (mean=18.7 years [SD=8.6]; range=0.3-29.0).

¹⁶ General model fit was evaluated with the Hosmer-Lemeshow (2000) test (a form of the Pearson χ^2 goodness-of-fit [GOF] statistic). This is a goodness-of-fit test that compares observed and expected events. Observations are sorted in increasing order of estimated probability of the event occurring and then divided into ~10 groups; the test statistic is calculated as the Pearson χ^2 statistic of observed and expected frequencies in these groups.

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1 provided a BMC of 1.8×10^{-2} fibers/cc, and a $BMCL_{10}$ of 8.5×10^{-3} fibers/cc for the average
2 work-duration exposure metric. This $BMCL_{10}$ is about 4-fold higher than the lifetime- $BMCL_{10}$
3 above from the primary analysis (1.96×10^{-3} fibers/cc).

4 The three methods provide PODs that vary by a factor of up to 4 (2.0×10^{-3} , 6.1×10^{-3} , or
5 8.5×10^{-3} fibers/cc) when expressed as a continuous air concentration. The primary analysis
6 assumes duration contributes to risk and thus calculates a concentration across a lifetime that
7 would yield the POD CE. The second analysis is consistent with assuming duration contributes
8 to risk but estimating the concentration only for the mean duration in the observed database. The
9 third analysis assumes duration does not contribute to risk and models the average work duration
10 continuous exposure equivalent for each worker.

11 The difference comes in whether the critical study is considered of adequate duration to
12 inform health effects from a lifetime exposure, or if further adjustment is needed across time.
13 The primary analysis provides this adjustment to a full lifetime. This sensitivity analysis
14 indicates that the approach taken to average the POD based on the CE metric (CHEEC) across a
15 lifetime was a reasonable approach, as similar results are obtained using different approaches
16 (i.e., within 4-fold).

18 **5.3.8. Sensitivity Analysis for Choice of Critical Effect and Selection of Benchmark** 19 **Response (BMR)**

20 The critical effect selected for RfC derivation is localized pleural thickening. Alternative
21 endpoints were not modeled using the preferred sub-cohort due to small numbers—there were
22 five cases of bilateral LPT, only one case of diffuse pleural thickening, and no individuals with
23 interstitial changes. As a sensitivity analysis, these three alternative endpoints (along with all
24 LPT) were modeled among all Marysville workers not previously exposed to other forms of
25 asbestos, with X-rays performed in 2002–2005 ($n = 250$). These analyses were performed using
26 the Michaelis-Menten model with a background rate of 1% and unlagged CHEEC as the
27 exposure metric. BMRs of 1, 5, and 10% were investigated (see Table 5-5). Use of the 10%
28 BMR for these alternative endpoints allows for comparison with a POD based on the selected
29 critical effect of LPT. In this larger cohort, the POD for a 10% increase in LPT was
30 0.06 fibers/cc-years (in comparison with the POD derived from the sub-cohort and used in RfC
31 derivation of 0.118 fibers/cc-years). Results for all pleural thickening (LPT and DPT) did not
32 differ from results for LPT. Bilateral localized pleural thickening was included as a rough
33 indication of increased severity within LPT, and as expected results in higher PODs at each
34 BMR than LPT. The resulting $BMCLs$ for DPT and small opacities (1.17 and 2.89
35 fibers/cc-years, respectively, 10% BMR) are higher than the POD for LPT (0.06 fibers/cc-years).

1 Thus, use of an alternative endpoint at the same BMR would provide a higher POD, and
 2 corresponding higher RfC.

3 However, a 10% BMR is not appropriate for more severe endpoints and BMCLs are
 4 calculated at 1 and 5% BMRs as well. If DPT is used as a critical effect, PODs of 0.081 and
 5 0.473 fibers/cc-years would be calculated for a 1% and 5% BMR, respectively. If small
 6 opacities are used as a critical effect, the PODs are higher at both a 1% and a 5% BMR
 7 (0.243 and 1.32, respectively). In summary, the use of more severe alternative endpoints (with
 8 appropriate BMRs) results in PODs higher than that estimated using the critical effect of LPT
 9 (0.06 fibers/cc-year, BMR 10%), and all are higher than the POD used in RfC derivation, with
 10 the exception of DPT at a 1% BMR (0.0814 fibers/cc-year). BMCLs for these more severe
 11 endpoints using a 1% BMR were within ~twofold of the preferred POD (0.0814 and
 12 0.2425 fibers/cc-year for diffuse pleural thickening and interstitial changes, respectively). There
 13 is uncertainty associated with these estimates due to the inclusion of individuals hired before
 14 1972, when no quantitative exposure measurements were available. Thus, a choice of alternative
 15 critical effects (even with lower BMRs) would not result in an RfC appreciably lower than the
 16 proposed RfC based on LPT and a 10% BMR.

17
 18 **Table 5-5. Modeling of alternative endpoints in the Marysville worker**
 19 **cohort members examined in 2002–2005**
 20

BMR	Parameter	Bilateral localized pleural thickening (n = 33) vs. no abnormalities (n = 181)	Diffuse pleural thickening (n = 10) vs. no abnormalities (n = 181)	Interstitial changes (n = 7) vs. no abnormalities (n = 181)
	AIC	164.6	64.1	45.9
	Alpha (SE)	0.2670 (0.5420)	-2.8434 (1.6617)	-4.0674 (0.5014)
	Plateau (SE)	0.4120 (0.0962)	0.6166 (0.6307)	1.0000 (--)
BMR = 1%	BMC	0.0193	0.2849	0.5899
	BMCL	0.0097	0.0814	0.2425
BMR = 5%	BMC	0.1075	1.5259	3.0739
	BMCL	0.0552	0.4728	1.3158
BMR = 10%	BMC	0.2501	3.3494	6.4894
	BMCL	0.1337	1.1715	2.8923

21
 22
 23 **5.4. CANCER EXPOSURE-RESPONSE ASSESSMENT**

24 **5.4.1. Overview of Methodological Approach**

25 The objective of this human health assessment is to derive a cancer estimate for
 26 inhalation exposure to Libby Amphibole asbestos. The inhalation unit risk (IUR) is defined as

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1 an upper-bound excess lifetime cancer risk estimated to result from continuous exposure to an
2 agent at a concentration of 1 µg/L in water, or 1 µg/m³ in air. However, current health standards
3 for asbestos are given in fibers/cc of air as counted by PCM, since they are based on health
4 effects observed in occupational cohorts and this is the standard for measuring fiber exposures in
5 an occupational environment (U.S. EPA, 1988; Occupational Safety and Health Administration
6 [OSHA], 2008). Similarly, when examining the available health effects data for Libby
7 Amphibole asbestos, the best available exposure metric at this time is fibers/cc counted by PCM
8 (see Section 4.1.1.2). Therefore, for Libby Amphibole asbestos, the IUR represents the lifetime
9 risk of mortality from either mesothelioma or lung cancer in the general U.S. population from
10 chronic inhalation exposure to Libby Amphibole asbestos at a concentration of 1 fiber/cc of air.

11 IURs are based on human data when appropriate epidemiologic studies are available.
12 The general approach to developing an IUR from human epidemiologic data is to quantitatively
13 evaluate the exposure-response relationship (slope) for that agent to derive a specific estimate of
14 its cancer potency in the studied population. For this current assessment, the first step was to
15 identify the most appropriate data set available, which in this case can be used to quantitatively
16 estimate the effects of Libby Amphibole asbestos exposure on cancer mortality. Once the
17 relevant data describing a well-defined group of individuals along with their exposures and
18 health outcomes were selected, an appropriate statistical model was selected that adequately fit
19 the data, and then individual-level exposures were modeled using a variety of possible exposure
20 metrics (see Section 5.4.2). The available epidemiologic data allowed for modeling of the
21 effects of estimated ambient occupational exposures to Libby Amphibole asbestos on the
22 observed cancer mortality risk in workers. Exposure-response modeling was conducted for each
23 cancer mortality endpoint individually, and in some cases, the statistical model and the specific
24 metric of exposure used for each cancer endpoint may have been different. For example, the
25 exposure metric that best describes the exposure-response relationship for mortality from
26 mesothelioma attributable to occupational exposure to Libby Amphibole asbestos was found to
27 be different from the exposure metric that best describes mortality from lung cancer (see
28 Section 5.4.3). Potential covariates that may also be important predictors of cancer mortality are
29 included in the statistical models. These models were then statistically evaluated to determine
30 which exposure metric representing estimated ambient occupational exposures provided the best
31 statistical fit to the epidemiologic data.

32 This cancer potency (slope) estimate derived from the epidemiologic data is then applied
33 to the general U.S. population to determine the exposure level that would be expected to result
34 in 1% extra cancer mortality risk over a lifetime of continuous exposure. For epidemiologic
35 studies, which may be based on larger numbers of individual observations, smaller response

1 levels that are closer to the background response levels are considered appropriate. Extra risk is
2 defined as equaling $(R_x - R_o) \div (1 - R_o)$, where R_x is the lifetime cancer mortality risk in the
3 exposed population, and R_o is the lifetime cancer mortality risk in an unexposed population (i.e.,
4 the background risk). For example, if the expected lifetime risk of lung-cancer mortality in the
5 unexposed general U.S. population is 5%, then this human health assessment seeks to estimate
6 the level of exposure to Libby Amphibole asbestos that would be expected to result in a lifetime
7 risk of lung-cancer mortality of 5.95%; this lifetime risk of mortality is equivalent to a 1% extra
8 risk: $(0.0595 - 0.05) \div (1 - 0.05) = 0.01$. For mesothelioma mortality, an absolute risk of 1% was
9 considered, rather than extra risk, for two reasons. First, because mesothelioma is very rare in
10 the general population (Hillerdal, 1983), and second, because mesothelioma is almost
11 exclusively caused by exposure to asbestos, including Libby Amphibole asbestos.

12 A life-table analysis (see Appendix G for details) was used to compute the 95% lower
13 bound on the lifetime exposure to Libby Amphibole asbestos that corresponds to a 1% extra risk
14 of cancer mortality in the general U.S. population using age-specific mortality statistics and the
15 exposure-response relationships for each cancer endpoint as estimated in the studied population.
16 This lower bound on the level of exposure serves as the POD for extrapolation to lower
17 exposures and for deriving the unit risk. Details of this analysis are presented in Section 5.4.5.
18 A cancer-specific unit risk was obtained by dividing the extra risk (1%) by the POD. The
19 cancer-specific unit risk estimates for mortality from either mesothelioma or lung cancer were
20 then statistically combined to derive the final IUR (see Section 5.4.5.3). Uncertainties in this
21 cancer assessment are described in detail in Section 5.4.6.

22

23 **5.4.2. Choice of Study/Data—with Rationale and Justification**

24 This human health assessment is specific to Libby Amphibole asbestos. This current
25 assessment does not seek to evaluate quantitative exposure-response data on cancer risks from
26 studies of asbestos that did not originate in Libby, MT.

27 The available sources of data included the cohort of workers employed at the vermiculite
28 mining and milling operation in and around Libby, MT. This cohort has been the subject of
29 several epidemiologic analyses (Amandus and Wheeler, 1987; Amandus et al., 1987a, 1987b;
30 McDonald et al., 1986; Sullivan, 2007; Larson et al., 2010a; Moolgavkar et al., 2010; and
31 described in detail in Section 4.1). There have also been published reports on cases of
32 mesothelioma in the Libby, MT area (Whitehouse et al., 2008) and mortality data published by
33 the Agency for Toxic Substances and Disease Registry (ATSDR, 2000). However, published
34 mortality data on Libby, MT residents (Whitehouse et al., 2008; ATSDR, 2000) could not be
35 used in exposure-response modeling due to lack of quantitative exposure data.

1 The other available cohort of workers exposed to Libby Amphibole asbestos was from an
2 Ohio vermiculite processing plant (see Section 4.1.3) (Lockey et al., 1984; Rohs et al., 2008).
3 Pleural changes were evaluated; however, no data were available pertaining to cancer incidence
4 or mortality in the Ohio cohort. No other worker cohorts exposed to Libby Amphibole asbestos
5 with cancer incidence or mortality data were available.

6 The most appropriate available data set with quantitative exposure data for deriving
7 quantitative cancer mortality risk estimates based on Libby Amphibole asbestos exposure in
8 humans is the cohort of workers employed at the vermiculite mining and milling operation in and
9 around Libby, MT (hereafter referred to as the Libby worker cohort). These data are considered
10 the most appropriate to inform this human health assessment for several reasons: (1) these
11 workers were directly exposed to Libby Amphibole asbestos, (2) detailed work histories and
12 job-specific exposure estimates are available to reconstruct estimates of each individual's
13 occupational exposure experience, (3) the cohort is sufficiently large and has been followed for a
14 sufficiently long period of time for cancer to develop (i.e., cancer incidence) and result in
15 mortality, and (4) the broad range of exposure experiences in this cohort provided an
16 information-rich data set, which allowed evaluation of several different metrics of exposure.
17 Uncertainties in these data are discussed in Section 5.4.6.

18 19 **5.4.2.1. Description of the Libby Worker Cohort**

20 The Libby worker cohort has been extensively studied. McDonald et al. published three
21 studies on a subset of the cohort (1986, 2002, 2004). Scientists from NIOSH conducted two
22 epidemiologic investigations, resulting in several published reports on different subsets of the
23 cohort (Amandus and Wheeler, 1987; Amandus et al., 1987a, b, 1988; Sullivan, 2007). Larson et
24 al. (2010a) analyzed an ATSDR reconstruction of the Libby worker cohort from company
25 records with exposure estimates obtained from NIOSH with mortality follow-up through 2006.
26 Moolgavkar et al. (2010) reanalyzed the Sullivan (2007) data with mortality follow-up through
27 2001 using a different statistical approach.

28 According to Sullivan (2007), nearly all of these study subjects were workers at the
29 Libby, MT vermiculite mine, mill, and processing plant. Although the mine was several miles
30 from Libby, MT, some of the study subjects worked in the town (see Section 4.1.1.1). Workers
31 may have also been assigned jobs as truck drivers, or jobs working in the screening plant,
32 railroad loading dock, expansion plants, or an office. Individuals' demographic and work history
33 data were abstracted from company personnel and pay records. A database created by NIOSH in
34 the 1980s contained demographic data and work history starting from September 1935, and vital
35 status at the end of 1981 for 1,881 workers. NIOSH compared these data with company records

1 on microfilm, and work history data were reabstracted to ensure data quality. One person was
 2 removed from the cohort because company records stated that he was hired but never worked
 3 (Sullivan 2007). Nine workers with Social Security numbers listed in company records were
 4 excluded because demographic and work history data were not available, leaving 1,871 workers
 5 in the cohort available for epidemiologic analysis. Table 5-6 shows the demographic and
 6 exposure characteristics of this cohort.

7 For the purposes of this current assessment, vital status follow-up was completed by
 8 NIOSH through 2006 using the National Death Index (NDI-Plus; Bilgrad, 1995). Workers
 9 known to be alive on or after January 1, 1979 (the date NDI began tracking deaths nationwide),
 10 but not found in the NDI search, were assumed to have been alive on December 31, 2006
 11 (Sullivan, 2007). Nearly 54% of workers in the cohort ($n = 1,009$) had died by
 12 December 31, 2006. NIOSH researchers obtained death certificates from across the United
 13 States (while exposure occurred in and around Libby, deaths could have occurred elsewhere) for
 14 deaths prior to 1979 and coded to the International Classification of Diseases (ICD) revision in
 15 effect at the time of death by a single National Center for Health Statistics-trained nosologist.
 16 After 1979, ICD codes were obtained from the NDI-Plus. For workers known to be deceased,
 17 the underlying cause of death was determined from death certificates and coded to the ICD codes
 18 using the rubrics of the ICD revision in effect at the time of death (ICD-5 [WHO, 1938], ICD-6
 19 [WHO, 1948], ICD-7 [WHO, 1957], ICD-8 [WHO, 1967], ICD-9 [WHO, 1977], or ICD-10
 20 [WHO, 1992]).

21
 22
 23 **Table 5-6. Demographic and exposure characteristics of the Libby worker**
 24 **cohort**
 25

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
Mean year of birth	1929
Mean year of hire	1959
Mean age at hire (years)	30.2
Mean person-years of follow-up (no lag)	35.9
Total person-years of follow-up (no lag)	67,101
Mean employment duration (years)	3.7
Mean cumulative exposure (fiber/cc-year)	96.0
Median cumulative exposure (fiber/cc-year)	9.8

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Range of cumulative exposures (no lag) (fiber/cc-year) ^a	0–1722
---------------------------------------------------------------------	--------

^aAccording 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.

Basic demographic information on the occupational cohort members was largely complete. However, when data were missing, they were imputed by NIOSH based on the following assumptions regarding gender, race, and date of birth. Seven workers with unknown gender were assumed to be male because 96% of the workforce was male, and NIOSH 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 indicate that 90–95% of the local population identify themselves as white (Sullivan, 2007). For four workers with unknown birth dates, date of birth was estimated by subtracting the mean age at hire for the cohort from the worker’s hire date. The potential impact of this imputation procedure on the analytic results is discussed in Section 5.4.6.

5.4.2.2. Description of Cancer Endpoints

This human health assessment of Libby Amphibole asbestos focuses on two cancer endpoints: mesothelioma and lung cancer. The endpoint for both mesothelioma and lung cancer was mortality, not incidence. Incidence data are not available for the Libby worker cohort. However, there is evidence that other cancer endpoints may also be associated with exposure to asbestos. The International Agency for Research on Cancer (IARC) concluded that there was sufficient evidence in humans that other types of asbestos (chrysotile, crocidolite, amosite, tremolite, actinolite, and anthophyllite) were 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 there were no deaths from ovarian cancer among the 84 female workers. The 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).

Mesothelioma did not have a distinct ICD code prior to introduction of the 10th revision (ICD-10), which was not implemented until 1999. Therefore, for deaths in the Libby worker cohort occurring from 1979 to 1998, death certificates were obtained if the NDI identified the death as being from one of the possible mesothelioma codes identified by Marsh et al. (2001), or from respiratory cancer, nonmalignant respiratory disease, digestive cancer, or unspecified cancer. Death certificates (1940–1998) were reviewed by the NIOSH principal investigator (Sullivan, 2007) to identify any mention of mesothelioma on the death certificate, as is the

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1 standard procedure for assessing mesothelioma mortality and as has been used in other analyses
2 of Libby worker cohort mesothelioma mortality (McDonald et al., 2004; Larson et al., 2010a).
3 In total, 18 mesothelioma deaths occurring from 1979 to 2006 were identified by NIOSH using
4 these methods, which serve as the basis for this current assessment; 19 mesothelioma deaths
5 were identified by Larson et al. (2010a) for the same cohort from death certificates for all causes
6 of death rather than the more targeted set of causes identified by Marsh et al. (2001) or Sullivan
7 (2007).

8 Whitehouse et al. (2008) identified four mesothelioma cases among workers that were
9 not included in Sullivan (2007) with mortality follow-up through 2001; no other information was
10 provided. Most likely, three mesothelioma cases from these four were accounted for during the
11 update of the NIOSH cohort to 2006, which serves as the basis for this current assessment.
12 Whitehouse et al. (2008) also provided detailed information on 11 residential cases, but this
13 information could not be used in exposure-response analyses for this current assessment because
14 there is no quantitative exposure information for these cases and no information defining or
15 enumerating the population from which these cases arose.

16 Mortality records (and death certificates) may not always reflect the true cause of death
17 for various reasons (e.g., misdiagnosis, improper recording on the death certificate, or miscoding
18 of the cause of death). For mesothelioma, the undercounting of cases (underascertainment) is a
19 particular concern given the limitations of the ICD classification systems used prior to 1999
20 (detection rates varied from 12% from ICD-9 codes alone to 83% from manual inspection of
21 death certificates [Davis et al., 1992]); recent studies demonstrated that ICD-10 coding has
22 detection rates similar to the latter rate above (Pinheiro et al., 2004; Camidge et al., 2006). The
23 appropriate procedure for pre-ICD-10 codes is not to use ICD codes alone but to manually
24 inspect death certificates, as was done by Sullivan (2007). There is also evidence that the
25 detection rate of peritoneal mesothelioma is much lower than pleural mesothelioma (Selikoff and
26 Seidman, 1992). This current assessment has accounted for the impact of this
27 underascertainment on the final IUR (see Section 5.4.5.1.1).

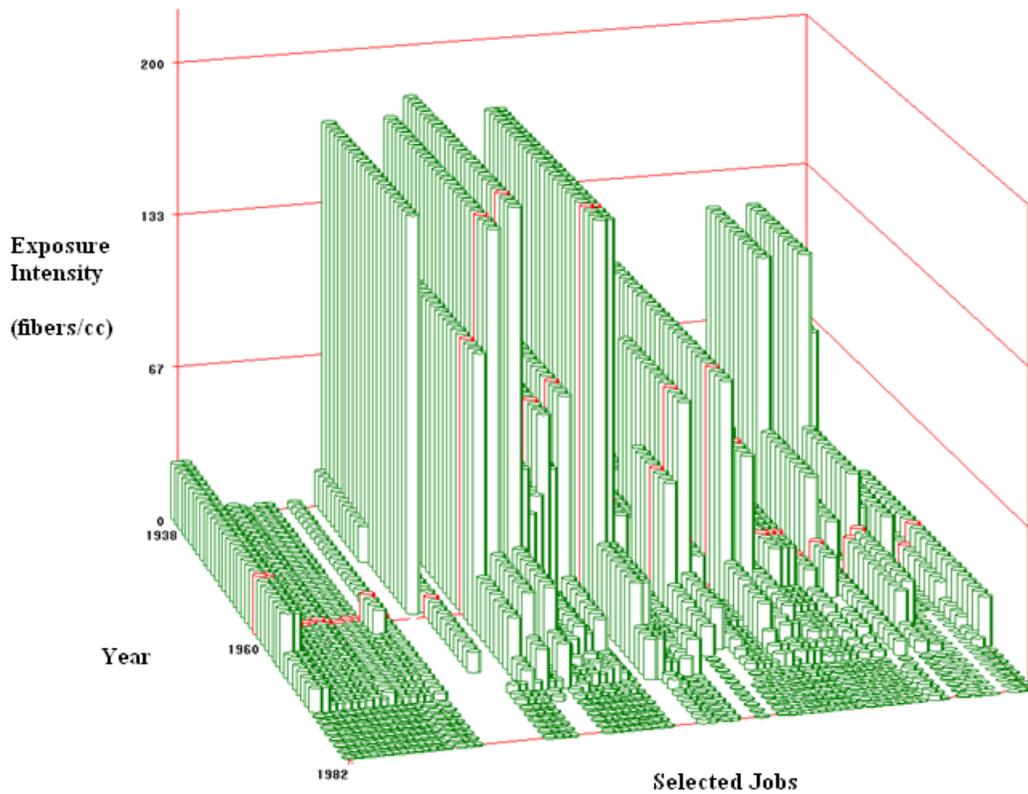
28 Lung-cancer mortality was based on the underlying cause of death identified by the ICD
29 code on death certificates according to the ICD version in use at the time of death. Based on
30 these different ICD codes, lung-cancer mortality included malignant neoplasms of the trachea,
31 bronchus, and lung, and was identified by the following codes: ICD-5 code '047' (excluding
32 '47c, Cancer of unspecified respiratory organs'), ICD-6 codes '162' or '163,' ICD-7 codes '162'
33 or '163' (excluding '162.2, Cancer of the pleura'), ICD-8 and ICD-9 code '162', and ICD-10
34 codes 'C33' or 'C34'. In all, there were 111 deaths, with an underlying cause attributed to lung
35 cancer. All deaths after 1960 were coded as bronchus or lung because the ICD versions in use as

1 that time distinguished malignant neoplasms of the trachea as distinct from bronchus and lung.
2 Other investigators of this cohort have used different definitions of lung cancer or used different
3 follow-up periods, as described in Section 4.1.1.2.2 (Description of Cohorts).
4

5 **5.4.2.3. *Description of Libby Amphibole Asbestos Exposures***

6 The mining, milling, and processing operations at the mine and in and around Libby,
7 conditions of exposure, and job-specific estimates of exposure intensity have been thoroughly
8 described in Section 4.1 (Amandus and Wheeler, 1987; Amandus et al., 1987a, b; McDonald et
9 al., 1986; Sullivan, 2007). Briefly, miners extracted vermiculite ore from an open-pit mine that
10 operated on Zonolite Mountain outside the town of Libby, MT. The ore was processed in a dry
11 mill (1935–1974) and/or two wet mills (1950–1974 and 1974–1990). The resulting concentrate
12 was transported by railroad to processing plants around the United States where the vermiculite
13 was expanded for use in loose-fill attic insulation, gardening, and other products (see
14 Section 2.1).

15 EPA adopted the JEM developed and used by Sullivan (2007) (see Figure 5-3), which was, in
16 turn, based on that used in the earlier NIOSH study for jobs through 1982 (Amandus and
17 Wheeler, 1987). As discussed in more detail in Section 4.1, Amandus et al. (1987a) defined
18 25 location operations to which they assigned exposure intensity based on available information
19 (see Table 5-7). A job category may have involved more than one location operation, and the
20 8-hour time-weighted average exposure (8-hour TWA) for each job category in the JEM was
21 calculated from the exposure intensity and time spent at each location operation (Amandus et al.,
22 1987a).
23



1

Figure 5-3. Plot of the 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.

2

3

Table 5-7. Exposure intensity (fibers/cc) for each location operation from the beginning of operations through 1982 (Amandus et al., 1987a; Table VII)

Location operation	Year									
	<50	50-59	60-63	64-67	68-70	71	72-74	75-76	77-79	80-82
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	--	--	--	--	--
Bagging plant	12.9	12.9	12.9	12.9	12.9	12.9	4.3	1.2	1.2	1.2
Tails belt	7.3	7.3	7.3	7.3	7.3	7.3	7.3	0.7	0.7	0.7

Table 5-7. Exposure intensity (fibers/cc) for each location operation from the beginning of operations through 1982 (continued)

Location operation		Year									
		<50	50-59	60-63	64-67	68-70	71	72-74	75-76	77-79	80-82
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

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1 For the later data in Table 5-7 from 1967 through 1982, over 4,000 air samples analyzed
2 for fibers by PCM analysis were available to inform the exposure intensity for the 25 location
3 operations (see Table 5-7). Therefore, the JEM for 1968–1982 is based on direct analytic
4 measurements in air for each location operation (Amandus et al., 1987a). With the exception of
5 the dry mill, no air samples were available for other location operations at the mine and
6 processing facilities prior to 1967. In order to estimate exposures that occurred before that
7 time, the NIOSH researchers interviewed plant employees and based estimates of exposure
8 intensities on known changes in operations over the years and professional judgments regarding
9 the relative intensity of exposure; exposure intensity for 23 of the pre-1967 location operations
10 was extrapolated from post-1967 measurements based on reasoned assumptions for each location
11 operation (Amandus et al., 1987a).

12 However, the amount and quality of measurement data in the facility in earlier years were
13 much more limited (Amandus et al., 1987a). A total of 40 dust samples were taken, exclusively
14 in the dry mill, over the years 1950–1964. Using these measurements, much higher exposures
15 were inferred to occur prior to 1964 than those measured in later years. Although air sampling
16 for fibers by PCM was available beginning in 1967, average fiber concentrations (dry mill)
17 differed rather widely between limited data sets from different investigators up through the early
18 1970s: 1967–1968, NIOSH data, 65 fibers/cc ($n = 14$); 1970, company data, 11 fibers/cc
19 ($n = 15$); 1971, Mine Safety and Health Administration (MSHA) data, 31 fibers/cc ($n = 52$);
20 1972, MSHA and company data, 15 fibers/cc ($n = 45$). Thus, estimated exposure levels continue
21 to be uncertain during the period when fiber concentration measurements by PCM became
22 available in 1967.

23 Air samples collected by the State of Montana were available for the dry mill
24 from 1956–1969, but these were analyzed for total dust, not asbestos fibers. Total dust samples
25 (collected by a midget impinger) were examined by light microscopy, but no distinction was
26 made between mineral dusts, debris, and asbestos fibers. All objects were counted and reported
27 in the units of million particles per cubic foot of air (mppcf). Amandus et al. (1987a) developed
28 a relationship between total dust and asbestos fiber counts based on the comparison of
29 contemporaneous air sampling in the dry mill (see Section 4.1.1.2). The conversion ratio of
30 4.0 fibers/cc per mppcf was used to estimate exposure intensity for two location operations in the
31 dry mill for the years prior to 1967.

32 The exposure intensity (fibers/cc) for each of the location operations (see Table 5-7) was
33 used to calculate an estimate of daily occupational exposure for each job category in the JEM
34 (see Figure 5-3). For each job, the time spent at each location operation and the exposure
35 intensity for each location operation were averaged to derive an estimate of the 8-hour TWA.

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1 The resulting JEM available for this current assessment and previous epidemiologic studies of
2 the Libby worker cohort is based on the air concentration of fibers as enumerated by PCM,
3 which measures fibers longer than 5 μm with an aspect ratio $>3:1$ (i.e., the fiber size regulated
4 under the OSHA standard [U.S. Department of Labor, 2006]). Additionally, only fibers that are
5 wide enough to be viewed on PCM can be detected with this method. Amandus et al. (1987a)
6 considered fibers $>0.44 \mu\text{m}$ in diameter to be visible by PCM in the historical filter analysis.
7 More recent techniques have refined the PCM method, and fibers greater than 0.25 μm in
8 diameter are now considered PCM fibers (WHO, 1980).

9 There was one important limitation of the NIOSH work history data. In the earlier study
10 (Amandus and Wheeler, 1987), workers with “common laborer” job assignments and some
11 workers with unknown job assignments hired between 1935 and 1959 were assigned the
12 relatively low exposure levels estimated for the mill yard (Sullivan, 2007). Of the 991 workers
13 hired before 1960, 811 workers had at least one job with an unknown job assignment, with
14 706 having all department and job assignments prior to 1960 listed as unknown. In the more
15 recent study by Sullivan (2007), these workers were assigned the same relatively high time
16 weighted average estimated exposure intensity (absolute majority of these workers were assigned
17 66.5 fibers/cc) for all jobs during that time period. The lack of information on specific job
18 assignments for such a large portion of these early workers when exposures were higher resulted
19 in the misclassification of the exposure and effectively yielded exposure metrics that were
20 differentiated only by the duration of each worker’s employment. Because of the lack of more
21 specific measured fiber exposure data during this early period, the EPA experienced difficulties
22 in identifying an adequate exposure-response model fit for the complete cohort. These
23 difficulties are described in detail in Section 5.4.3.5.

24 As a result, the IUR analyses were based on the subset of workers hired after 1959 (i.e.,
25 on or after January 1, 1960) and consisted of 880 workers. Of these 880 workers hired after
26 1959, 28 workers had at least one job with an unknown job assignment with 9 having all job and
27 department assignments between 1960-63 listed as unknown. These workers were assigned a
28 time-weighted average estimated exposure intensity of 66.3 fibers/cc. In addition, reabstracting
29 work histories for the more recent study (Sullivan, 2007) identified several job assignments not
30 mentioned in the earlier publications. Sullivan (2007) estimated exposure for the additional job
31 and calendar time period-specific combinations based on professional experience and review of
32 exposure records from earlier studies of the Libby worker cohort (Amandus and Wheeler, 1987;
33 Amandus et al., 1987a, b; McDonald et al., 1986). Uncertainties in the exposure assessment for
34 this sub-cohort are described in Section 5.4.6.1.2.4. While the Sullivan (2007) study was limited
35 to the white male workers, EPA’s analysis includes all workers regardless of race or gender.

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1 Table 5-8 shows the demographic and exposure characteristics of the sub-cohort hired after
 2 1959. Figure 5-3 shows a three-dimensional representation of the job-exposure matrix used by
 3 Sullivan (2007) and in this current assessment. Not all jobs were included; thus, the figure is not
 4 comprehensive but rather illustrative. The three axes show the intensity of fiber exposure as an
 5 8-hour TWA (fibers/cc, vertical axis) for selected job categories over time (horizontal axes). For
 6 several jobs, the estimated 8-hour TWA was greater than 100 fibers/cc for the decades prior to
 7 1963. Figure 5-3 shows the variability in exposures across jobs and over time. From
 8 1967–1982, all exposure measurements that inform the JEM are based on location-specific air
 9 samples analyzed for fibers by PCM. As stated above, pre-1968 exposures in the dry mill were
 10 based on the measurement of dust levels from 1956–1967 that were converted to PCM by
 11 Amandus et al. (1987a) and extrapolated backwards in time. Pre-1968 exposures for all other
 12 locations within the JEM were extrapolated from post-1967 fiber levels based on reasoned
 13 assumptions (Amandus et al., 1987a).

14
 15
 16 **Table 5-8. Demographic and exposure characteristics of the subset of the**
 17 **Libby worker sub-cohort hired after 1959**
 18

Characteristic	Sub-cohort 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
Mean year of birth	1942
Mean year of hire	1971
Mean age at hire (years)	28.6
Mean person-years of follow-up (no lag)	32.2
Total person-years of follow-up (no lag)	28,354
Mean employment duration (years)	3.3
Mean cumulative exposure (fiber/cc-year)	19.2
Median cumulative exposure (fiber /cc-year)	3.4
Range of cumulative exposures (no lag) (fiber/cc-year) ^a	0–462

19
 20 ^aAccording to the work histories and JEM, there were 21 sub-cohort workers who had zero cumulative
 21 exposure. These 21 individuals all worked at the office downtown.
 22

23
 24 Amandus et al. (1987a) recognized the uncertainty in the pre-1968 exposures assigned to
 25 the cohort. Although there is some uncertainty in the dust-to-fiber conversion, this conversion

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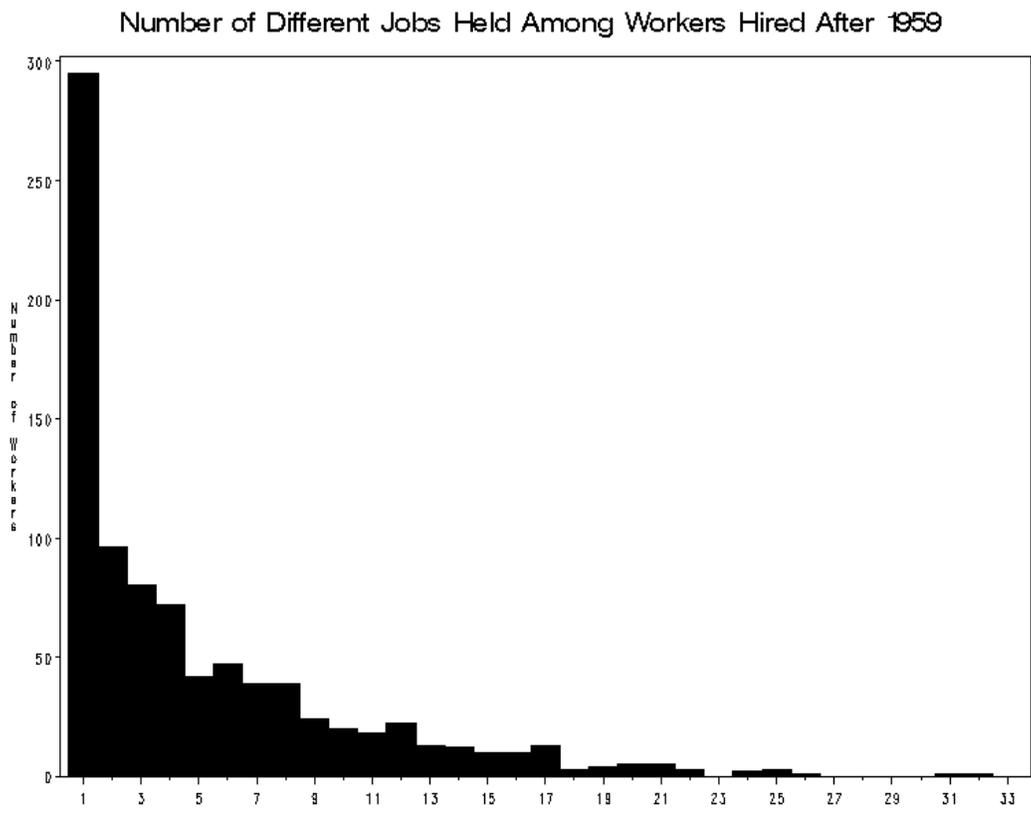
1 (4.0 fibers/cc per mppcf) was based on contemporaneously collected dust and fiber data collected
2 in the dry mill and only applied to the dry mill environment. Amandus et al. considered a range
3 of possible conversion factors (1.2–11.5 fibers/cc per mppcf). Greater uncertainty may lie with
4 the reasoned assumptions used to extrapolate exposures to the early decades for all location
5 operations considered. For example, there were four location operations for which Amandus et
6 al. estimated a range of possible exposure intensities: drilling, ore loading, the river dock, and the
7 bagging plant, where intensity of exposure may vary as much as threefold between the low and
8 high estimates (see Table 5-8). Finally, some workers were employed after 1982 through 1993
9 when demolition of the facilities was completed (Larson et al., 2010b). These exposures were
10 not evaluated by Sullivan (2007) and were not included in the NIOSH JEM. However, only
11 148 sub-cohort workers were still employed on May 31, 1982, according to the NIOSH records.
12 Because exposure concentrations in 1982 (see Table 5-7) were generally below 1 fiber/cc, with
13 only two locations having concentrations of 1.2 fibers/cc, it is unlikely that these workers’
14 exposures were significantly underestimated. Uncertainties in all aspects of JEM are described
15 in Section 5.4.6.1.2.

16

17 **5.4.2.4. Description of Libby Worker Cohort Work Histories**

18 NIOSH staff abstracted demographic data and work history data from company personnel
19 and payroll records, including W-4 federal tax forms. An individual’s work history was
20 determined from job change slips, which recorded new job assignment, date of change, and
21 change in hourly pay rate (which differed by the job assignment). Work history records span the
22 time period from September 1935 to May 1982. Dates of termination were unknown for 58 of
23 640 workers (9%), who left employment before September 1953. EPA adopted the assumption
24 used by NIOSH (Sullivan, 2007) that these people worked for 384 days, based on the mean
25 duration of employment among all workers with known termination dates before September
26 1953. The majority of workers in this cohort as a whole and among those hired on or after
27 January 1, 1960, worked at multiple jobs; many of the workers switched jobs repeatedly or had
28 the estimated exposure for a job change from one year to the next. Of the 880 workers hired in
29 1960 or afterwards in the sub-cohort, the mean number of times a worker’s exposure level
30 changed according to the JEM was 5, the median was 2, and the maximum number of changes
31 was 32 (see Figure 5-4; see also Figure 5-3 for a depiction of job-exposure intensities for
32 different jobs over time).

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Figure 5-4. Histogram showing the number of workers who experienced each incremental number of different jobs among the 880 workers hired after 1959.

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.

1
2
3 In asbestos epidemiology the usual measure of exposure is the product of the
4 concentration of asbestos dust in the air (fibers or particles per ml) and the
5 duration of exposure to each concentration summed over the entire duration of
6 exposure (years); this measure is the cumulative exposure....
7
8

9 Cumulative exposure has been the traditional method of measuring exposure in
10 epidemiologic analyses of many different occupational and environmental exposures and was the
11 exposure metric applied to the risk of lung-cancer mortality in the Integrated Risk Information
12 System (IRIS) assessment for general asbestos (U.S. EPA, 1988). Two alternative approaches to
13 developing exposure metrics to describe the effects of concentrations of asbestos dust in the air
14 on the risks of mortality have also been proposed. The first alternative was proposed by
15 Jahr (1974), who studied silica-induced pneumoconiosis and suggested that exposures to
16 occupational dusts could be weighted by the time since exposure. This yields an exposure metric
17 that gives greater weight to earlier exposures. Berry et al. (1979) subsequently suggested the
18 application of exposure metrics that allowed for the clearance of dust or fibers by using a decay
19 term on exposures. For the evaluation of mortality risk from mesothelioma, U.S. EPA (1988)
20 used a different exposure metric than was used for lung-cancer mortality, which factored in the
21 time since first exposure. As observed in U.S. EPA (1988), it is important to note that different
22 characterizations of estimated ambient exposures may be reasonably expected to be associated
23 with different endpoints.

24 Most studies of asbestos-related mortality have evaluated either cumulative exposure,
25 exposure concentration, or the duration of employment as exposure metrics. Many studies have
26 been limited in the availability of detailed exposure data—especially at the individual level. In
27 the Libby worker cohort data developed by NIOSH and used in this current assessment, detailed
28 work histories, together with job-specific exposure estimates, allowed for the reconstruction of
29 each individual’s estimated occupational exposure over time to define multiple exposure metrics.

30 From this information-rich, individual-level data set from NIOSH, EPA constructed a
31 suite of the different metrics of occupational exposure, which had been proposed in the asbestos
32 literature or used in the IRIS asbestos assessment (U.S. EPA, 1988). This suite of models was
33 defined a priori to encompass a reasonable set of proposed exposure metrics to allow sufficient
34 flexibility in model fit to these data. These exposure metrics were evaluated in
35 analytic-regression models to test which exposure metrics were the best empirical predictors of
36 observed cancer mortality, and the better fitting models were advanced for consideration as the
37 basis of the exposure-response relationship for the IUR. The types of exposure metrics evaluated

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1 were intended to allow for variations of the classic metric of cumulative exposure, allowing for
2 more or less weight to be placed on earlier or later exposures. These simulated exposure metrics
3 were derived mathematically to approximate underlying processes that are not well understood
4 (see Section 5.4.6). Thus, the fit of exposure metrics is evaluated on the basis of maximizing the
5 likelihood for the Libby worker cohort, and the estimated parameters do not necessarily have
6 biological interpretations.

7 The first exposure metric—cumulative exposure (CE)—is a simple addition of each day
8 of exposure across time (see Eq. 5-1). CE has been widely used in modeling risk of cancer in
9 occupational epidemiology and has been used for modeling lung cancer (McDonald et al., 2004,
10 Sullivan, 2007, Larson et al., 2010a; Moolgavkar et al., 2010) and mesothelioma (McDonald et
11 al., 2004) in the Libby worker cohort. When using this exposure metric in the risk model, all
12 exposures have equal weight regardless of when they occurred and lead to the same estimated
13 cancer risk whether exposure happened early or later in life.

14 EPA calculated each individual’s occupational CE to Libby Amphibole asbestos over
15 time from their date of hire until the date they ceased to be employed in the Libby operations or
16 until the date NIOSH collected the work history data, if still employed in May 1982. Workers
17 were assumed to remain at their final occupational CE level until death or the end of the
18 follow-up period on December 31, 2006. Each worker’s CE at any time point (daily increment)
19 since their date of hire was computed as the sum of their exposure intensity (fibers/cc) on each
20 specific occupational day (x_t) from day 1 through day k . Mathematically, this was defined as

$$\text{CE at time } t_k = \sum_{j=1}^k x_{t_j} \quad (\text{Eq. 5-1})$$

21
22
23
24
25 where

26 x_{t_j} = the estimated job-specific exposure intensity for the day t_j , and

27 t_k = the day on which the exposure is estimated.
28
29

30 A second exposure metric—residence time-weighted (RTW) exposure—gives additional
31 weight to early exposures. By doing so, the RTW exposure metric allows the possibility that
32 early exposures are more influential on cancer mortality predictions in the model. Unlike many
33 chemicals that are rapidly metabolized in the body and excreted, asbestos fibers are durable, and
34 some may remain in the body for years. Fibers that remain in the lung may continue to damage
35 lung cells and tissue until they are removed or cleared (see Section 3.2). Similarly, fibers that
36 translocate to the pleura may damage cells as long as they remain in this tissue. Therefore, a

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1 fiber exposure may not only damage tissue during the exposure, but fibers may remain in these
2 tissues, with cellular and tissue damage accumulating over time.

3 The RTW exposure metric in this current assessment is sometimes called the cumulative
4 burden, or the area under the curve. A type of RTW metric was proposed for modeling of
5 mesothelioma mortality by Newhouse and Berry (1976) based on a general understanding of the
6 relationship between tumor incidence rate and time to cancer (Cook et al., 1969) as well as
7 animal models of mesothelioma (Berry and Wagner, 1969). Similar types of RTW metrics were
8 applied to the insulators asbestos cohort by Peto et al. (1982), discussed by Finkelstein (1985),
9 and applied in the derivation of the IUR in the IRIS assessment for asbestos (U.S. EPA, 1988).
10 McDonald et al. (2004) and Moolgavkar et al. (2010) used RTW-type metrics for modeling
11 mesothelioma in the Libby worker cohort, and McDonald et al. (2004) applied an RTW metric
12 for modeling lung-cancer mortality in the Libby worker cohort.

13 In calculating RTW, each day's exposure is multiplied by the time since the exposure
14 occurred (see Eq. 5-2). RTW CE was calculated as a cumulative function of each time-interval's
15 CE such that earlier exposures contribute greater weight.

$$\text{RTW CE at time } t_k = \sum_{j=1}^k \sum_{i=1}^j x_{t_i} \quad (\text{Eq. 5-2})$$

16
17
18
19
20 where

21 x_{t_i} = the estimated job-specific exposure intensity for the day t_i , and

22 t_k = the day on which the exposure is estimated.

23
24
25 The CE and RTW exposure metrics result in increasing or sustained metrics of exposure
26 across time. However, it is known that some cellular and genetic damage may be repaired over
27 time, which could decrease cancer risk from exposure over time. Additionally, asbestos fibers
28 are cleared (removed) from the lung through natural processes and translocated to other tissues
29 (see Section 3.2.1.1). Therefore, when considering lung cancer, it is possible that removal of
30 asbestos fibers from the lung would reduce lung cancer risk over time. Although less is known
31 about removal of asbestos from the pleura, there may be clearance mechanisms operative in that
32 tissue as well (see Section 3.2.1.2). As noted earlier, Berry et al. (1979) proposed the use of
33 exposure metrics based on occupational exposures, which addressed the issue of clearance
34 through a mathematical decay term that modified measured ambient exposures. For

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1 mesothelioma, modeling a decay term on exposure has been proposed by Berry (1999). Based
 2 on this proposal, several recent papers applied a decay term to modeling mesothelioma mortality
 3 (Reid et al., 2009; Berry et al., 2009; Barone-Adese et al., 2008; Gasparrini et al., 2008; Clemens
 4 et al., 2007; Hodgson et al., 2005; Berry, 2004). Similarly, recent publications indicate that the
 5 relative risk of lung cancer due to asbestos exposure declines 15–20 years after the cessation of
 6 exposure to asbestos (Magnani et al., 2008; Hauptmann et al., 2002).

7 Mathematically allowing for the magnitude of earlier exposures to diminish with
 8 advancing time was considered to be a method of giving less weight in the analyses to earlier
 9 exposures compared to the previous two exposure metrics. Therefore, two additional exposure
 10 metrics were considered, where a decay rate was applied to the CE and RTW exposure metrics
 11 (see Eq. 5-3 and 5-4).

12 For each exposure metric, the application of a half-life was calculated by depreciating
 13 each time-interval's ($t_{j-1};t_j$) exposure according to a model of exponential decay with various
 14 half-lives ($T_{1/2}$) of 5, 10, 15, and 20 years. Note that the particular kinetics of Libby Amphibole
 15 asbestos fibers are not fully understood, and the relevance of these particular half-lives was
 16 determined from the statistical fit of these exposure metrics to the risk of cancer mortality, rather
 17 than the biological half-life of the fibers. For a very large half-life, decay is very slow, and these
 18 metrics would be very similar to the CE and RTW exposure metrics.

$$21 \quad \text{CE with half-life at time } t_k = \sum_{j=1}^k \left\{ x_{t_j} * \exp \left[\frac{\ln(0.5) * (t_k - t_j)}{T_{1/2}} \right] \right\} \quad (\text{Eq. 5-3})$$

22 where

23 x_{t_j} = the estimated job-specific exposure intensity for the day t_j , and
 24 t_k = the day on which the exposure is estimated.
 25
 26

$$27 \quad \text{RTW with half-life at time } t_k = \sum_{j=1}^k \sum_{i=1}^j \left\{ x_{t_i} * \exp \left[\frac{\ln(0.5) * (t_k - t_i)}{T_{1/2}} \right] \right\} \quad (\text{Eq. 5-4})$$

28
 29
 30 In addition to the exposure metrics used in the lung-cancer mortality analysis, modeling
 31 of mesothelioma mortality (see Section 5.4.3.1) included the exposure model used in the IRIS
 32 assessment for asbestos (U.S. EPA, 1988), originally proposed in Peto et al. (1982):
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$$I_m = C \cdot Q \cdot KM \quad (\text{Eq. 5-5})$$

where

- I_m = the observed deaths from mesothelioma/person-years,
- C = the average concentration of asbestos in the air,
- KM = an estimated slope describing the relationship between Libby Amphibole asbestos exposure and mesothelioma mortality, and
- Q = the function of the time since first exposure (t) and the duration of employment (d):

$$\begin{aligned} \text{For } t \leq 10, Q &= 0 \\ \text{For } 10 < t \leq d + 10, Q &= (t - 10)^3 \\ \text{For } t > d + 10, Q &= (t - 10)^3 - (t - 10 - d)^3. \end{aligned}$$

The asbestos IUR (U.S. EPA, 1988) metric (see Eq. 5-5) was originally fit to aggregate cohort data and was based on a function of average cohort exposure, time since first exposure, and duration of employment. The analysis here of individual data for Libby Amphibole asbestos is, therefore, a different application of this exposure metric, and its fit to the mesothelioma mortality of the Libby worker cohort is evaluated in this current assessment.

In addition to the use of these methods of describing exposure metrics representing estimated ambient exposure to Libby Amphibole asbestos dust 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 ultimately resulting 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 as an expression of a lag time between exposure and mortality. 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

1 calculation of the exposure metric. Cohort members who died or were lost within the initial
2 years of follow-up were assigned lagged exposure values of zero if they had not been followed
3 for longer than the lag time. The various exposure metrics were lagged at 10, 15, and 20 years to
4 account for different potential cancer latencies within the limitations of the available data.
5 Metrics without a lag were fit for comparison purposes but were not considered to be
6 biologically reasonable, given that the outcome under analysis is cancer mortality (specifically,
7 mesothelioma and lung cancer), for which latency periods of 10 years or more have been
8 established for asbestos (U.S. EPA, 1988). Consequently, metrics that were not adjusted by
9 lagging exposure in the final years before mortality (or the end of follow-up) were not
10 considered further in the development of an IUR for Libby Amphibole asbestos.

11 12 **5.4.3. Exposure-Response Modeling**

13 Sufficient biological information to select models for the epidemiology data on the basis
14 of biological mechanism (see Section 3) is not available. In this situation, EPA's practice is to
15 investigate a range of model forms to determine how to best empirically model the
16 exposure-response relationship in the range of the observed data. For Libby Amphibole
17 asbestos, possible exposure metrics were explored for model fit to the chosen models. The
18 exposure metric options were selected to provide a range of shapes that was sufficiently flexible
19 to allow for a variety of ways that time and duration might relate to cancer risk in the data being
20 modeled. EPA then evaluated how well the models and exposure metric combinations fit the
21 data being modeled. Metrics that did not fit the data well were rejected. For purposes of
22 calculating a reasonable upper bound on the risk per exposure, two different types of uncertainty
23 were accounted for. The first uncertainty is in the estimated slope for each exposure metric, and
24 this was accounted for by using the upper bound estimated using the statistical variance of the
25 estimated slope. EPA accounted for the second uncertainty that stemmed from the choice of
26 exposure metrics among the set that fit the data by using the exposure metric (among those few
27 with a reasonable fit) that estimated the highest risk (because formal estimation of an upper
28 bound was not possible). This is explained in more detail below and in Section 5.4.5.

29 The risk estimates are based on epidemiological analysis of the primary NIOSH data
30 (Libby worker cohort). The rationale for selection of the Libby worker cohort is presented in the
31 previous section (see Section 5.4.2). Analysis of this primary epidemiologic database allows the
32 comparison of multiple metrics of exposure to quantify the exposure-response relationship. This
33 approach is intended to support the empirical representation of the exposure-response
34 relationship of estimated ambient occupational exposure to Libby Amphibole asbestos with
35 observed cancer mortality risk. The exposure-response modeling may be influenced by

1 uncertainties in the magnitude and time course of the exposure estimates and, therefore, may not
2 necessarily reflect the biologic disposition of inhaled fibers (see Section 5.4.6).

3 The following sections provide information about modeling of the full cohort first, the
4 difficulties in identifying adequately fitting models to these data, and the decision to base the
5 analysis on a sub-cohort of workers that did allow for identifying adequately fitting models.
6

7 **5.4.3.1. Modeling of Mesothelioma Exposure Response in the Libby Worker Cohort**

8 The background incidence of mesothelioma is extremely rare (Hillerdal, 1983). Since
9 there is a very low background risk, the exposure-response model applied here examines the
10 relationship of the absolute risk of mesothelioma mortality that is attributable to Libby
11 Amphibole asbestos exposure because there is not a true background risk of mesothelioma
12 mortality among people who were truly unexposed to Libby Amphibole asbestos (as opposed to
13 the relative risk model, which is used for lung-cancer mortality; see Section 5.4.3.3). Poisson
14 regression models are employed here for estimating the absolute risk of mesothelioma, as the
15 Poisson distribution is an appropriate model for use with data that are counts of a relatively rare
16 outcome, such as observed mesothelioma deaths in the Libby worker cohort. Other analyses of
17 mesothelioma mortality in the Libby worker cohort have also used the Poisson regression model
18 (McDonald et al., 2004; Moolgavkar et al., 2010). In the Poisson regression model, probability
19 of k events is specified as
20
21

$$22 \quad P(k) = \frac{\lambda^k e^{-\lambda}}{k!} \quad (\text{Eq. 5-6})$$

23
24
25 where λ is parameterized with the exposure metric (defined in Section 5.4.2.5). Then, life-table
26 analysis is used to estimate risks in the general U.S. population for the derivation of the unit risk
27 of mesothelioma mortality (see Section 5.4.5.1).

28 Estimation of the exposure-response relationship for mesothelioma mortality using the
29 Poisson regression model was performed using a Monte Carlo Markov Chain (MCMC) Bayesian
30 approach with an uninformative or diffuse prior (WinBUGS Version 1.4 [Spiegelhalter et al.,
31 2003]). Use of diffuse priors is a standard procedure in Bayesian analysis, in situations like this
32 one, when there is no prior knowledge about the toxicity of Libby Amphibole asbestos under a
33 particular model. Since this analysis focuses only on the Libby worker cohort and does not try to
34 factor in data from other sources in estimating potency, use of a diffuse prior is considered
35 appropriate for this analysis.

1 The benefit of using the WinBUGS software is its computational ease and that it provides
2 a posterior distribution of β (the mesothelioma slope factor) rather than just a point estimate. A
3 diffuse (high variance) Gaussian distribution, truncated to exclude negative parameter values, is
4 used as a diffuse prior. With such a prior, results of MCMC analysis are expected to be similar
5 to maximum likelihood estimation in a non-Bayesian analysis. Standard practices of MCMC
6 analysis were followed for verifying convergence and sensitivity to the choice of initial values.
7 The posterior distribution is based on three chains with a burn-in of 10,000 (i.e., the first
8 10,000 simulations are dropped so that remaining samples are drawn from a distribution close
9 enough to the true stationary distribution to be usable for estimation and inference) and thinning
10 rate of 10 (i.e., only each 10th simulation is used - thus reducing autocorrelation) such that
11 3,000 total simulations constitute the posterior distribution of β . The mean of the posterior
12 distribution served as a central estimate, and the 90% credible interval¹⁷ defined the 5th percentile
13 and the 95th percentile of the distribution, which served as bounds for the 95th lower and upper
14 one-sided confidence intervals, respectively.

15 Multiple metrics of exposure (see Section 5.4.2.5) as well as exposure intensity, duration
16 of employment, age at death or loss to follow-up, and time since first exposure were compared
17 using the Deviance Information Criterion (DIC). The DIC (Spiegelhalter et al., 2002) is used in
18 Bayesian analysis and is an analogue of the AIC, with smaller values indicating a better
19 statistical fit to the data. Use of the DIC and AIC is standard practice in comparing the fit of
20 nonnested models to the same data set with the same dependent outcome variable but different
21 independent covariates. According to Burnham and Anderson (2002), “These methods allow the
22 data-based selection of a “best” fitting model and a ranking and weighting of the remaining
23 models in a predefined set.” Because of the small number of deaths from mesotheliomas in
24 absolute terms, only uni- and bi-variate models (with age or time since first exposure as the
25 second covariate) were considered. Sex and race were not used as covariates since all
26 mesotheliomas were observed in men assumed to be white (Sullivan, 2007). Each exposure
27 metric was lagged by 0, 10, 15, or 20 years. The use of a lag period aims to account for the
28 latency period between the onset of mesothelioma (which occurs some time before clinical
29 diagnosis) and mesothelioma mortality.

30

31 **5.4.3.2. Mesothelioma Mortality Analysis in the Libby Worker Cohort**

32 For the full Libby worker cohort ($n = 1,871$), the duration of employment provided a
33 considerably better univariate model fit than the other possible exposure metrics, indicating that
34 this exposure metric was the best single predictor of mesothelioma mortality in the full Libby

¹⁷ A credible interval is the Bayesian analogue of a confidence interval.

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1 worker cohort. The bivariate model, which included duration of employment and age at death or
2 censoring, provided the overall best fit (DIC = 196). The inclusion of information on the
3 concentration of exposure beyond the duration of employment resulted in a degradation in model
4 fit (see Table 5-9). The metric used in the IUR for asbestos (U.S. EPA, 1988) (see Eq. 5-5) had a
5 much higher DIC of 233.7 in the analysis here. It is likely that the poorer fit seen when using
6 information on exposure concentration is the result of the fact that duration of employment is
7 measured with comparatively little error, while derivation of specific exposure concentrations
8 may be subject to a sizable measurement error. Moreover, as described in Section 5.4.2.3, for
9 706 of 991 (71%) workers hired from 1935 to 1959, only the duration of employment was
10 known, but not the job category or department code, and, thus, the same time-weighted average
11 estimated exposure intensity for that time period had been assigned to 653 of these workers¹⁸
12 (Sullivan, 2007). It is likely that because of the potential for particularly large exposure
13 measurement error among more than two thirds of the workers hired prior to 1960 who were
14 assigned the same exposure intensity, this resulted in the duration of employment being the best
15 predictor of mesothelioma mortality. Additionally, estimates of exposure intensity prior to 1968
16 have greater uncertainty associated with them than more recent exposure measurements, which
17 are based on fiber counts in air samples analyzed by PCM. For the majority of job locations
18 (23 of 25), no exposure measurements were available prior to 1968, and exposures were
19 estimated based on employee interviews (in 1982) and what was known about major changes in
20 operations between 1935 and 1967. For two exposure locations, the dust-to-fiber conversion
21 ratio is based on measurements taken in the late 1960s, so extrapolations from the mid-1960s to
22 the early 1960s is likely to be more certain than extrapolation further back in time. The fact that
23 the metric using only duration of employment fit best and the additional incorporation of
24 exposure intensity information worsened the fit indicates that it is unlikely that IUR estimates
25 can be developed using the full cohort data because exposure values were not predictive of
26 mesothelioma mortality.

27

¹⁸ Note that Sullivan (2007) analyzed the population of 1,672 white male workers rather than all 1,871 workers so the numbers of workers with missing job category and department information were different.

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Table 5-9. Comparison of univariate model fit of various exposure metrics for mesothelioma mortality in the full Libby worker cohort ($n = 1,871$)^{a,b}

Variable	DIC
Duration of employment	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 ½ life	210.4
CE lagged 10 yr with 20-yr ½ life	210.6
RTW with 5-yr ½ life	210.7
RTW with 10-yr ½ life	211.0
CE	211.4
Time since first exposure	211.4

^aSince one of the mesothelioma deaths occurred less than 20 years 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 years.

^bLower DIC values represent better fits. Models with DIC within 10 units of the DIC of the model with the lowest DIC are shown.

DIC = Deviance Information Criterion.

The DIC values for models that included lag and/or half-life adjustments to the exposure metrics were not penalized in the regression analyses for including these extra parameters because those factors were not represented as covariates but rather were embedded in the exposure metrics. While these results were obtained using each instance with lag and/or half-life as a separate model fit, it may be appropriate to penalize the DIC values from these results for inclusion of these parameters. Note that if the DIC values from the lag and/or half-life models were penalized, this would serve to improve the relative fit of the model using only duration as a parameter in comparison with the lag and/or half-life models because the DICs for the penalized models would increase while the DIC for the unpenalized models would be unchanged.

5.4.3.3. Modeling of Lung Cancer Exposure Response in the Libby Worker Cohort

To develop an exposure-response relationship for lung cancer, the lung-cancer mortality data were modeled as a function of the historical exposure data for the Libby worker cohort. The mesothelioma mortality data were modeled to estimate the absolute risk because it is very rare in the general population (Hillerdal, 1983). Lung-cancer mortality does have a known background risk, and, thus, modeling of lung-cancer mortality is based on the relative risk rather than the absolute risk. As such, there are different analytic methods available that can use information on

1 time-varying exposures. The NIOSH-developed individual-level exposure data for the Libby
2 worker cohort are very detailed, with start and stop dates for each of the workers' jobs and
3 estimated fiber exposures for 25 specific location-operations (Amandus et al., 1987). It is,
4 therefore, important to find a model that makes efficient and effective use of these
5 time-dependent data.

6 The Cox proportional hazards model (Cox, 1972) is one of the most commonly used
7 statistical models for the epidemiologic analysis of survival and mortality in cohort studies with
8 extensive follow-up (Larson et al., 2010a; Moolgavkar et al., 2010). In the Cox proportional
9 hazards model, the conditional hazard function, given the covariate Z , is assumed to have the
10 form

$$\lambda(t | Z) = \lambda_0(t) \exp(\beta^T Z) \quad (\text{Eq. 5-7})$$

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16 where β is the vector of regression coefficients, $\lambda_0(t)$ denotes the baseline hazard function, and T
17 denotes transposition of the vector. One of the strengths of this model is that knowledge of the
18 baseline risk function is not necessary, and no particular shape is assumed for the baseline
19 hazard; rather, it is estimated nonparametrically. The contributions of covariates to the hazard
20 are multiplicative. When Z represents exposure and $\beta^T Z$ is small, the Cox proportional hazards
21 model is consistent with linearity of dose response for low doses.

22 When the proportional hazards assumption holds, it is possible to estimate the hazard
23 ratio of exposure (relative risk) without estimating the hazard function in the unexposed (or in
24 the lowest exposures seen within the study group) since this baseline hazard function drops out
25 of the calculations. The Cox proportional hazards model assumes that a function of covariates
26 (i.e., exposures) result in risks that are a constant multiple of the baseline hazard in unexposed
27 individuals over some timescale, typically calendar time or age. This proportionality is assumed
28 to be constant across the range of observed exposures, given the set of modeled covariates, and
29 can be evaluated across time.

30 The Cox proportional hazards model was chosen to represent the lung-cancer mortality
31 data for several reasons. Of primary importance is that it takes statistical advantage of the
32 extensive exposure data collected for the cohort on time-varying exposures to Libby Amphibole
33 asbestos. There are no other standard model formulations that allow for the analysis of
34 time-varying exposures in the manner achieved by the Cox proportional hazards model. The
35 exposure-response relationship (proportional hazards ratio) determined in this model intrinsically
36 takes into account the effects of other causes of mortality that are unrelated to exposure (i.e.,

1 independent censoring). Further, all comparisons are made within the cohort by comparing the
2 mortality experience of people with different exposures within the same cohort population. The
3 issue of competing risks that are dependent on exposure (e.g., asbestosis or nonmalignant
4 respiratory disease) is an acknowledged uncertainty for this type of analysis (see Section 5.4.6).

5 Other methods common to occupational epidemiology, such as the use of standardized
6 mortality ratios typically rely upon comparisons of the mortality experience in an exposed
7 population group compared to that in the general population. However, the comparison
8 population may not always be appropriate due to differences in general health status (e.g., the
9 healthy worker effect) and differences in exposure to other risk factors for a specific disease
10 (e.g., smoking history). The lack of comparability between the study population and the
11 comparison population can lead to confounding by other measured or unmeasured
12 characteristics, which may be statistically associated with both the exposure of interest and the
13 endpoint. The Cox proportional hazards model controls for such potentially confounding
14 characteristics by using a comparison group from within the study population (i.e., internal
15 controls). Internal controls are a statistically appropriate comparison group because they are
16 expected to be more similar in potentially confounding characteristics to the remainder of the
17 cohort, thereby controlling for both measured and unmeasured confounding and helping ensure
18 that comparisons are more statistically valid.

19 20 **5.4.3.4. Lung-Cancer Mortality Analysis in the Libby Worker Cohort**

21 As described in the previous section, quantitative exposure-response relationships for
22 lung-cancer mortality were evaluated using the Cox proportional hazards model. Cox
23 proportional hazards models of this type require the specification of a timescale. Age is typically
24 the time-related variable with the strongest relationship to cancer mortality and was used as the
25 timescale in these analyses. Use of age as the timescale in a time-varying Cox proportional
26 hazards model controls for age as a risk factor by design rather than by parametric modeling and
27 effectively rules out age as a potential confounder. Individual covariates available to EPA in the
28 complete analytic data set compiled from the NIOSH data were evaluated for their ability to
29 explain the lung-cancer mortality. These included sex, race, birth year, age at hire, and various
30 exposure-related variables including TWA workplace intensity of exposure in fibers/cc, job type,
31 and the start and stop date of each different job. These data allowed for the computation of
32 cumulative exposure, cumulative exposure with application of a half-life, and RTW cumulative
33 exposure, with and without application of a half-life (see Section 5.4.2.5). Each exposure metric
34 was also lagged by 0, 10, 15, or 20 years. The use of a lag period aims to account for the latency

1 period between the onset of lung cancer (which occurs some time before clinical diagnosis) and
2 lung-cancer mortality.

3 All lung-cancer mortality analyses were conducted using SAS software version 9.1 (SAS,
4 Cary, NC). EPA fit the extended Cox proportional hazards model (Kleinbaum, 1996; Tableman
5 and Kim, 2004), which included both time-independent factors such as sex, race, and date of
6 birth, as well as time-dependent measures of Libby Amphibole asbestos exposure over the entire
7 time course of each individuals' lifetime from their date of hire until death or loss to follow-up.
8 This method allows for control of potential confounding by age by design rather than through
9 multivariate covariate modeling. The inclusion of date of birth in these analyses controls for any
10 potential birth cohort effect.

11 EPA's analyses of time-dependent exposure data included goodness-of-fit testing of the
12 proportionality assumption for the Libby worker cohort. Because Cox proportional hazard
13 models rely on the assumption that the hazard rate among the exposed is proportional to the
14 hazard rate among the unexposed, it is important to evaluate the model against this assumption.
15 Therefore, analyses of extended Cox proportional hazards models tested this assumption using a
16 Wald test on the model interaction term between the Libby Amphibole asbestos exposure metric
17 and the timescale (i.e., age). As a general rule, a nonzero slope that is either increasing or
18 decreasing indicates a violation of the proportional hazards assumption. Wald tests for the
19 complete cohort consistently showed that the interaction term was a statistically significant
20 predictor of lung-cancer mortality ($p < 0.05$) and was interpreted as evidence that the hazards did
21 not remain proportional over time. The cause of the lack of proportionality is unknown, but
22 several likely explanations are discussed in Section 5.4.3.5 below and in the discussion of
23 uncertainties in Section 5.4.6.1.

24 25 **5.4.3.5. Summary of Mesothelioma and Lung Cancer Analysis of Libby Worker Cohort**

26 Several possible explanations exist for the finding that duration of employment was the
27 best fitting exposure metric for mesothelioma mortality, as well as the finding of the lack of
28 proportionality of hazards in the lung-cancer mortality modeling.

- 29
30
31 1) Duration of employment, but neither department code nor job category, was known for
32 706 of 991 (71%) workers hired from 1935 to 1959. Without knowledge of the job
33 category, the same exposure concentration had been assigned to almost all of these
34 workers, likely resulting in a particularly large measurement error for exposure in
35 approximately one third of the total cohort of 1,871 workers. This is a very likely
36 explanation for the superior fit for duration of employment in modeling of mesothelioma

1 mortality relative to the other exposure metrics based on measured exposures. Assigning
2 the same exposure concentration to so many of the workers hired before 1960, regardless
3 of job, likely resulted in significant exposure misclassification. Random error in
4 exposure measurements generally attenuates the strength of epidemiologic associations
5 between exposure and observed effect, weakening the predictive ability of any of the
6 exposure-based metrics compared to duration of employment, which was more accurately
7 determined for all workers in the cohort.

8 2) Even where the job category was identified, few exposure data exist prior to 1968. For
9 the majority of job locations (23 of 25), no exposure measurements were available prior
10 to 1967, and so exposures were estimated based on employee interviews (conducted in
11 1982) to determine what was known about major changes in operations between 1935
12 and 1967. For two job locations, dust-to-PCM extrapolations are based on measurements
13 taken in the late 1960s, so extrapolating from the mid-1960s to the early 1960s is likely to
14 be more certain than extrapolating further back in time. Random error in these exposure
15 measurements would also generally attenuate the strength of association between
16 exposure and observed effect during the earlier years of mine operation and, thus, a
17 greater degree of measurement error in the earlier years could have resulted in the lack in
18 proportionality of the hazard ratios for lung cancer over time. A greater degree of
19 measurement error in the earlier years could also provide an explanation for the worse fit
20 of the mesothelioma models that incorporated these exposure measures.

21 3) Another explanation for the lack of proportional hazards in modeling lung-cancer
22 mortality may be that this cohort has an anomalous age structure due to the hiring of
23 much older individuals during the time of the Second World War. Among those workers
24 in the cohort hired prior to 1960, 9% were older than 50 years at the time of hire, and
25 22% were older than 40 years. Among those workers hired in 1960 or afterwards, only
26 4% were older than 50 years, and 14% were older than 40 years. Older workers differ
27 from younger workers in several potentially important ways that could alter their
28 response to exposures. Older workers were born in a different era, with different
29 nutritional and public health standards which may influence mortality patterns.

30 4) The lack of proportional hazards in modeling lung-cancer mortality may also be a
31 reflection of confounding or effect modification, which can change in magnitude over
32 time. The most likely candidate for confounding or effect modification is smoking.
33 NIOSH records show that of the 1,871 workers in the full Libby workers cohort,
34 1,121 workers (60%) were missing smoking status data, while 750 (40%) had data with
35 values “S” (Smoker), “Q” (Former Smoker), or “N” (Nonsmoker). Given this high
36 percentage of missing values, EPA did not consider these smoking data to be adequate
37 for use in the evaluation of confounding or effect modification.

38 Smoking rates, over time, among the sub-cohort of workers hired after 1959 are likely to
39 have been more similar since smoking rates change more slowly over shorter periods of
40 time than over longer ones. This restriction in time period of hiring would also result in
41 less variation by birth year cohort, which is strongly related to smoking patterns as people
42 of different generations developed different smoking rates. Thus, this restriction in the

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1 time period of hiring may make the cohort members more similar to each other, thereby
2 reducing the potential impact of any smoking-related confounding. Further discussion of
3 the relevance of smoking can be found in the section on uncertainties (see Section 5.4.6).
4

5
6 When the assumption of proportionality is not met, the potential influence of
7 confounding factors in the full-cohort analysis is of concern. Additionally, the lack of job
8 category information for 69% of the workers hired prior to 1960 and greater measurement error
9 in early exposures may result in significant random exposure measurement error, which may bias
10 the observed exposure-response relationships towards the null.

11 Although duration of employment was the best exposure metric for modeling
12 mesothelioma mortality in the full cohort, it made quantitatively estimating an exposure-response
13 relationship difficult. In addition, violation of the underlying statistical assumptions adversely
14 impacted modeling of lung-cancer mortality in the full cohort. Therefore, EPA chose to
15 undertake a sub-cohort analysis.

16 In particular, because uncertainty in retrospective assessment of workplace exposures is
17 reduced in the later years, EPA decided to analyze a sub-cohort of all the workers with as late a
18 starting employment date as possible, while still maintaining a sufficient number of lung cancer
19 and, especially, mesothelioma mortalities. Nearly all of the workers with completely missing
20 data on job category or department code and only duration of employment available were hired
21 before 1960, and so EPA developed a sub-cohort analysis by dividing the total cohort into those
22 hired prior to 1960 ($n = 991$) and those hired after 12/31/1959 ($n = 880$). This cut point roughly
23 divided the cohort in half. For the sub-cohort of those workers hired after 1959, there were
24 sufficient numbers of both mesothelioma and lung cancer mortalities to apply the Poisson and
25 Cox proportional hazards model, correspondingly. EPA initially examined the fit of these
26 models using several exposure metrics to predict mortality from mesothelioma and found that in
27 this sub-cohort, the exposure metrics that included information on exposure concentration
28 provided superior statistical fits to the exposure metrics based only on employment duration. In
29 this same sub-cohort, the assumptions of the Cox proportional hazards model were also satisfied
30 for the modeling of time-varying exposure.

31 While it is generally true that the use of more data is an advantage in statistical analyses
32 because it allows for the computation of more statistically precise effect estimates, this advantage
33 could not be utilized, because of the difficulty in deriving risks from the full cohort analysis (see
34 also Section 5.4.6 on uncertainties remaining in the sub-cohort).
35

1 **5.4.3.6. Analysis of Sub-Cohort of Employees Hired After 1959**

2 The reasons stated in Section 5.4.2 for choice of Libby worker cohort data are still valid
3 for the sub-cohort. In particular, (1) these workers were directly exposed to Libby Amphibole
4 asbestos, (2) detailed work histories and job-specific exposure estimates are available to
5 reconstruct estimates of each individual’s occupational exposure experience with only 9 workers
6 completely missing job and department codes during the period when relatively high average
7 time-weighted estimated exposure intensity was assigned, (3) the sub-cohort is still sufficiently
8 large and has been followed for a sufficiently long period of time for cancer to develop (i.e.,
9 cancer incidence) and result in mortality, and (4) the broad range of exposure experiences in the
10 sub-cohort provided an information-rich data set.

11
12 **5.4.3.6.1. Results of analysis of mesothelioma mortality in the sub-cohort**

13 Of the 880 workers hired after 1959, 230 (26%) had died by December 31, 2006. The
14 number of mesothelioma deaths in the sub-cohort is 7 (2 deaths coded in ICD-10 and 5 deaths
15 coded in ICD-9), and the mesothelioma death rate of 24.7 per 100,000 person-years for the
16 sub-cohort is similar to the mesothelioma death rate of 26.8 per 100,000 person-years for the full
17 cohort (18 mesothelioma deaths), with a difference of less than 10%.

18 Table 5-10 shows the relative fit of various exposure metrics for mesothelioma mortality
19 in the sub-cohort hired after 1959, including only those exposure metrics whose information
20 weight was greater than 0.01. Information weights are computed from the DICs (Burnham and
21 Anderson, 2002). As discussed below, metrics with higher DICs and lower information weights
22 are unlikely to provide a good fit and are, thus, not included in Table 5-10. Information weights
23 are commonly used in Bayesian analyses. Information weights can be computed by first
24 assessing the differences between the best DIC and each of the others (ΔDIC_i).

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27
$$DIC w_i = \exp\left(-\frac{1}{2} \Delta DIC_i\right) / \sum_{r=1}^R \exp\left(-\frac{1}{2} \Delta DIC_i\right) \quad (\text{Eq. 5-8})$$

Table 5-10. Comparison of model fit of exposure metrics for mesothelioma mortality in the sub-cohort hired after 1959^{a,b}. Only the model fits with information weights greater than 0.010 are shown

Exposure metric	Lag(yr)	DIC	Information Weight
CE with 5-year ½ life	15	70.6	0.428
CE with 5-year ½ life	10	72.8	0.143
CE with 10-year ½ life	10	73.9	0.082
CE with 10-year ½ life	15	74.0	0.078
CE with 10-year ½ life	0	74.5	0.061
CE with 5-year ½ life	0	75.0	0.047
CE with 15-year ½ life	10	75.7	0.033
CE with 15-year ½ life	0	76.0	0.029
CE with 15-year ½ life	15	76.1	0.028
CE with 20-year ½ life	10	76.7	0.020
CE with 20-year ½ life	0	77.0	0.017
CE with 20-year ½ life	15	77.2	0.016

^aLower DIC values represent better fits.

^bSince one of mesothelioma deaths occurred in less than 20 years 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.

DIC = Deviance Information Criterion.

The other exposure metrics that were fit included those metrics used in the full cohort analysis (duration of employment, time since first exposure, age at death or censoring, RTW metrics, CE with lag metrics, and IRIS IUR [1988] metric), but all of them fit worse than any of the metrics in Table 5-10, irrespective of possible penalization for extra parameters as discussed in the analysis of the full cohort. 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 5-10). 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 5-10 contain a decay term and have the same number of parameters in their corresponding model, allowing for a direct comparison of the DIC values (DICs are similar to AICs in what is considered an important difference) and information weights. It is important to note that the suite of exposure metrics that were applied in this current assessment to modeling mesothelioma mortality encompass the range of choices described in the asbestos literature including CE, RTW, and decay metrics as well as the IRIS IUR (1988) metric.

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1 In the sub-cohort hired after 1959, the DIC value for mesothelioma using the IRIS IUR
 2 (1988) metric (see Eq. 5-5) is substantially higher (DIC = 98.4) than for any of the metrics in
 3 Table 5-10. This indicates that the IRIS IUR (1988) metric does not provide as good a fit for the
 4 Libby Amphibole asbestos worker cohort, using the estimated historical exposure levels, as the
 5 other metrics in Table 5-10. Setting the exponents in the IRIS IUR (1988) metric to the values
 6 of 2 and 4, as suggested by Nicholson et al. (1980), did not improve the fit of the metric to the
 7 Libby Amphibole asbestos worker cohort data (results not shown). A substantial difference of
 8 this analysis from the IRIS IUR (1988) modeling is that this analysis is based on individual-level
 9 data, whereas the IRIS IUR (1988) application was to aggregate data. Also, cohorts used in the
 10 IRIS IUR (1988) did not include cohorts exposed to Libby Amphibole asbestos. Alternately, the
 11 relative fit of this model may have been affected by uncertainties in the estimated exposure
 12 described in detail in Section 5.4.6.

13 Next, EPA considered which covariates should be added to the model with the exposure
 14 metric that provided the best fit. The addition of covariates "age at death or censoring" and
 15 "time since first exposure" did not improve the fit, as measured by DIC (results not shown).

16 As described in Section 5.4.2.5, only metrics with nonzero lag were retained for
 17 derivation of unit risks. Table 5-11 shows slopes and credible intervals for all retained metrics
 18 from Table 5-10. The units of the slopes are fiber/cc-year. These slopes and credible intervals
 19 represent calendar year continuous environmental exposure as described above and define the
 20 "Exposed Hazard Rate" in the life-table procedure when multiplied by the exposure level (see
 21 Appendix G for details).

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Table 5-11. Mesothelioma mortality exposure metrics fits, slopes, and credible intervals

Exposure metric	Lag years	DIC	Slope $\times 10^{-5}$	90% CI for slope $\times 10^{-5}$
CE – 5-yr ½ life	15	70.6	20.6	(10.2, 34.3)
CE – 5-yr ½ life	10	72.8	31.1	(15.2, 50.8)
CE – 10-yr ½ life	10	73.9	9.93	(5.00, 16.3)
CE – 10-yr ½ life	15	74.0	7.78	(3.72, 12.9)
CE – 15-yr ½ life	10	75.7	6.17	(3.04, 10.1)
CE – 15-yr ½ life	15	76.1	5.30	(2.63, 8.69)
CE – 20-yr ½ life	10	76.7	4.71	(2.34, 7.71)
CE – 20-yr ½ life	15	77.2	4.27	(2.12, 6.98)

26
27 CI = credible interval.

28
29

1 Based on the results from the exposure metric with the lowest DIC (cumulative exposure
2 with a 5-year half life for decay and a 15-year lag for cancer mortality latency), the slope was
3 2.06×10^{-4} per fiber/cc-year based on a 365-day calendar year, and the 95% upper bound on the
4 slope was 3.43×10^{-4} per fiber /cc-year. This point estimate and 95% upper bound represent the
5 relative risk (including statistical uncertainty within the exposure metric) of mesothelioma
6 mortality observed from exposure to Libby Amphibole asbestos fibers in the worker cohort for
7 this exposure metric. Issues related to uncertainty in the choice of exposure metric are described
8 further in the section on the derivation of the combined IUR of mesothelioma and lung cancer
9 (see Section 5.4.5.3).

10 11 **5.4.3.6.2. Results of the analysis of the lung-cancer mortality in the sub-cohort**

12 EPA based its final analyses for lung-cancer mortality on the subset of workers hired
13 after 1959. Thus, this analysis is based on 32 deaths from lung cancer¹⁹ (ICD-8: two deaths with
14 the code 162.1; ICD-9: one death with the code 162.2, 20 deaths with the code 162.9; ICD-10:
15 nine deaths with the code C349) out of 230 deaths that occurred in the sub-cohort of 880
16 workers.

17 All multivariate Cox proportional hazards models with time-varying exposures were
18 initially fit, using one exposure metric at a time, to the sub-cohort hired after 1959 with
19 covariates for sex, race, and date of birth. Lung-cancer mortality was modeled using CE and
20 RTW exposure, where each metric was potentially modified by four different half-lives (5, 10,
21 15, or 20 years). Each of these exposure metrics was also evaluated with four different lag
22 periods to allow for cancer latencies of 0, 10, 15, or 20 years. The lag period is defined as
23 immediately prior to observed cancer death, where exposure is not considered to be causally
24 related to mortality. In all, 40 exposure response multivariate models were evaluated for the
25 adequacy of the exposure metric to fit the epidemiologic data. Each exposure metric and the
26 comparative model fit statistics are presented in Table 5-12.

27 The assumptions of the Cox proportional hazards model were reevaluated for the
28 sub-cohort. Restricting the cohort addressed each of the previously listed potential explanations
29 for the lack of hazard proportionality (see Section 5.4.3.3). First, measurement error for
30 exposures is likely to have been smaller after 1959 for several reasons. One reason is that the
31 706 workers for whom job category and department code information was missing during all of

¹⁹ Note that in the full cohort, it was unclear whether there were cases of tracheal cancer 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 sub-cohort 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 there were no deaths from tracheal cancer.

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1 their employment prior to 1960 were removed from the analysis. Also, beginning in 1968, fiber
2 concentrations by PCM analysis of site-specific air samples were available for all location
3 operations to inform the JEM. Prior to 1968, the exposure intensity for 23 of 25 location
4 operations was estimated based on reasoned assumptions informed by employee interviews in
5 the early 1980s. It is likely the uncertainty of these reasoned assumptions increased the farther
6 back in time that exposures were estimated, making the earliest exposure estimates (1940s and
7 1950) less certain than those only a few years before fiber count data were available. Finally,
8 between 1956 and 1967, dust-to-PCM extrapolation data were used to estimate exposures in the
9 dry mill based on measurements taken in the late 1960s. Although there is some uncertainty in
10 the conversion ratio selected by Amandus et al. (1987a), dust-to-fiber conversions are likely to
11 be less uncertain than extrapolations further backwards in time to the 1950s and 1940s, where
12 only one air sample for dust was available in 1944. Thus, the potential attenuation effect of
13 nondifferential measurement error is likely to be reduced by examining the post-1959 cohort
14 alone compared to the entire cohort.

15 In addition, by focusing on the more homogeneous age distribution of workers hired after
16 1959, concerns about differential cancer mortality latency were diminished. Third, smoking
17 rates among this more narrowly defined sub-cohort are likely to have been more homogeneous,
18 and, thus, restricting analysis to this sub-cohort would help to limit any potential confounding
19 due to smoking. Finally, EPA conducted goodness-of-fit testing of the extended Cox
20 proportional hazards model as applied to the sub-cohort hired post-1959. There was no evidence
21 to reject the hypothesis of proportionality, and the exposure models demonstrated adequate fits to
22 the data, with statistically significant effect estimates. In each of the Cox proportional hazards
23 model analyses with time-varying exposures—across all the exposure metrics and across all the
24 lag lengths—no violations of the assumption of proportionality of hazards were found.

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Table 5-12. Model fit comparison for different exposure metrics and lung-cancer mortality associated with Libby Amphibole asbestos, controlling for age, gender, race, and date of birth

Ordered by exposure metric			Ordered by model fit				
Exposure metric	Lag (yr)	AIC	Exposure metric	Lag (yr)	AIC	Multivariate model <i>p</i> -value	Exposure <i>p</i> -value
CE	0	361.610	CE 10-yr ½ life	10	358.400	0.0071	0.0009
CE	10	361.073	CE 5-yr ½ life	10	358.502	0.0075	0.0010
CE	15	363.124	CE 15-yr ½ life	10	358.777	0.0084	0.0015
CE	20	364.964	CE 20-yr ½ life	10	359.122	0.0098	0.0022
CE 20-yr ½ life	0	361.123	CE 5-yr ½ life	15	359.910	0.0138	0.0032
CE 20-yr ½ life	10	359.122	CE 10-yr ½ life	15	360.543	0.0181	0.0079
CE 20-yr ½ life	15	361.533	CE	10	361.073	0.0227	0.0188
CE 20-yr ½ life	20	364.703	CE 20-yr ½ life	0	361.123	0.0232	0.0155
CE 15-yr ½ life	0	361.382	CE 15-yr ½ life	15	361.129	0.0232	0.0162
CE 15-yr ½ life	10	358.777	CE 15-yr ½ life	0	361.382	0.0258	0.0184
CE 15-yr ½ life	15	361.129	CE 20-yr ½ life	15	361.533	0.0276	0.0254
CE 15-yr ½ life	20	364.588	RTW 5-yr ½ life	0	361.593	0.0283	0.0309
CE 10-yr ½ life	0	362.169	CE	0	361.610	0.0285	0.0307
CE 10-yr ½ life	10	358.400	CE 10-yr ½ life	0	362.169	0.0360	0.0358
CE 10-yr ½ life	15	360.543	RTW 10-yr ½ life	0	362.283	0.0378	0.0588
CE 10-yr ½ life	20	364.342	RTW 15-yr ½ life	0	362.714	0.0452	0.0863
CE 5-yr ½ life	0	364.225	RTW 20-yr ½ life	0	362.973	0.0503	0.1084
CE 5-yr ½ life	10	358.502	CE	15	363.124	0.0535	0.1215
CE 5-yr ½ life	15	359.910	RTW 5-yr ½ life	10	363.224	0.0558	0.1343
CE 5-yr ½ life	20	363.644	CE 5-yr ½ 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 ½ life	10	364.041	0.0778	0.2810
RTW	15	364.990	CE 5-yr ½ life	0	364.225	0.0838	0.2908
RTW	20	364.502	RTW 15-yr ½ life	10	364.336	0.0876	0.3733
RTW 20-yr ½ life	0	362.973	CE 10-yr ½ life	20	364.342	0.0878	0.3661
RTW 20-yr ½ life	10	364.477	RTW 20-yr ½ life	10	364.477	0.0927	0.4314
RTW 20-yr ½ life	15	365.011	RTW	20	364.502	0.0936	0.5307
RTW 20-yr ½ life	20	364.628	CE 15-yr ½ life	20	364.588	0.0969	0.4815
RTW 15-yr ½ life	0	362.714	RTW 20-yr ½ life	20	364.628	0.0985	0.5763
RTW 15-yr ½ life	10	364.336	RTW 15-yr ½ life	20	364.662	0.0998	0.5909
RTW 15-yr ½ life	15	365.001	CE 20-yr ½ life	20	364.703	0.1014	0.5530
RTW 15-yr ½ life	20	364.662	RTW 10-yr ½ life	20	364.719	0.1021	0.6188
RTW 10-yr ½ life	0	362.283	RTW 5-yr ½ life	15	364.768	0.1041	0.6021
RTW 10-yr ½ life	10	364.041	RTW 5-yr ½ life	20	364.831	0.1067	0.6884

5

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Table 5-12. Model fit comparison for different exposure metrics and lung-cancer mortality associated with Libby Amphibole asbestos, controlling for age, gender, race, and date of birth (continued)

Ordered by exposure metric			Ordered by model fit				
Exposure metric	Lag (yr)	AIC	Exposure metric	Lag (yr)	AIC	Multivariate model <i>p</i> -value	Exposure <i>p</i> -value
RTW 10-yr ½ life	15	364.962	RTW	10	364.835	0.1069	0.6586
RTW 10-yr ½ life	20	364.719	RTW 10-yr ½ life	15	364.962	0.1124	0.8173
RTW 5-yr ½ life	0	361.593	CE	20	364.964	0.1125	0.8204
RTW 5-yr ½ life	10	363.224	RTW	15	364.990	0.1136	0.8809
RTW 5-yr ½ life	15	364.768	RTW 15-yr ½ life	15	365.001	0.1141	0.9100
RTW 5-yr ½ life	20	364.831	RTW 20-yr ½ life	15	365.011	0.1146	0.9599

1
2 CE: Cumulative exposure with or without exponential decay modeled with different half-lives.
3 RTW: Residence-time weighted exposure with or without exponential decay with different half-lives.
4 AIC: Akaike Information Criterion.
5
6

7 As the exposure-response models cannot strictly be considered to be nested, a standard
8 measure of fit called the Akaike Information Criterion (AIC [Burnham and Anderson, 2002])
9 was used for comparison of goodness of fit across models based on the same data set. In their
10 text on model selection, Claeskens and Hjort (2008) state that "...for selecting a model among a
11 list of candidates, Akaike's information criterion (AIC) is among the most popular and versatile
12 strategies." Claeskens and Hjort (2008) also state that the model yielding the smallest AIC is
13 judged the best one and it is a common practice in environmental epidemiology to simply select
14 the single model with the best statistical fit (i.e., the lowest AIC) among the models that were
15 evaluated. Smaller AIC values generally indicate a better fitting model relative to larger AIC
16 values. While large differences in AIC values can reveal important differences in model fit,
17 small differences are less conclusive. For example, models differing in AIC by 2 or less units
18 can be considered to have a substantial level of empirical support (Burnham and Anderson,
19 2002; p. 70).

20 Table 5-12 shows the models and exposure metrics ordered by fit. Of interest is whether
21 there are models with distinct exposure metrics that adequately fit these data (as measured by
22 statistical significance of the model *p*-value) and then, a measure of relative fit among these
23 adequately fitting models. Of the 40 exposure-response metrics, 14 demonstrated an adequate fit
24 to the data as measured by the overall model fit, with the likelihood ratio test being statistically
25 significant (*p* < 0.05), as well as having statistically significant exposure metrics (*p* < 0.05).
26 However, note that only the nine models that demonstrated adequate model and exposure metric
27 fit and incorporated a lag period to account for lung-cancer mortality latency were advanced for

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1 potential use in developing a unit risk. While metrics that did not include an adjustment for lag
2 on the exposure metric to account for cancer mortality latency were fit to these data for the sake
3 of completeness, they were dropped from further consideration because they implicitly assume
4 no passage of time between the initiation of cancer, subsequent promotion of that cancer, and
5 mortality.

6 Several general patterns were discernable with respect to which exposure metrics best
7 predicted lung-cancer mortality when comparing AICs for relative model fit. The data show that
8 lagging exposure by 10 years best predicts lung-cancer mortality compared to other lags. This
9 trend is seen across both the cumulative exposure without decay and the various half-life
10 cumulative exposure metrics where a 10-year lag of exposure best predicts lung-cancer mortality
11 for all cumulative exposure metrics compared to other lags; metrics with 15-year lags were
12 generally the next best in terms of fit. Another conclusion is that the models that included RTW
13 exposure metrics, regardless of half-life or lag, were less suitable than the models that employed
14 cumulative exposure and its variants.

15 Among the 40 exposure metric models that were evaluated, the exposure model with the
16 lowest AIC value was for cumulative exposure with a 10-year half life for decay and a 10-year
17 lag for cancer mortality latency and had a model p -value of 0.0071 (see Table 5-12). This
18 multivariate model controlled for age, gender, race, and date of birth. This model estimated a
19 slope (beta) of 1.26×10^{-2} per fiber/cc-year based on a 365-day calendar year,²⁰ and the
20 95th percentile upper bound on this parameter was 1.88×10^{-2} per fiber/cc-year. The p -value for
21 the Libby Amphibole asbestos regression coefficient (slope) was <0.001, indicating that this
22 parameter was statistically significantly greater than zero. Table 5-13 shows the slopes and
23 confidence intervals for all retained metrics from Table 5-12.

24 According to the model results presented in Table 5-12, there were other exposure
25 metrics that predicted lung-cancer mortality and exhibited statistically significant effect
26 estimates. Several other metrics were considered to fit nearly as well as the model with the
27 smallest AIC since their AIC values were within two units of the exposure model with the lowest
28 AIC, a proximity that can be considered to be a range that cannot clearly differentiate between
29 models (Burnham and Anderson, 2002). As each of the other exposure metrics was based on a
30 different reorganization of the same exposure data, the different slopes are not directly
31 comparable, but all adequately fitting lagged models also produce statistically significant slopes
32 for the exposure-response relationship ($p < 0.05$). Of particular note are the results of the

²⁰ The two-sided 90% confidence interval is (6.00×10^{-3} , 1.88×10^{-2}); the two-sided 95% confidence interval is (5.12×10^{-3} , 2.00×10^{-2}).

1 cumulative exposure model, with a 10-year lag for latency, but without a decay function, since it
 2 showed the lowest AIC among nondecay models.

3
 4 **Table 5-13. Lung-cancer mortality exposure metrics fits, slopes, and**
 5 **confidence intervals for all retained metrics from Table 5-12. Subset of lung**
 6 **cancer models with lagged exposures that yielded statistically significant**
 7 **model fit ($p < 0.05$) and exposure metric fit ($p < 0.05$) to the epidemiologic**
 8 **data**
 9

Exposure metric	Lag years	AIC	Slope (Beta)	SE	Exposure p -value	90% CI for the slope
CE 10-yr ½ life	10	358.400	0.0126	0.0038	0.0009	(0.0063, 0.0188)
CE 5-yr ½ life	10	358.502	0.0179	0.0055	0.0010	(0.0089, 0.0269)
CE 15-yr ½ life	10	358.777	0.0106	0.0033	0.0015	(0.0052, 0.0160)
CE 20-yr ½ life	10	359.122	0.0095	0.0031	0.0022	(0.0044, 0.0146)
CE 5-yr ½ life	15	359.910	0.0155	0.0052	0.0032	(0.0069, 0.0241)
CE 10-yr ½ 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 ½ life	15	361.129	0.0097	0.0040	0.0162	(0.0031, 0.0163)
CE 20-yr ½ life	15	361.533	0.0087	0.0039	0.0254	(0.0023, 0.0151)

10
 11 CI = confidence interval
 12
 13

14 The AIC values for models that included lag and/or half-life adjustments to the exposure
 15 metrics were not penalized in the regression analyses for using these extra parameters because
 16 these factors were not represented as covariates but rather were embedded in the computation.
 17 While these results were obtained using each instance of lag and/or half-life terms in separate
 18 model fit, it may be appropriate to mathematically penalize the AICs for inclusion of these
 19 additional parameters. AIC values, as typically computed by regression software, include the
 20 addition of a penalty for model complexity as measured by the number of parameters that are fit
 21 in the regression model (thereby increasing the AIC). In the AIC calculations presented in
 22 Table 5-12, the models are treated as having the same number of parameters since each model
 23 represents the same exposures in a different way but with a single exposure parameter in the
 24 regression models and are, therefore, equally penalized in the software’s AIC calculation.
 25 Because an argument can be made that exposure metrics that do not include a decay function
 26 with their half-life term are implicitly more parsimonious (simpler), a comparison of the AICs is
 27 not straightforward. If the decay model fits were penalized for the inclusion of the decay
 28 function in the computation of the exposure metric, then with such an adjustment, the relative fit

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1 of the CE models would be somewhat improved in terms of their comparison with the values in
2 Table 5-12 (AICs are generally penalized 2 units for each additional parameter).

3 Table 5-13 displays the lagged exposure-response models and metrics with adequate
4 model fit ($p < 0.05$) to the epidemiologic data that were further considered. The units of the
5 slopes are fiber/cc-year. These slopes and confidence intervals represent calendar year
6 continuous environmental exposure as described above and define the “Exposed Hazard Rate” in
7 the life-table procedure when multiplied by the exposure level (see Appendix G for details).

8 9 **5.4.3.6.3. Summary of results of the analysis of the lung-cancer mortality in the sub-cohort**

10 As presented in Table 5-13, the CE model with 10-year half life and lag provided an
11 adequate fit to the data ($p < 0.05$) and had the lowest AIC value. The cumulative exposure
12 model with a 10-year lag also yielded a statistically adequate fit to these data ($p < 0.05$), as did
13 several decay models with a 15-year lag. These results demonstrate reasonable uncertainty in the
14 metric of exposure such that no single exposure model can be definitively selected based on
15 goodness of fit alone, because IUR is based on the plausible upper bound of the effect estimate.
16 Based on the results from the lowest AIC multivariate model (i.e., cumulative exposure with a
17 10-year half life for decay and a 10-year lag for cancer mortality latency), the slope was
18 1.26×10^{-2} per fiber/cc-year based on a 365-day calendar year, and the 95% upper bound on the
19 slope was 1.88×10^{-2} per fiber/cc-year. This point estimate and 95% upper bound represent the
20 relative risk (including statistical uncertainty within exposure metric) of lung-cancer mortality
21 observed from exposure to Libby Amphibole asbestos fibers in the worker cohort for this
22 exposure metric. Issues related to uncertainty in the choice of exposure metric are described
23 further in the section on the derivation of the combined IUR of mesothelioma and lung cancer
24 (see Section 5.4.5.3).

25 26 **5.4.3.6.4. Sensitivity analysis of the influence of high exposures in early 1960s on the model** 27 **fit in the sub-cohort**

28 As discussed in Section 5.4.2.5, the comparison of model fit between various exposure
29 metrics is an empirical process and does not necessarily reflect either a specific biological or
30 other factor as an underlying cause for model fit. Although data do not exist to evaluate
31 biological bases for model fit, other potential factors can be explored where data allow. For
32 example, because of concerns that very high (>100 fibers/cc) 8-hour TWA exposures during
33 1960–1963 (see Table 5-7) could have influenced the relative fit of the various exposure metrics,
34 EPA conducted a sensitivity analysis of the impact on the relative model fit of reducing all
35 estimated exposure intensities for 1960–1963 by 50%.

1 For modeling mesothelioma mortality on this revised data set, there was one change in
 2 the relative fit of 3rd and 4th best fit decay models, but the observation that exposure metrics
 3 including decay fit better than exposure metrics without decay was unchanged (see Table 5-14).
 4 However, the fit of all the metrics decreased slightly, with each DIC increased between 0.3 and
 5 1.1. The metrics without decay and RTW metrics had DIC values higher than those in Table
 6 5-14. The revised data set DIC for the model used in IRIS IUR (1988) was 97.9.

7
 8
 9 **Table 5-14. Sensitivity analysis of model fit comparison for different**
 10 **exposure metrics and lung-cancer mortality associated with Libby**
 11 **Amphibole asbestos.** Estimated exposure intensities for all jobs during
 12 1960–1963 were reduced by 50%.
 13

Exposure Metric	Lag (yr)	All workers hired after 1959 (<i>n</i> = 880) Based on seven mesothelioma deaths (as shown in Table 5-11)	All workers hired after 1959 (<i>n</i> = 880) Based on seven mesothelioma deaths Exposures during 1960–1963 at 50%
		DIC	DIC
CE 5-yr ½ life	15	70.6	71.2
CE 5-yr ½ life	10	72.8	73.9
CE 10-yr ½ life	10	73.9	74.9
CE 10-yr ½ life	15	74	74.6
CE 15-yr ½ life	10	75.7	76.4
CE 15-yr ½ life	15	76.1	76.7
CE 20-yr ½ life	10	76.7	77.3
CE 20-yr ½ life	15	77.2	77.7

14
 15 CE = Cumulative Exposure with exponential decay modeled with different half-lives; DIC = Deviance Information Criterion.
 16
 17

18 For modeling lung-cancer mortality on this revised data set, there was no difference in
 19 the order of the relative fit between the same exposure models that fit the sub-cohort of workers
 20 hired after 1959 and included the exposures as estimated by Amandus et al. (1987a) during
 21 1960–1963 (see Table 5-15). The models based on the revised data set fit marginally better
 22 based on AIC.

23 This sensitivity analysis reduces some of the potential uncertainty in the results that may
 24 have been attributed to exposure measurement error specific to the 1960–1963 time period when
 25 some of the estimated exposures were particularly high.
 26
 27

Table 5-15. Sensitivity analysis of model fit comparison for different exposure metrics and lung-cancer mortality associated with Libby Amphibole asbestos, 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 (<i>n</i> = 880) based on 32 deaths from lung cancer (as shown in Table 5-13)			All workers hired after 1959 (<i>n</i> = 880) based on 32 deaths from lung cancer exposures during 1960–1963 at 50%		
		AIC	Multivariate model <i>p</i> -value	Exposure <i>p</i> -value	AIC	Multivariate model <i>p</i> -value	Exposure <i>p</i> -value
CE 10-yr ½ life	10	358.400	0.0071	0.0009	357.644	0.0051	0.0004
CE 5-yr ½ life	10	358.502	0.0075	0.0010	357.781	0.0054	0.0005
CE 15-yr ½ life	10	358.777	0.0084	0.0015	357.966	0.0059	0.0006
CE 20-yr ½ life	10	359.122	0.0098	0.0022	358.283	0.0068	0.0009
CE 5-yr ½ life	15	359.910	0.0138	0.0032	359.456	0.0113	0.0025
CE 10-yr ½ 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 ½ life	15	361.129	0.0232	0.0162	360.810	0.0203	0.0138
CE 20-yr ½ 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.
AIC = Akaike Information Criterion.

5.4.3.6.5. Additional analysis of the potential for confounding of lung cancer results by smoking in the sub-cohort of workers hired after 1959

In the full cohort analysis, the proportional hazard assumption was not found to hold, and it was possible that one of the reasons for this failure was the 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. By restricting the dates of hire in the sub-cohort, those workers in the sub-cohort may be made more similar to each other in ways that would reduce the potential for confounding by smoking and, in this sub-cohort, the proportional hazards assumption was found to hold, thus statistically eliminating concern regarding confounding by smoking (because smoking, in general, is known as a very strong confounder).

As an additional check on the potential for confounding, a new method was evaluated to test for confounding by smoking in occupational cohorts that do not have data on smoking. Confounding, which can bias observed results when there is an uncontrolled variable, which is correlated with both the explanatory variable and the outcome variable, is a distinct concept from

1 effect-measure modification (i.e., synergy), which might reflect different observed effects of
2 exposure to Libby Amphibole asbestos among smokers as compared to nonsmokers. The extent
3 of effect-measure modification cannot be assessed without adequate data on smoking; however,
4 the issue is discussed in Section 5.4.6.

5 A method has been described by Richardson (2010) to determine if an identified
6 exposure relationship with lung cancer is confounded by unmeasured smoking in an occupational
7 cohort study. Richardson (2010) demonstrated that an exposure of interest (i.e., Libby
8 Amphibole asbestos) can be used to predict an outcome other than lung cancer such as chronic
9 obstructive pulmonary disease (COPD), which is known to be caused by smoking, but not
10 thought to be related to the exposure of concern.²¹ If a positive relationship is identified where
11 no causal association is suspected, this would suggest that smoking and the exposure metric
12 (Libby Amphibole asbestos) were positively correlated and that the identified exposure-response
13 relationship was, in fact, confounded by smoking. EPA implemented this methodology to model
14 the potential effects of Libby Amphibole asbestos on the risk of COPD mortality on the
15 sub-cohort of workers hired after 1959. Using the exposure metric defined as cumulative
16 exposure with a 10-year lag, the extended Cox proportional hazards model with time-varying
17 exposures estimated a slope (beta) for COPD of -0.056 per fiber/cc-year based on a 365-day
18 calendar year. The *p*-value for the coefficient (slope) was 0.102, indicating that this parameter
19 was not statistically significantly different from zero. Using the exposure metric defined as
20 cumulative exposure with a 10-year half life for decay and a 10-year lag for cancer latency, the
21 extended Cox proportional hazards model with time-varying exposures estimated a slope (beta)
22 of -0.135 per fiber/cc-year based on a 365-day calendar year. The *p*-value for the coefficient
23 (slope) was 0.116, indicating that this parameter was not statistically significantly different from
24 zero.

25 Summarizing these findings, EPA used the method described by Richardson (2010) to
26 evaluate whether exposures to Libby Amphibole asbestos predicted mortality from COPD as an
27 indication of potential confounding by smoking and found a nonsignificant negative relationship,
28 which was inconsistent with confounding by smoking in the sub-cohort of workers hired after
29 1959.

²¹ Richardson (2010) cited articles by Rushton (2007a, b) 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.

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1 **5.4.4. Exposure Adjustments and Extrapolation Methods**

2 The estimated exposures based on JEM and work histories are discussed in
3 Section 5.4.2.5. Note that all slopes presented with units of fiber/cc-year are for calendar year
4 and not for occupational year.
5

6 **5.4.5. Inhalation Unit Risk (IUR) of Cancer Mortality**

7 The derivation of the unit risk estimates, defined as the lifetime risk of mortality from
8 either mesothelioma or lung cancer from chronic inhalation of Libby Amphibole asbestos at a
9 concentration of 1 fiber/cc of air, is presented in the following subsections. Note that all slopes
10 are presented as per fiber/cc-year for a 365-day calendar year rather than for an occupational
11 year. Also, note that while the slopes are not adjusted for differences in breathing rates and the
12 number of hours of exposure in an occupational (8-hour) day as compared to a whole (24-hour)
13 day, the central risk and unit risk estimates do incorporate this adjustment.
14

15 **5.4.5.1. Unit Risk Estimates for Mesothelioma Mortality**

16 Computational details of the methodology and tables for deriving the unit risk for
17 mesothelioma mortality are presented in Appendix G. The modeling analysis presented above
18 showed that metrics including lag and half-life parameters provided the best empirical fit to the
19 Libby worker sub-cohort data. Although there is uncertainty in applying these models for
20 occupational mortality to estimation of risks for different exposure levels and time patterns (see
21 Section 5.4.6), following the recommendations of the *Guidelines for Carcinogen Risk*
22 *Assessment* (U.S. EPA, 2005a), a linear low-dose extrapolation below the POD was used because
23 the mode of action for Libby Amphibole asbestos for mesothelioma is largely unknown. Using
24 the results of the cumulative exposure model with best-fitting lag and decay parameters, the
25 LEC_{01} for the adult-only-exposures was determined to be 0.245 fibers/cc, which yielded an
26 adult-based unit risk of mesothelioma mortality of 0.041 (POD of 1% divided by the LEC_{01}),
27 which when scaled by 70/54 to encompass the whole lifespan, yielded a lifetime unit risk of
28 0.053 per fibers/cc. The value of the risk corresponding to the measure of central tendency
29 involves EC_{01} rather than LEC_{01} . The EC_{01} for the adult-only-exposures was determined to be
30 0.406 per fibers/cc, which when divided into a POD of 1%, yielded an adult-based central
31 estimate for mesothelioma mortality of 0.025, which when scaled by 70/54 to encompass the
32 whole lifespan, yielded a lifetime central estimate of 0.032 per fibers/cc.

33 The mesothelioma unit risks for model results presented in Table 5-11 and discussed in
34 Section 5.4.3.6.1 are presented in Table 5-16. All of the metrics in Table 5-16 are CE metrics
35 lagged 10–15 years (the fit of 20-year lag models was much worse since one of seven

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1 mesothelioma deaths occurred before 20 years; lags longer than 15 years are possible, and this is
 2 an uncertainty described in Section 5.4.6). Issues related to uncertainty in the choice of exposure
 3 metric are described further in the section on the derivation of the combined IUR of
 4 mesothelioma and lung cancer (see Section 5.4.5.3).

5
 6
 7 **Table 5-16. Mesothelioma mortality exposure metrics unit risks**
 8

Exposure metric	Lag years	DIC	Information weight	Central risk estimate	Unit risk
CE – 5-yr ½ life	15	70.6	0.428	0.032	0.053
CE – 5-yr ½ life	10	72.8	0.143	0.054	0.088
CE – 10-yr ½ life	10	73.9	0.082	0.028	0.047
CE – 10-yr ½ life	15	74.0	0.078	0.020	0.032
CE – 15-yr ½ life	10	75.7	0.033	0.022	0.036
CE – 15-yr ½ life	15	76.1	0.028	0.017	0.027
CE – 20-yr ½ life	10	76.7	0.020	0.020	0.032
CE – 20-yr ½ life	15	77.2	0.016	0.015	0.025

9
 10
 11 **5.4.5.1.1. Adjustment for mesothelioma underascertainment**

12 For mesothelioma, the undercounting of cases (underascertainment) is a particular
 13 concern given the limitations of the ICD classification systems used prior to 1999. In practical
 14 terms, this means that some true occurrences of mortality due to mesothelioma are missed on
 15 death certificates and in almost all administrative databases such as the National Death Index.
 16 Even after the introduction of a special ICD code for mesothelioma with the introduction of
 17 ICD-10 in 1999, detection rates are still imperfect (Pinhiero et al., 2004; Camidge et al., 2006),
 18 and the reported numbers of cases typically reflect an undercount of the true number. Kopylev et
 19 al. (2011) reviewed the literature on this underascertainment and developed general methodology
 20 to account for the likely numbers of undocumented mesothelioma deaths using the Libby worker
 21 cohort as an example. Because the analysis of mesothelioma mortality was based on absolute
 22 risk, it was possible to compensate for mesothelioma underascertainment in the Libby worker
 23 sub-cohort. As the number of peritoneal mesotheliomas is partially known in the Libby worker
 24 sub-cohort, the appropriate adjustment factor for the sub-cohort is 1.39 (Kopylev et al., 2011,
 25 Table 3).

26 The adjusted mesothelioma central risk (based on the EC₀₁), corresponding to the best-fit
 27 metric, was 0.044 (0.032 × 1.39) per fibers/cc, and adjusted mesothelioma mortality unit risk was
 28 0.074 (0.053 × 1.39) per fibers/cc. Mesothelioma mortality-adjusted unit risks are listed in
 29 Table 5-17 along with their information weights.

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1 **Table 5-17. Adjusted for underascertainment unit risks for the sub-cohort**
 2 **hired after 1959 corresponding to the different metrics**
 3

Exposure metric	Lag years	Information weight	Adjusted central risk estimate	Adjusted unit risk
CE – 5-yr ½ life	15	0.428	0.044	0.074
CE – 5-yr ½ life	10	0.143	0.075	0.122
CE – 10-yr ½ life	10	0.082	0.039	0.065
CE – 10-yr ½ life	15	0.078	0.028	0.044
CE – 15-yr ½ life	10	0.033	0.031	0.050
CE – 15-yr ½ life	15	0.028	0.024	0.038
CE – 20-yr ½ life	10	0.020	0.028	0.044
CE – 20-yr ½ life	15	0.016	0.022	0.035

4
 5
 6 **5.4.5.2. Unit Risk Estimates for Lung-Cancer mortality**

7 Computational details of the methodology and tables for deriving the unit risk for
 8 lung-cancer mortality are presented in Appendix G. Although there is uncertainty in applying
 9 these models for occupational mortality to the estimation of risks for different exposure levels
 10 and time patterns (see Section 5.4.6), following the recommendations of the *Guidelines for*
 11 *Carcinogen Risk Assessment* (U.S. EPA, 2005a), a linear low-dose extrapolation below the POD
 12 was used because the mode of action for Libby Amphibole asbestos for lung cancer is
 13 undetermined. The nine exposure-response models retained from Table 5-12 (shown in
 14 Table 5-13) all had reasonably similar goodness of fits. No single model stands out as clearly
 15 statistically superior; however, there is a range of quality of fit within the set that could be
 16 considered adequate. The lung-cancer mortality unit risks are shown in Table 5-18.

17 Using the results of the exposure model with the lowest AIC value (i.e., cumulative
 18 exposure with a 10-year half life for decay and a 10-year lag for cancer latency) alone, the LEC₀₁
 19 for the adult-only-exposures was determined to be 0.333 fibers/cc, which yielded an adult-based
 20 unit risk of lung-cancer mortality of 0.0300 (POD of 1% divided by the LEC₀₁), which when
 21 scaled by 70/54 to encompass the whole lifespan, yielded a lifetime unit risk of 0.0389 per
 22 fibers/cc. The value of the risk that would correspond to the measure of central tendency
 23 involves EC₀₁ rather than LEC₀₁. The EC₀₁ for the adult-only exposures was determined to be
 24 0.499 per fibers/cc, which when divided into a POD of 1%, yielded an adult-based central
 25 estimate for lung-cancer mortality of 0.0200, which when scaled by 70/54 to encompass the
 26 whole lifespan, yielded a lifetime central estimate of 0.0260 per fibers/cc.
 27

Table 5-18. 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})
CE 10-yr ½ life	10	358.400	0.0009	0.0260	0.0389
CE 5-yr ½ life	10	358.502	0.0010	0.0195	0.0293
CE 15-yr ½ life	10	358.777	0.0015	0.0300	0.0455
CE 20-yr ½ life	10	359.122	0.0022	0.0326	0.0501
CE 5-yr ½ life	15	359.910	0.0032	0.0167	0.0260
CE 10-yr ½ life	15	360.543	0.0079	0.0231	0.0375
CE	10	361.073	0.0188	0.0399	0.0679
CE 15-yr ½ life	15	361.129	0.0162	0.0258	0.0434
CE 20-yr ½ life	15	361.533	0.0254	0.0280	0.0486

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 fibers/cc, which yielded an adult-based unit risk of lung-cancer mortality of 0.0524 (POD of 1% divided by the LEC_{01}), which when scaled by 70/54 to encompass the whole lifespan, yielded a lifetime unit risk of 0.0679 per fibers/cc. The EC_{01} for the adult-only exposures was determined to be 0.325 per fibers/cc, which when divided into a POD of 1%, yielded an adult-based central estimate for lung-cancer mortality of 0.0308, which when scaled by 70/54 to encompass the whole lifespan, yielded a lifetime central estimate of 0.0399 per fibers/cc.

The resulting unit risks in Table 5-18 ranged from 0.0260 to 0.0679 fibers/cc. This shows that the unit risk (i.e., 0.0389 per fibers/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 5.4.3.6.2), 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 AIC for the CE models may reasonably be thought to be somewhat lower than through the standard calculation of AIC. The CE metric with a 10-year lag does fit these data, is a simpler and more

1 straightforward metric, and has an extensive tradition of use in the epidemiologic literature and
2 in the practice of risk assessment.

3 Issues related to uncertainty in the choice of exposure metric are described in the section
4 on the derivation of the combined IUR of mesothelioma and lung cancer below.

6 **5.4.5.3. IUR Derivation for Combined Mesothelioma and Lung-Cancer Mortality**

7 Before risks can be combined, it is important to understand several concepts that are
8 pertinent to the evaluation and comparison of the cancer-specific mortality unit risks that will be
9 combined. First, there is statistical uncertainty in the potency estimate within the
10 exposure-response model defined by each exposure metric. This within-metric uncertainty is
11 accounted for by the Bayesian credible interval around the potency estimates (slopes) for
12 mesothelioma mortality (see Table 5-11) and by the confidence interval around the potency
13 estimates (slopes) for lung-cancer mortality (see Tables 5-13). Next, there is uncertainty in the
14 choice of metrics for developing an IUR (called cross-metric uncertainty, described below).
15 Finally, when unit risks corresponding to metrics are chosen accounting for uncertainty, these are
16 statistically combined into the IUR. Details are provided below.

17 For this current assessment, EPA obtained the best available demographic, exposure, and
18 vital status data from NIOSH. Subsequently, the best-fitting statistical models were identified,
19 which were then applied to derive central estimates of the lifetime combined mesothelioma and
20 lung-cancer mortality risk in the general population exposed to a continuous concentration of
21 1 fiber/cc of Libby Amphibole asbestos. Then, the individual exposure metric-specific risks
22 were calculated as the statistical (95%) upper confidence bounds on these central estimates. Use
23 of the upper confidence bound accounts for uncertainty in the effect estimate for each metric—
24 otherwise referred to as the within-metric uncertainty.

25 Another source of uncertainty is the choice of the appropriate exposure metric among a
26 set of results that appear to fit the data similarly well. This uncertainty is referred to as the
27 between-metric or cross-metric uncertainty. For the Libby worker cohort data, the best-fit
28 (lowest information criterion values) metrics lead to estimates of risks that are more like
29 mid-range estimates among the other metrics (see Tables 5-17 and 5-18) with sufficiently close
30 information criterion values, rather than upper bound estimates. While the lung cancer unit risk
31 computed from the model with the lowest AIC appears to be robust, Table 5-18 shows that there
32 is a range of possible unit risk values from the set of models with adequate fit (as measured by a
33 statistically significant p -value for the exposure metric term) and similar goodness of fit.
34 Likewise, for mesothelioma mortality, among the models with adequate fit shown in Table 5-17,
35 there is a range of possible unit risk values.

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1 The IUR should be a reasonable upper bound on the extra risk. As is clear from
2 Tables 5-17 and 5-18 in the preceding sections, the unit risks based on the metrics with the
3 lowest information criterion values provide a lower estimate of cancer mortality risk than some
4 other similarly fitting metrics. While the models with the lowest information criterion values
5 have the greatest statistical support, other models that yield higher unit risks are also statistically
6 plausible. This current assessment selected the upper bound unit risk among the plausible
7 exposure metrics (regardless of the small residual differences in quality of fit) to account for
8 cross-metric uncertainty. Because there were few metrics with unit risks higher than the best
9 fitting metric's unit risk for each cancer mortality endpoint, this method effectively selects the
10 highest unit risk among those considered for each cancer mortality endpoint.

11 Once the cancer-specific mortality unit risks are selected, the two are then combined.
12 Because each of the unit risks is itself an upper bound estimate, summing such upper bound
13 estimates across mesothelioma and lung-cancer mortality is likely to overstate the overall risk.
14 Therefore, following the recommendations of the *Guidelines for Carcinogen Risk Assessment*
15 (U.S. EPA, 2005a), a statistically appropriate upper bound on combined risk was derived in order
16 to gain an understanding of the overall risk of mortality resulting from mesothelioma and from
17 lung cancers. It is important to note that this estimate of overall potency describes the risk of
18 mortality from cancer at either of the considered sites and is not just the risk of both cancers
19 simultaneously.

20 Because the estimated risk for both mesothelioma and lung-cancer mortality was derived
21 using Poisson and Cox proportional hazards models, correspondingly, it follows from statistical
22 theory that each of these estimates of risk is approximately normally distributed. For
23 independent normal random variables, a standard deviation for a sum is easily derived from
24 individual standard deviations, which are estimated from confidence intervals: standard
25 deviation = (unit risk – central risk) ÷ $Z_{0.95}$, where $Z_{0.95}$ is a standard normal quantile equal
26 to 1.645. For normal random variables, the standard deviation of a sum is the square root of the
27 sum of the squares of individual standard deviations.

28 The upper bound among the mesothelioma mortality unit risks was 0.122 per fibers/cc.
29 The upper bound among the computed lung-cancer mortality unit risks was 0.0680 per fibers/cc.
30 The central estimate of risk was 0.075 for mesothelioma mortality per fibers/cc and 0.0399 per
31 fibers/cc for lung-cancer mortality (see Tables 5-17 and 5-18, respectively).

32 In order to combine the unit risks, one first obtains an estimate of standard deviation of
33 the sum of the individual unit risks as

34
35
36
$$\sqrt{\{ [(0.122 - 0.075) \div 1.645]^2 + (0.068 - 0.0399) \div 1.645 \}^2} = 0.033 \text{ per fibers/cc (Eq. 5-9)}$$

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1 Then, the combined central estimate of risk of mortality from either mesothelioma or
 2 lung cancer is $0.0399 + 0.075 = 0.115$ per fibers/cc, and the combined IUR is
 3 $0.115 + 0.033 \times 1.645 = 0.169$ per fibers/cc.

4 Selecting the upper bound unit risk estimates for use in combining unit risks accounts for
 5 many potential uncertainties. It accounts for uncertainty in the effect estimate (i.e., the
 6 within-metric uncertainty) and the uncertainty attributable to the choice of exposure metric (i.e.,
 7 the cross-metric uncertainty). The combined IUR from the best fitting mesothelioma and
 8 lung-cancer mortality models (using two different model selection criteria) can be computed for
 9 comparison with Tables 5-17 and 5-18, respectively, by the same steps as above, and the results
 10 are shown in Table 5-19.

11
 12
 13 **Table 5-19. Reasonable upper bound and lowest information criteria**
 14 **estimates of central risks and unit risks, per fibers/cc, for mesothelioma**
 15 **mortality, lung-cancer mortality, and the IUR for the combined mortality**
 16 **risk from mesothelioma and lung cancer**
 17

Model	Mesothelioma		Lung cancer		Combined mesothelioma and lung cancer	
	Central estimate	Unit risk	Central estimate	Unit risk	Central estimate	IUR
Reasonable upper bound ^a	0.075	0.122	0.040	0.068	0.115	0.169
Lowest information criteria ^b	0.044	0.074	0.026	0.040	0.070	0.103

18
 19 ^aFor mesothelioma, the selected model parameterized exposure as cumulative exposure with exponential decay
 20 half-life of 5 years and a 15-year lag. For lung cancer, the selected model parameterized exposure as cumulative
 21 exposure without decay and a 10-year lag.

22 ^bFor mesothelioma, the selected model parameterized exposure as cumulative exposure with exponential decay
 23 half-life of 5 years and a 10-year lag. For lung cancer, the selected model parameterized exposure as cumulative
 24 exposure with exponential decay half-life of 10 years and a 10-year lag.
 25
 26

27 Compared to the combined IUR from the best fitting exposure models, the EPA's
 28 selected combined IUR of mesothelioma and lung-cancer mortality accounts for both the
 29 demonstrated cross-metric uncertainty as well as several additional potential uncertainties, which
 30 could have resulted in underestimates of the mesothelioma and lung-cancer mortality risks from
 31 the epidemiologic data. These additional uncertainties are discussed in Section 5.4.6. The IUR
 32 value of 0.169 per fibers/cc accounts for important quantitative uncertainties in the selection of
 33 the specific exposure metric that may have remained in an IUR that might otherwise have been
 34 based on the best fitting exposure models alone.

1 **5.4.5.3.1. Comparison with other published studies of Libby workers cohort**

2 For lung cancer, two alternative analytic approaches to the use of EPA’s extended Cox
3 proportional hazards models could have been used for the calculation of a unit risk of
4 lung-cancer mortality. All of the choices are based on different analyses of the Libby worker
5 cohort; however, inclusion criteria differ among the analyses as does the length of mortality
6 follow-up. Each of the two approaches has two options to estimate the slope of the
7 exposure-response relationship in place of the regression slope estimated from the Cox
8 proportional hazards model and follow through with the same life-table procedure to calculate
9 the unit risk of lung-cancer mortality.

10 The first approach would be to use the published categorical results based on Sullivan
11 (2007). The first option in this approach was for EPA to estimate a slope to those categorical
12 data. The second option was to use the slope estimated in a published reanalysis of categorical
13 data of the Sullivan (2007) cohort by Berman and Crump (2008). The second approach would
14 be to use the published regression results of other researchers who modeled the underlying
15 continuous data. The first option in this approach was to use the slope estimated by Larson et al.
16 (2010a). The second option was to use the slope estimated by Moolgavkar et al. (2010).

17 For comparison purposes, the lung cancer unit risk from these alternatives is computed,
18 however, as all analyses are based upon different subsets of the Libby workers cohort and used
19 different analytic methods, the results are not necessarily interchangeable. Table 5-20
20 summarizes lung cancer risks derived from these studies.

21 The first alternative analytic approach to estimating the extra risk from a linear regression
22 of individual mortality data was to use a standard technique used in EPA cancer risk assessments
23 (U.S. EPA, 2005a) when individual-level data are not available. This approach used a weighted
24 linear regression of standardized rate ratio (SRR) estimators for lung-cancer mortality in white
25 males, as calculated in the NIOSH cohort analysis (Sullivan, 2007), with categorical cumulative
26 exposure and a 15-year lag. The Sullivan (2007) analysis was based only on those who have not
27 died or been lost to follow-up before January 1, 1960 (in contrast to employment beginning after
28 January 1, 1960), because the NIOSH software program (Life Table Analysis System) used for
29 this analysis only has statistics on external comparison rates for asbestosis (one of the primary
30 outcomes of interest in the Sullivan [2007] analysis) beginning in 1960. The SRR analysis
31 involves internal comparisons of lung-cancer mortality rates in the higher exposure categories to
32 the lung-cancer mortality rates in the lowest exposure category. The weights used for the SRRs
33 were the inverses of the variances. Midpoints of the exposure intervals were used, and for the
34 unbounded interval, the midpoint was assumed to be twice the starting point of that interval.

Table 5-20. 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 fiber/cc-year $\times 10^{-3}$ (calendar year)	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 ^b	Still alive post-1959 White males Exposures 1960–1982	2001	95/1,662	1.69	0.011
Berman and Crump, 2008 ^a	Still alive post-1959 White males Exposures 1960–1982	2001	93/1,672	3.96	0.079
Larson et al., 2010a	Full cohort Exposures 1935–1993	2006	98/1,862	1.61	0.010

^aSullivan (2007) and reanalysis of Sullivan (2007) state slightly different number of lung cancers. It is impossible to reconcile these numbers from published information.

^bReanalysis of Sullivan (2007).

Using this approach, a regression coefficient of 4.2×10^{-3} per fiber/cc-year ([SE] = 7.7×10^{-4} per fiber/cc-year, $p = 0.03$) 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 $LEC_{01} = 0.272$ fibers/cc, resulting in the lung cancer unit risk of 0.0368 per fibers/cc.

The Berman and Crump (2008) reanalysis was based on the Sullivan (2007) summary results except they used a lag of 10 years (Sullivan, 2008, personal communication to Berman and Crump). They fit the IRIS IUR (1988) lung cancer model to aggregate data using an extra multiplicative parameter α (in this model, the relative risk at zero exposure is estimated α rather than 1). 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

1 “informal” 90% confidence interval by the union of two confidence intervals (this upper bound is
2 shown in see Table 5-20). This was done to address uncertainty in the estimated parameter α ,
3 similar to what is done in this current assessment with estimated lag and decay. Note also, that
4 Berman and Crump (2008) also provide an UF to adjust for several sources of uncertainty in
5 exposures, resulting in an upper bound risk of 0.3162.

6 The second alternative analytic approach to estimating the extra risk of lung cancer from
7 a Cox regression with time-dependent covariates of individual mortality data was to use the
8 results published by Larson et al. (2010a), with cumulative exposure and a 20-year lag. This
9 analysis of lung-cancer mortality was based on the full cohort of 1,862 workers updated until
10 2006 and using the same model form as the current EPA analysis (the extended Cox proportional
11 hazards model). Larson et al. (2010a) reported a regression coefficient of 1.06×10^{-3} per
12 fiber/cc-year (SE = 3.1×10^{-4} per fiber/cc-year, $p = 0.0006$).²² EPA assumed that the cumulative
13 exposures reported by Larson et al. (2010) were based on years of occupational exposure
14 (240 days per year) during a 365-day calendar year. In order to account for exposure on every
15 day of the year for a calculation of unit risk, an adjustment for exposures during the length of an
16 occupational year (240 days) to the length of an calendar year (365 days) and an adjustment for
17 the volume of inhaled air were performed to match EPA’s analyses. The concentration estimate
18 obtained using the Larson et al. (2010) regression modeling and the life-table analysis procedure
19 was $LEC_{01} = 1.26$ fibers/cc, resulting in a lung cancer unit risk of 0.0103 per fibers/cc.

20 Moolgavkar et al. (2010) also used the Cox proportional hazards model with
21 time-dependent covariates for analysis of the Sullivan (2007) cohort with a 15-year lag. The
22 parameter in this study estimates 1.11×10^{-3} per fiber/cc-year (SE = 2.5×10^{-4} per
23 fiber/cc-year), which is very close to Larson et al. (2010a), and, therefore, the lung cancer unit
24 risk based on their analysis would be very close to Larson et al. (2010a). Comparison with
25 McDonald et al. (2004) is difficult, since their outcome is defined as respiratory cancer (ICD-9
26 160-165), which is more expansive than other researchers’ definitions of the outcome as lung
27 cancer, and their sub-cohort of 406 white men employed before 1963—a time period when
28 exposure assessment was less reliable and more likely to include exposure-measurement error;
29 nonetheless, the parameter estimate resulting from the Poisson analysis by McDonald et al.
30 (2004) was 3.6×10^{-3} per fiber/cc-year.

31 EPA based their analyses on the exposures that occurred after 1959, while the Sullivan
32 (2007), Larson et al. (2010a), and Moolgavkar et al. (2010) analyses were based on the cohort
33 including those hired before 1960, and McDonald et al. (2004) included only workers hired

²² Note that EPA results based on the sub-cohort 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 fibers/cc-year (SE = 2.48×10^{-3} per fiber/cc/year, $p = 0.018$).

1 before 1964. As explained in detail in the discussion (see Section 5.4.6) on uncertainty in the
2 exposure assessment, there were only several measurements from the 1950s and one from 1942,
3 and most of the exposure estimation for the early years of the cohort's experience were based on
4 estimates of the ratio of dust to fibers estimated in the late 1960s and extrapolated backwards in
5 time for several decades. Moreover, 706 of the workers hired before 1960 (not necessarily
6 short-term) did not have an exposure measurement assigned to them at all, leading to much
7 larger measurement error. These limitations in the underlying exposure assessment for the years
8 prior to 1968 likely resulted in exposure measurement error that could have attenuated the
9 analytic regression results, thereby yielding a smaller effect estimate for the whole cohort
10 compared to the sub-cohort hired after 1959. It appears the differences in results are mostly
11 attributable to the time periods of analysis and corresponding to the time period measurement
12 errors rather than the analytic approach. The small discrepancy between observed lung cancer
13 deaths between this current assessment and Larson et al. (2010a), described in Section 4.1.1.1, is
14 unlikely to play a role in the difference between risk estimates. Moreover, for the sub-cohort
15 hired after 1959, all deaths are included in the Larson et al. (2010a) lung cancer-counting rules.

16 None of the approaches used by McDonald et al. (2004), Sullivan (2007), nor Larson et
17 al. (2010a) could have been appropriately used for the unit risk of mesothelioma as they are not
18 based on absolute risk metrics of association, and the current assessment considered the relevant
19 metric of association to be the absolute risk. Berman and Crump (2008) did not evaluate risk of
20 mesothelioma. Moolgavkar et al. (2010) used an absolute risk model for mesothelioma. These
21 results are summarized in Table 5-21. The upper bound results for the full cohort presented by
22 Moolgavkar et al. (2010) are about 80% of the IRIS IUR (1988) estimate of mesothelioma slope
23 factor in a similar RTW-type metric, leading to an approximately 80% estimate of the
24 mesothelioma unit risk, as dependence is linear in the mesothelioma slope factor (see Eq. 5-5).
25 This is very close to this current assessment's estimate based on the sub-cohort, which is also
26 about 80% of the IRIS IUR (1988) estimate of mesothelioma risk. Duration of employment is
27 the best metric for the full cohort, and it does not support exposure-response estimation.

28

1 **Table 5-21. Mesothelioma regression results from different analyses of**
 2 **cumulative exposure in the cohort of workers in Libby, MT.** All analyses
 3 used NIOSH-collected exposure data but different cohort definitions, lengths of
 4 follow-up, and lengths of exposure lags to account for cancer latency
 5

Mesothelioma analysis	Cohort definition	Follow-up	Mesothelioma cases/N	Mesothelioma risk (absolute risk model) (per fibers/cc)
This current assessment	Hired post-1959 Exposures 1960–1982	2006	7/880	Upper Bound = 0.12 Central = 0.08
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., 2010a	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

6
 7 ^aReanalysis of Sullivan (2007).
 8
 9

10 **5.4.5.4. Applications of the Combined Mesothelioma and Lung-cancer mortality IUR to**
 11 **Partial Lifetime Environmental Exposure Scenarios**

12 In the application of the IUR, scenarios other than lifetime environmental exposure are
 13 often of interest to risk assessors. The life-table analysis in the (general) IRIS IUR for asbestos
 14 (U.S. EPA, 1988) predicts risk increases as the age of the first exposure decreases. The authors
 15 of that analysis recommended the life-tables in that analysis be consulted when assessing partial
 16 lifetime exposures (U.S. EPA, 1986). In 2009, EPA (Office of Solid Waste and Emergency
 17 Response) provided guidance for calculating risk estimates for less-than-lifetime exposures
 18 based on the source life-table analysis (U.S. EPA, 2009). The age-at-onset of exposure and
 19 duration-dependent unit risks reflect the influence of the time-cubed function in the
 20 mesothelioma model (see Eq. 5-5) (U.S. EPA, 1986, 2009) used in the 1986 assessment.
 21 Because the time-cubed mesothelioma model, or parameterization of exposure metrics, did not
 22 fit the data for mesothelioma mortality from exposure to the Libby Amphibole asbestos, the
 23 approach to estimating risk of partial life exposure recommended by EPA when applying the
 24 general IRIS IUR for asbestos (U.S. EPA, 1988) is not appropriate when applying the Libby
 25 Amphibole asbestos-specific IUR.

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1 Thus, this current assessment recommends that estimates of the risks of less-than-lifetime
2 exposures be computed by simple calculations of average lifetime exposure concentration
3 multiplied by the IUR. This recommendation is consistent with standard Superfund guidance
4 (U.S. EPA, 1986b), where exposures are estimated and averaged across a lifetime exposure, and
5 the IUR is simply applied to calculate excess cancer risk (U.S. EPA, 2005).

6 7 **5.4.6. Uncertainties in the Cancer Risk Values**

8 It is important to consider uncertainties in the derivation of the mesothelioma and
9 lung-cancer mortality risks in this assessment in the context of uncertainties in animal-based
10 health assessments. This assessment does not involve extrapolation from high doses in animals
11 to low doses in humans. This assessment is based on a well-documented and well-studied cohort
12 of workers with adequate years of follow-up to evaluate mesothelioma and lung-cancer mortality
13 risks with PODs within the range of the data. The discussions below explore uncertainty in the
14 derivation of the IUR in order to provide a comprehensive and transparent context for the
15 resulting cancer mortality risk estimates.

16 17 **5.4.6.1. Sources of Uncertainty**

18 Sources of uncertainty in this assessment include

- 19
- 20
- 21 *1) Uncertainty in low-dose extrapolation,*
- 22 *2) Uncertainty in exposure assessment, including analytical measurements*
23 *uncertainty,*
- 24 *3) Uncertainty in model form,*
- 25 *4) Uncertainty in selection of exposure metric,*
- 26 *5) Uncertainty in assessing mortality corresponding to the cancer endpoints,*
- 27 *6) Uncertainty in control of potential confounding in modeling lung-cancer*
28 *mortality,*
- 29 *7) Uncertainty due to potential effect modification,*
- 30 *8) Uncertainty due to length of follow-up,*
- 31 *9) Uncertainty in use of life-tables to calculate cancer mortality unit risks,*

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1 10) *Uncertainty in combining of mortality risks to derive a composite cancer*
2 *mortality IUR,*

3 11) *Uncertainty due to extrapolation of findings in adults to children.*
4
5

6 **5.4.6.1.1. *Uncertainty in low-dose extrapolation***

7 A common source of uncertainty in quantitative cancer risk assessments generally derives
8 from extrapolating from high doses in animals to low doses in humans. Compared to
9 assessments based on animal data, the uncertainty from low-dose extrapolation in this
10 assessment employing occupational epidemiology data is considered to be somewhat reduced for
11 the following reasons. The NIOSH worker cohort developed by Sullivan (2007) includes
12 410 workers employed less than 1 year among the 880 workers hired on or after January 1, 1960.
13 Although short-term workers, on average, experience a mean exposure intensity per day worked
14 greater than workers employed more than a year (Sullivan, 2007), the cohort nevertheless
15 includes many short-term workers with relatively low cumulative occupational exposures.
16 Further, inclusion of salaried workers in the NIOSH cohort (Sullivan, 2007) adds many workers
17 with lower workplace exposure. Thus, while occupational exposure concentrations may be
18 generally higher than typical ongoing environmental concentrations, the low-dose exposures in
19 this occupational database may be representative of nonoccupational exposures.

20 While many occupational epidemiology studies are based on relatively high exposure
21 levels that are beyond the range of common environmental exposures, many in the Libby
22 workers cohort experienced exposures that were near or below the PODs derived from the
23 life-table analysis. The POD for the selected lung-cancer mortality exposure metric was
24 0.191 fibers/cc. The POD for the selected mesothelioma mortality exposure metric was
25 0.106 fibers/cc. Among the workers hired after 1959 who had at least 1 year of occupational
26 exposure ($n = 470$; 20 lung cancer deaths), there were 19 (4%) with average occupational
27 exposure concentrations of less than 0.3 fibers/cc, including 1 lung cancer death (5%).

28 Although data might have been modeled down to a very low cumulative exposure level,
29 the *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a) recommend defining a POD
30 for low-dose extrapolation in order to increase the stability of the IUR estimate at lower
31 exposures, where fewer cancers might be expected. Thus, the uncertainty associated with
32 low-dose extrapolation is somewhat mitigated since the linear extrapolations from the dose
33 associated with the POD from the life-table analyses of each cancer endpoint were encompassed
34 within the observed data range. Nonetheless, some uncertainty remains in the extrapolation from
35 occupational exposures to lower environmental exposures when using a POD.

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1 **5.4.6.1.2. *Uncertainty in exposure assessment***

2 Accurate exposure assessment is generally considered to be a major challenge for
3 occupational epidemiologic studies and is a challenge that is well recognized by the NIOSH
4 investigators (Amandus et al., 1987a). As stated previously in Section 5.4.3.3, while it is
5 generally true that the use of more data is an advantage in statistical analyses because it allows
6 for the computation of more statistically precise effect estimates, this advantage in precision may
7 be offset by a negative impact on the accuracy of the effect estimate if an increase in sample size
8 is accompanied by greater exposure misclassification or other biases. Therefore, EPA decided to
9 base this Libby Amphibole asbestos-specific human health risk assessment upon the mortality
10 experience of workers hired on or after January 1, 1960. EPA's use of the sub-cohort analysis is
11 based on the belief that it is important to accurately estimate the true underlying
12 exposure-response relationships by relying on the most accurate exposure data. The use of this
13 sub-cohort greatly reduces the uncertainty in exposure error compared to evaluations based on
14 the entire cohort. More specifically,

- 15
16
- 17 a) Job category and department codes were completely unknown for 706 of the
18 991 workers' jobs from 1935 to 1959 (71% of the cohort for this time period). These
19 workers were assigned the same exposure concentration (66.5 fibers/cc) for all years
20 without this information. Examination of the post-1959 cohort removes this
21 significant source of exposure misclassification (only 9 of 880 sub-cohort workers did
22 not have department code and job category information).

 - 23 b) Using the more recently hired cohort minimizes the uncertainty in estimated worker
24 exposures based on the JEM, which was informed by air sampling data available in
25 1956 and later years. Although there are still uncertainties in the task-specific
26 exposure estimates from 1960–1967, uncertainty in the assessment of earlier
27 exposure levels is considerably greater.

 - 28 c) Exposure measurements were collected from the area samples and represented
29 exposures for all the workers with the same job code. Statistically, this causes
30 Berkson measurement error effect, which is described later in this section.

31
32 As the EPA exposure-response modeling for mesothelioma and lung-cancer mortality is
33 based on the post-1959 sub-cohort, the remaining discussion of uncertainty in exposure
34 measurement will address these data.

1 **5.4.6.1.2.1. Sources of uncertainty in job history information**

2 Worker exposures for the EPA exposure-response modeling were calculated based on job
3 histories and the JEM from 1960 through 1982 (see Figure 5-3). Overall, there is little
4 uncertainty in the job history information. Regarding exposure estimation for the occupational
5 cohort, the NIOSH investigators (Amandus et al., 1987a) conducted a detailed retrospective
6 exposure assessment to estimate the individual worker exposures. NIOSH used extensive
7 occupational exposure data to construct the time-specific JEM, spanning decades (Amandus et
8 al., 1987a). These data were reabstracted from the workers' employment records for quality
9 assurance (Sullivan, 2007). NIOSH records on work histories and job-specific exposure
10 extended from the 1930s through May 1982. But, the vermiculite mining and milling operation
11 continued on for several years, and some workers were retained through 1993 for plant close-out
12 activities. Only 148 members of the post-1959 cohort ($n = 880$) were employed as of the May
13 1982 employment records when the cohort was enumerated by NIOSH (Sullivan, 2007).
14 Because exposure concentrations in 1982 (see Table 5-7) were generally below 1 fiber/cc with
15 only two locations having concentrations of 1.2 fibers/cc, it is unlikely that these workers'
16 exposures were significantly underestimated.

17
18 *Sources of uncertainty in exposure intensity for the identified location operations*

19 The available exposure data that inform the JEM include over 4,000 air samples, the
20 majority of which were collected after 1967 (see Table 4-1). All of the job location exposure
21 estimates (see Table 5-7) from 1968–1982 were directly informed from air samples collected on
22 membrane filters and analyzed for fibers by PCM. The availability of site- and task-specific air
23 samples for these years provides a good basis for the exposure estimates. However, there are
24 some uncertainties in estimating asbestos exposures using air samples analyzed by PCM.

- 25
26
- 27 **1) PCM analysis does not determine the mineral or chemical make-up of the fiber:** The
28 PCM method defines and counts fibers based on the size (aspect ratio and length) of the
29 particle without regard for the material that makes up the fiber being viewed. The PCM
30 method was developed for use in occupational environments where asbestos was present,
31 and the nature of the fibers should be further evaluated to confirm the fibers viewed
32 under PCM are asbestos. McGill University researchers evaluated the fibers collected on
33 membrane filters in the early 1980s and confirmed the presence of asbestos fibers in the
34 tremolite-actinolite solution series consistent with the Libby Amphibole asbestos
35 (McDonald et al., 1986). NIOSH researchers confirmed the presence of tremolite
36 asbestos in bulk dust samples but not in air samples from the facility (Amandus et al.,
37 1987a). Although less specific to fibers, 60–80% of the airborne dust in the mills in 1968
38 was tremolite, further supporting the presence of asbestos in the air (based on State of

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1 Montana air sampling, and X-ray diffraction analysis by the Public Health Service [PHS
2 correspondence, October 17, 1968]). However, although the presence of mineral fibers in
3 the actinolite-tremolite series was confirmed in the work environment, it is possible that
4 there were also fibers counted by PCM from other materials (such as textiles from clothes
5 and packaging materials). Therefore, it is unknown from these data what proportion of
6 the counted PCM fibers was mineralogically asbestos, or other materials present in the
7 workplace.

8 **2) PCM defines fibers as particles with an aspect ratio greater than 3:1:** There is an
9 ongoing debate in the literature on asbestos toxicity regarding the influence of aspect
10 ratio on relative toxicity. Specifically, in mining environments, it has been speculated
11 that a larger proportion of low aspect ratio fibers from mineral dusts may significantly
12 impact the apparent cancer potency of the measured PCM fibers in those environments
13 (IRIS IUR, 1988, Berman, 2010). There are few data available to understand fiber
14 morphology and fiber aspect ratios in the Libby cohort working environment.
15 Considering the post-1959 cohort, PCM fiber size distribution and aspect ratio data only
16 exist for a set of eight air samples (599 fibers) collected from the wet mill and screening
17 operations and analyzed by the NIOSH researchers (Amandus et al., 1986a). For these
18 air samples, over 96% of the fibers viewed by PCM had an aspect ratio greater than 10:1
19 (see Table 4-2, Amandus et al., 1987a)²³. However, because these samples were
20 provided by the company in the early 1980s, they do not represent conditions in the old
21 wet mill or dry mill operations, which were significantly dustier environments (Amandus
22 et al., 1987a). It is possible that prior to industrial hygiene (IH) modifications in 1974,
23 the dry and old wet mills generated proportionally more mineral dusts than screening and
24 new wet mill operations after IH modifications. No data are available for the mining
25 environment, which would also be expected to generate a range of mineral dusts.
26 Therefore, there is a significant uncertainty about the size and aspect ratio of fibers
27 included in PCM fiber counts for the majority of the post-1960 workers cohort.

28 **3) The resolution of visible PCM fibers:** Current analytical instruments used for PCM
29 analysis have resulted in a standardization of minimum fiber width considered visible by
30 PCM between 0.2 and 0.25 μm . Historical PCM analysis (1960s and early 1970s)
31 generally had less resolution, and fibers with minimum widths of 0.4 or 0.44 μm were
32 considered visible by PCM (Skinke, 1980; Amandus et al., 1987a). McDonald et al.
33 (1986) compared fibers viewed by PCM and TEM and estimated that approximately
34 1/3 of the total fibers could be viewed by the optical microscope. Because 38% of the
35 fibers were $<5 \mu\text{m}$ in length, this implies approximately 30% were not viewable by
36 optical microscopy for other reasons, such as width. However, it is unknown what
37 proportion of that 30% would be viewed with the minimum width resolution of 0.25 μm
38 for later optical microscopy. It is likely that early PCM counts were underestimated
39 relative to the later data for the cohort but by less than a factor of 2.

40

²³ Although Amandus et al. (1987a) 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.

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1
2 Prior to 1968, no air sampling data were available for 23 of the 25 job location operations
3 (see Table 4-2), and the exposure estimates were extrapolated from later air sampling data.
4 Amandus et al. (1987) recognized there is significant uncertainty in the extrapolation of available
5 air sampling data to previous time periods. The researchers took into account major changes in
6 operations and interviewed employees in the early 1980s regarding previous years of operation.
7 The assumptions used to make these extrapolations are clearly stated for each of the plant
8 operations. For four operations, high and low estimates of pre-1968 exposures were provided
9 based on different sets of exposure assumptions (see Table 5-7). For ore loading, there were
10 negligible differences in the exposure estimates for the period from 1960–1967 (10.7 versus
11 9 fibers/cc). For drilling, the river dock, and the bagging plant, there were 3.4-, 2.6-, and
12 2.8-fold differences, respectively, between the high and low estimates of exposure between 1960
13 and 1968.

14 Dry mill exposures between 1960 and 1968 were informed by air sampling for total dust
15 collected in the dry mill facility from 1956–1969 (where total dust was collected by midjet
16 impingers). Amandus et al. (1987a) derived a conversion factor of 4.0 fibers/cc per mppcf to
17 apply to the two location operations in the dry mill during these years. There was a range of
18 conversion factors considered for the dry mill depending on how the dust and fiber air samples
19 (PCM) were grouped and averaged (1.2 to 11.5 fibers/cc per mppcf). A subset of dust and fiber
20 samples available over the same time period (1967–1968) resulted in a ratio of 8.0 fibers/cc per
21 mppcf. In contrast, a ratio of 1.9 fibers/cc resulted when total dust samples from 1969 were
22 compared with fiber samples from 1970. However, both of these subsets had limited numbers of
23 samples available. Therefore, the conversion factor of 4.0 fibers/cc per mppcf was selected
24 based on using the maximum samples available over a time period when the dry mill exposures
25 were considered similar: dust samples (1965–1969) and fiber samples (1967–1971).

26 27 **5.4.6.1.2.2. Sources of uncertainty in the calculation of the job-exposure matrix (JEM)**

28 The exposures in the JEM (see Figure 5-3) were calculated from the exposure intensities
29 of the various task-specific exposure intensities shown by job location operation (see Table 5-7).
30 The uncertainties in the exposure intensity for the job location operations will impact the JEM.
31 Additionally, for each of the job categories in the JEM, NIOSH researchers defined which tasks
32 (job location operations) were conducted and for what proportion of the work day. A TWA
33 exposure for each job category across time was calculated based upon these assumptions and the
34 task-specific exposure estimates. There is a measure of uncertainty in these assumptions for

1 each job category. Additionally, there is inter-individual variation within the job categories.
2 These uncertainties are common to exposure reconstruction for epidemiological cohorts.

3 4 **5.4.6.1.2.3. Uncertainty in the exposure metric**

5 The PCM measurement is the available exposure metric for analysis of Libby worker
6 cohort at this time. Currently, there is no optimal choice of the best dose metric for asbestos, in
7 general, and, in particular, for Libby Amphibole asbestos, even if a TEM-based dose-response
8 JEM was available. Uncertainties related to PCM analytical method are discussed in Section 2.
9 Briefly, PCM cannot distinguish between asbestos and nonasbestos material or differentiate
10 between specific types of asbestos. Further, due to limitations of this methodology, PCM does
11 not take into account fibers smaller than 5 μm in length.

12 13 **5.4.6.1.2.4. Evaluation of the effects of uncertainties in exposure measurement**

14 An understanding of the effects of exposure measurement error on the risks estimated
15 from epidemiologic analyses is important to place these possible exposure measurement errors in
16 context. The effect of exposure measurement error on estimates of the risk of mesothelioma or
17 lung-cancer mortality attributable to exposure depends upon the degree to which that error may
18 be related to the likelihood of mesothelioma or lung-cancer mortality. Exposure measurement
19 error that is similar in pattern among workers who died of lung cancer to exposure measurement
20 error in people who did not die of lung cancer is a nondifferential exposure measurement error.
21 Differential exposure measurement error that is associated with the outcome can cause bias in an
22 effect estimate towards or away from the null, while nondifferential exposure error typically
23 results in bias towards the null (Rothman, 1998). From the above evaluation of uncertainties,
24 there is no indication that the uncertainties in job history information, exposure estimates for
25 specific tasks, or calculation of the JEM would be differential based on the cancer health
26 outcome data. Therefore, these uncertainties are considered nondifferential, and the general
27 result is likely to be an attenuation in risk estimates towards the null (that is, the addition of
28 random noise to a clear signal tends to reduce the clarity of the observed signal and the
29 avoidance of random noise—here from poor quality exposure measurements—results in a
30 stronger observed signal).

31 Generally speaking, if the exposure concentrations estimated by NIOSH were
32 systematically too high, then the associated risks of exposure estimated in the regression analysis
33 would be low since the same actual risk would be spread across a larger magnitude of exposure.
34 Similarly, if the exposure concentrations estimated by NIOSH were systematically too low, then
35 the associated risks of exposure estimated in the regression analysis would be too high. From the

1 above evaluation, the majority of the sources of uncertainty are not systematic. There are a few
2 areas of uncertainty that may be classified as biased:

- 3
4
- 5 1) High- and low-exposure estimates for four job location operations were provided
6 between 1960 and 1967. Amandus et al. (1987a) chose the high estimates of
7 exposure for these job location operations when calculating the JEM. Therefore,
8 there will be a bias towards the high end for the job categories informed by these
9 data. There was a 1.1- to 3.4-fold difference between the high and low estimates.
10 This difference will be less pronounced where these exposure concentrations are
11 averaged with other job location operations in the JEM and across multiple jobs for
12 the majority of the workers (see Figure 5-3).

 - 13 2) Current PCM analysis would count more fibers relative to early PCM methods based
14 on minimum fiber width resolution. For example, Amandus et al. (1987a) used a
15 minimum width cutoff of 0.44 in their review of PCM fibers in the 1980s, which may
16 have resulted in as much as a twofold underestimate compared to current PCM
17 methods with a width resolution of 0.25 μm . Additionally, as PCM methodology has
18 developed over time, it is unknown when PCM results from company records would
19 be considered relatively standard to a minimum width resolution between 0.2 and
20 0.25 μm . Also, prior to standardization of PCM to 0.25- μm minimum width, there
21 was inter-laboratory variability as well. Therefore, the size distribution of PCM
22 fibers (e.g., minimum width) reported in the JEM may have changed over time.
23 Although theoretically a systematic bias, given the years for which PCM data are
24 available, this is likely an insignificant effect.

 - 25 3) Asbestos was a contaminant of vermiculite that was the primary object of production.
26 Mine, old dry mill, and wet mill ambient air may have contained material other than
27 asbestos that could have contributed to PCM fiber count. The exposures in the old
28 dry and wet mills and mine location may have included a greater proportion of dust to
29 fibers than tasks using the ore and refined vermiculite after the new wet mill became
30 operational. It is possible there is a systematic over-count of fibers in the dusty
31 environment due to interference from mineral fragments. This likely impacts the
32 exposure intensity for 23 of 25 job location operations within the mine and old dry
33 mill. Estimated exposures from job categories that include these operations may be
34 biased upwards.

35
36
37 Nondifferential measurement error in a continuous exposure can be of the classical or
38 Berkson type and typically arises in environmental and occupational settings as a mixture of the
39 two forms (Zeger et al., 2000). Classical measurement error occurs when true exposures are
40 measured with additive error (Carroll et al., 2006) and the average of many replicate

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1 measurements, conditional on the true value, equals the true exposure (Armstrong, 1998). This
2 error is statistically independent of the true exposure that is being measured and attenuates true
3 linear effects of exposure, resulting in effect estimates in epidemiologic studies that are biased
4 towards the null (Zeger et al., 2000; Armstrong, 1998; Heid et al., 2004). Such errors occur
5 when the mean values of multiple local air samples are used.

6 Berkson measurement error is independent of the surrogate measure of exposure (Heid et
7 al., 2004; Berkson, 1950) and is present when the average of individuals' true exposures,
8 conditional on the assigned measurement, equals the assigned measurement. Berkson
9 measurement error can arise from the use of local area mean sampled exposures to represent the
10 individual exposures of people in that area—even when the estimated area mean is equal to the
11 true underlying mean (i.e., no classical measurement error). Examples of random variability in
12 personal behavior that may produce Berkson measurement error in personal exposure estimates
13 include the volume of air breathed per day among the workers and the effectiveness of an
14 individual's nasal filtration at removing contaminants. In general, Berkson measurement error is
15 not thought to bias effect estimates but rather increases the standard errors of effect estimates
16 (Zeger et al., 2000). However, some epidemiologic studies have suggested that Berkson
17 measurement error can produce a quantitatively small bias towards the null in some analyses
18 (Burr, 1988; Reeves et al., 1998; Kim et al., 2006; Bateson and Wright, 2010).

19
20 **5.4.6.1.2.5. Uncertainties in the levels and time course of asbestos exposure for the libby**
21 **workers also adds uncertainty to the evaluation of the relative fit of different**
22 **exposure metrics exposure to other kinds of asbestos and residential exposure**

23 Another source of uncertainty in the estimation of exposures in the Libby workers cohort
24 is the potential contribution of nonoccupational or residential exposures as well as exposures to
25 other kinds of asbestos in employment before or after working in Libby.

26 Many of the workers resided in Libby, MT, before and/or after their employment at the
27 mining and milling facilities ended. The vermiculite from the mine had been used at numerous
28 sites around the town, including baseball fields around the expansion plant and as filler in
29 gardens (U.S. EPA, 2001, 2010). Exposure to asbestos could have occurred among individuals
30 outside of the workplace, particularly through activities with the potential of stirring up of dirt or
31 other materials that had been mixed with the vermiculite (Weis, 2001). The results of
32 community sampling indicated that even 10 years after mill operations ceased during some
33 activities, asbestos fiber concentrations in the air could exceed OSHA standards established for
34 the protection of workers (Weis, 2001).

35 Therefore, the workers' actual personal exposures as the sum of occupational and
36 nonoccupational exposures are likely to have been underestimated by the use of estimated

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1 Libby-related occupational exposure alone. The difficulty stems from the lack of data on
2 residential exposures and lack of information on pre- and postemployment residence of the
3 Libby workers. Nonoccupational exposures were likely to have been smaller in magnitude than
4 the occupational exposures, but workers may have lived in and around Libby, MT, for many
5 more years than they were exposed occupationally. The impact of residential exposure could be
6 more prominent for workers with lower occupational exposure who resided in Libby for a long
7 time. Whitehouse et al. (2008) has reported several cases of mesothelioma among residents of
8 the Libby, MT region who were not occupationally exposed. However, since the report by
9 Whitehouse et al. (2008) details only the cases and does not define or enumerate the population
10 from which those cases were derived, computed relative risks from nonoccupational exposures
11 were not available. ATSDR (2000) reported higher relative risks of mesothelioma among the
12 population of Libby, MT, including former workers residing in Libby, but did not provide
13 relative risk for nonoccupational exposure. Instead, the ATSDR report on mortality (2000)
14 grouped cases among the former workers with nonoccupationally exposed cases. Therefore, it is
15 not clear what the magnitude of the contribution of workers' nonoccupational exposures was to
16 their overall risk.

17 Some of the occupational workers with lower exposures, such as short-term workers, may
18 have either been high school or college students working during the summer or may have been
19 transient workers who may not have stayed for a long time in Libby. Sullivan (2007) analyzed
20 differences between short- and long-term workers and reported little difference between the
21 groups except for age at hire. As the short-term workers were younger on average, this
22 supported the suggestions that some of the short-term workers may have been college students
23 working during the summer. This population of short-term workers is not well defined;
24 however, it is possible that short-term transient workers could potentially have been exposed to
25 other kinds of asbestos or other lung carcinogens in their non-Libby occupational career, which
26 might have affected their pre- and post-Libby risk profile for asbestos exposure. While their
27 occupational histories other than working in Libby are unknown, it is very unlikely that they
28 include exposures of the magnitude that were encountered in the Libby mine and mill. The
29 impact of these uncertainties on regression slopes is difficult to evaluate. However the slope
30 may be somewhat underestimated as an observed increase in risk would be attributed to a larger
31 exposure differential than might have been present due to the addition of nonoccupational
32 exposures. There will also be a downward bias from random exposure measurement error with
33 lower occupational exposure affected disproportionately; however, the magnitude of this bias
34 would be expected to be small.

35

1 **5.4.6.1.2.6. Conclusion regarding uncertainty in exposure assessment**

2 Overall, there are likely to be multiple sources of uncertainty attributable to exposure
3 measurement error. It is possible that systematic error may have been introduced into the
4 exposure intensities assigned to several of the job location operations discussed above. In each
5 case, these errors in estimating exposures were overestimates. The magnitude of the potential
6 overestimates of drilling and dry and old wet mill exposures is uncertain. The dust-to-fiber
7 conversion ratio applied to the dry mill during 1960–1967 could be an over or underestimate by
8 as much as twofold. Random error in the measurement of dust or fibers would likely have
9 produced an underestimation of risk. There is no known bias in the assumptions to extrapolate
10 exposure to pre-1968 location operations outside of the dry mill, and random bias would also
11 likely have produced an underestimation of risk.

12
13 **5.4.6.1.3. *Uncertainty in model form***

14 For mesothelioma mortality, the Poisson regression model is commonly used for rare
15 outcomes and has been applied by McDonald et al. (2004) and Moolgavkar et al. (2010) to
16 model mesothelioma risk in the Libby worker cohort. For lung-cancer mortality, the Cox
17 proportional hazards model is a well-established method that is commonly used in cohort studies,
18 including by Larson et al. (2010a) and Moolgavkar et al. (2010) for the Libby worker cohort,
19 because this type of survival analysis takes into account differences in follow-up time among the
20 cohort. Larson et al. (2010a) conducted Poisson regression analyses and reported that their lung
21 cancer results using this different model form were similar to those from their extended Cox
22 proportional hazards models, but those results were not shown.

23 Both of these model forms allow for the evaluation and control of important potential
24 confounding factors such as age, sex, and race, and for the modeling of exposure as a continuous
25 variable. Both model forms yielded exposure-response results with good fit to the occupational
26 exposure data. The default assumption of the extended Cox proportional hazards model as well
27 as the Poisson regression model is that all censoring (due to death or loss to follow-up) is
28 assumed to be independent of exposure to the Libby Amphibole asbestos (e.g., death in an
29 automobile accident or moved to Canada). However, exposure to Libby Amphibole asbestos
30 may be causing deaths from other causes such as asbestosis or nonmalignant respiratory disease
31 (Larson et al., 2010a), which is referred to as dependent censoring. The concern is that the
32 observation of lung-cancer mortality may be precluded by mortality from other causes.

33 In the cohort of 880 workers hired after 1959, 32 died of lung cancer, while 10 died of
34 asbestosis, and 21 died of nonmalignant respiratory disease. The mean length of follow-up from
35 the date of hire until death for the workers who died of lung cancer was 24.9 years. However,

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1 the mean length of follow-up for the workers who died of asbestosis or nonmalignant respiratory
2 disease was 30.4 years, so it does not appear that early deaths from other causes associated with
3 exposure to the Libby Amphibole asbestos (Larson et al., 2010a) would have precluded many
4 cases of lung cancer. This implies that any potential bias in the lung cancer risk estimates due to
5 dependent competing risks is small.

6 With respect to mesothelioma mortality, it should be noted that the exposure-response
7 modeling is limited by the number of deaths. However, dependent censoring, as described
8 above, is not accounted for in the Poisson regression model and likely causes a downward bias in
9 the estimation of risk. The mean length of follow-up for the workers who died of mesothelioma
10 was 30.1 years, and there is some evidence that early deaths from other exposure-related causes
11 precluded an individual's risk of death from mesothelioma; only lung cancer exhibited a shorter
12 average follow-up time compared to mesothelioma, and in 419 cases of mesothelioma,
13 mesothelioma and lung cancer were never coidentified (Roggli and Vollmer, 2008).

14 15 **5.4.6.1.4. *Uncertainty in selection of exposure metric***

16 There is uncertainty about what metric should be used for modeling exposure to Libby
17 Amphibole asbestos. The previous IRIS IUR assessment for asbestos (1988) found that
18 cumulative exposure with a 10-year lag was the best metric for lung-cancer mortality, and a more
19 complicated model (see Eq. 5-5) based on average cohort exposure intensity, average cohort time
20 since first exposure, and average duration of employment was the best metric for mesothelioma
21 mortality. This current assessment evaluated these models, but also models that include
22 unlagged and lagged cumulative exposure with and without a half-life of various lengths, and
23 RTW exposure with and without a half-life. In the analysis of comparative model fit, lagged
24 cumulative exposure with a half-life provided the best fits for both mesothelioma and
25 lung-cancer mortality associated with Libby Amphibole asbestos. However, evaluation of
26 20-year lag and longer lag times for mesothelioma was not possible, as the earliest mesothelioma
27 death happened less than 20 years from the start of the exposure, and, hence, exposure was
28 zeroed out, and the fit of any model with 20-year lag was very poor. Latency time for
29 mesothelioma may be as long as 60–70 years (e.g., Bianchi and Bianchi, 2009), so the precise
30 lag time is uncertain.

31 In evaluating the data on lung fiber burden, Berry et al. (2009) estimated the range of the
32 half-life for crocidolite to be between 5 and 10 years. That range is consistent with the finding of
33 a 5 to 10-year half life with 10–15 years lag that provided the best fit to the Libby workers cohort
34 mesothelioma mortality data. Similarly, recent publications indicate that the relative risk of lung
35 cancer due to asbestos exposure declines 15–20 years after the cessation of exposure to asbestos

1 (Hauptmann et al., 2002; Magnani et al., 2008). The marginally best fit for the Libby workers
2 cohort lung-cancer mortality data was for CE models with a 5 to 20-year half life and 10-year
3 lag. However, the precise lag and half-life times are somewhat uncertain. Sensitivity analysis
4 that excluded people with high exposure during 1960–1963 (see Section 5.4.3.6.4) provides
5 further evidence that distinguishing between various lags and decays may be difficult with these
6 data. A limitation of this sensitivity analysis is the decrease in the number of cases, especially
7 for mesothelioma. Resolving this uncertainty would require longer follow-up time, which would
8 allow for a sub-cohort analysis of workers hired in 1967 or afterwards (when exposure estimates
9 began to be based on PCM measurements) until a sufficient number of cases would be available
10 for additional analysis.

11 These simulated decay models were derived mathematically to approximate underlying
12 biological processes that are not well understood, and their better fit is based on maximizing the
13 likelihood for the workers cohort and may not necessarily apply to the environmental exposure
14 patterns. Nonetheless, while the mode of action for carcinogenicity is unknown, the models
15 incorporating a half-life in the exposure metric were clearly preferable for mesothelioma
16 mortality, and the goal of the regression modeling effort was to identify the best fitting exposure
17 model for the Libby worker cohort.

18 The selection of the exposure metric is a source of cross-metric variability discussed in
19 Section 5.4.5.3, and the IUR incorporates this variability. The difference between this value and
20 the value derived from the best fitting exposure model describes the quantitative uncertainty,
21 which is less than twofold.

22 23 **5.4.6.1.5. *Uncertainty in assessing of mortality corresponding to the cancer-specific endpoints***

24 As well established in the literature, mortality rates calculated from death certificates are
25 lower than the true rate of death due to both lung cancer, and to a larger degree, mesothelioma
26 (lung cancer sensitivity: ranging from 86% in an asbestos cohort [Selikoff and Seidman, 1992] to
27 95% in general [Percy et al., 1981]; mesothelioma sensitivity: ranging from 40% for ICD-9
28 [Selikoff and Seidman, 1992] to about 80% for ICD-10 [Camidge et al., 2006; Pinhiero et al.,
29 2004]). This underestimation of the true rate will result in a lower estimated risk compared with
30 that which would be estimated based on the true rate. The underestimation of risk is much more
31 pronounced for the absolute risk model (mesothelioma) than for the relative risk model (lung
32 cancer). Misdiagnosis rates would need to be quite disparate in the cohort and the comparison
33 population to impact relative risks, and this is unlikely for internal controls that were used in the
34 lung cancer analysis using the Cox proportional hazards model. Therefore, EPA considered use
35 of a procedure to adjust risks for mesothelioma—but not for lung cancer—underascertainment

1 (see Section 5.4.5.1.1). This procedure makes certain assumptions, in particular, that an
2 adjustment factor derived for the full cohort applies to the sub-cohort hired after 1959, and that
3 the rate of misdiagnosis of peritoneal mesotheliomas has not improved recently, and that the
4 proportion of peritoneal mesotheliomas in the cohort is estimated from the available information
5 on the type of mesothelioma in one-third of mesothelioma cases. However, overall uncertainty
6 in this adjustment is low, and the application of the adjustment reduces the bias associated with
7 the diagnostic underascertainment.

8 The endpoint for both mesothelioma and lung cancer was mortality, not incidence. The
9 latter is generally desirable, but median survival with lung cancer and, especially, mesothelioma
10 is not very long, so uncertainty related to the endpoint being death and not incidence is low.

11 There is evidence that other cancer endpoints may also be associated with exposure to the
12 commercial forms of asbestos. IARC concluded that there was sufficient evidence in humans
13 that commercial asbestos (chrysotile, crocidolite, amosite, tremolite, actinolite, and
14 anthophyllite) was causally associated with lung cancer and mesothelioma, as well as cancer of
15 the larynx and the ovary (Straif et al., 2009). Among the entire Libby workers cohort, only
16 2 deaths were found to be due to laryngeal cancer, and there were no deaths from ovarian cancer
17 among the 24 deaths of 84 female workers. The lack of sufficient number of workers to estimate
18 risk of ovarian cancer is an uncertainty in an overall cancer health assessment.

19 The remaining uncertainties attributed to assessing mortality corresponding to the cancer
20 endpoints are considered to be low.

22 **5.4.6.1.6. *Uncertainty in control of potential confounding in modeling lung cancer***

23 It is well known that smoking is a strong independent risk factor for lung cancer and may
24 have a synergistic effect with asbestos exposure (Wraith and Mengersen, 2007). In contrast,
25 smoking is not considered a risk factor for mesothelioma (Mossman et al., 1990; Selikoff and
26 Lee, 1978).

27 As an important potential confounder of the lung-cancer mortality analysis, the possible
28 effect of smoking on the estimated risk of lung-cancer mortality associated with exposure to
29 Libby Amphibole asbestos needs to be evaluated to the fullest extent possible. This
30 consideration was discussed in Amandus and Wheeler (1987) and in Section 4.1.1.3.

31 Additionally, W.R. Grace and Co. instituted a smoking ban on the property in 1979
32 (Peacock, 2003). Information is not available as to the effect of this smoking ban at work on
33 smoking patterns outside of the work environment. About 30% of the sub-cohort was still
34 employed in 1979 and all of the post-1959 cohort had been terminated by May 1982, so the
35 impact of a workplace smoking ban on cohort smoking history may explain the higher proportion

1 of former smokers in the Amandus and Wheeler (1987) data. Lung cancer risks in ex-smokers
2 decrease over time compared to lung cancer risks in continued smokers. A reduction of smoking
3 in the Libby worker population may lead to fewer observations of lung cancer deaths in later
4 years of the cohort study than would have occurred in the absence of the smoking restrictions.
5 Changes in smoking behavior during the course of the epidemiological observation period would
6 lead to changes in the observed time course of lung cancer death rates. This issue is related to
7 potential effect modification of lung-cancer mortality described in Section 5.4.6.1.7.

8 Without high-quality individual-level data on smoking that could be used to control for
9 potential confounding, it is still possible to comment upon the likelihood and potential magnitude
10 of confounding and the impact any confounding would be expected to have on the lung-cancer
11 mortality risk estimates. Confounding can be controlled for in a number of ways including by
12 modeling and by restriction. Restriction of the study population can reduce any potential
13 confounding by making the resulting population more similar. For instance, there can be no
14 confounding by gender when a study population is restricted to only men. This assessment
15 restricted the study population to those workers hired after 1959. Smoking habits have changed
16 over time, and it can reasonably be assumed that the range of smoking habits among those hired
17 after 1959 is less variable than that among the whole cohort, particularly because of the narrower
18 range of birth cohorts represented in this sub-cohort. This should have the effect of reducing
19 some of the potential for confounding. Analytic examinations of potential confounding are
20 discussed below.

21 Additionally, the extended Cox proportional hazards models controlled for date of birth,
22 which effectively controls for any secular trends in confounders over time (Tableman and Kim,
23 2004). Amandus and Wheeler (1987) cite data from the U.S. Public Health Service (1979)
24 showing a steady decrease in the prevalence of current smoking from 52.9% in 1964 when the
25 U.S. Surgeon General's report on smoking was released to 42.3% in 1970 and 37.5% in 1978
26 (U.S. Surgeon General, 1990). If current smoking were a meaningful confounder, such a
27 reduction in smoking rates over time should have produced a noticeable distortion in the
28 proportionality of the hazards as the magnitude of confounding by smoking changes with
29 smoking prevalence. No violation of the proportional hazards assumption was observed in the
30 context of the Cox proportional hazards model; hence, there is no evidence of confounding by
31 smoking in the analyses of workers hired after 1959.

32 Lastly, Richardson (2010) describes a method to determine if an identified exposure
33 relationship with lung cancer is confounded by unmeasured smoking in an occupational cohort
34 study. EPA implemented this methodology to model the potential effects of Libby Amphibole
35 asbestos on the risk of COPD mortality on the sub-cohort of workers hired after 1959 (see

1 Section 5.4.3.6.5). Summarizing these findings, EPA used the method described by Richardson
2 (2010) to evaluate whether exposures to Libby Amphibole asbestos predicted mortality from
3 COPD as an indication of potential confounding by smoking and found a nonsignificant negative
4 relationship, which was inconsistent with confounding by smoking.
5

6 **5.4.6.1.7. *Uncertainty due to potential effect modification***

7 Among the 32 deaths from lung cancer in workers hired after 1959 that were used to
8 estimate the unit risk of lung-cancer mortality (see Section 5.4.5.2), data on smoking listed 16 as
9 smokers, 4 as former smokers, and 12 of the 32 had missing data. Thus, data to support an
10 estimate of the risk of Libby Amphibole asbestos among known nonsmokers were not available.

11 It is theoretically possible that the risk of lung-cancer mortality estimated in this current
12 assessment is a reflection of a positive synergy between smoking and asbestos, and that the
13 adverse effect of Libby Amphibole asbestos among the potentially nonsmoking workers has been
14 overestimated. The unit risk of the lung cancer estimate herein and the combined mesothelioma
15 and lung-cancer mortality IUR would then be health protective for any population that had a
16 lower prevalence of smoking than that of the Libby worker cohort. However, if the smoking ban
17 did diminish the effect of smoking, then any overestimation would be somewhat mitigated.
18

19 **5.4.6.1.8. *Uncertainty due to length of follow-up***

20 There is some potential uncertainty regarding the length of follow-up for cancer
21 mortality, even more so with the restriction of the cohort to those workers hired after 1959. The
22 hire dates among this subset of the cohort ranged from January 1960 to November 1981 (the
23 mean date of hire was May 1971). Follow-up continued until the date of death or
24 December 31, 2006, whichever occurred first. Therefore, the range of follow-up was from 25 to
25 46 years, with a mean of more than 35 years.

26 However, for mesothelioma mortality, the length of the latency period is considerably
27 longer. Suzuki (2001) reviewed 1,517 mesothelioma cases from 1975 through 2000 and was
28 able to estimate the latency for 800. Suzuki (2001) reported 17% of cases had a latency of less
29 than 30 years with 52% of cases with a latency of less than 40 years. Bianchi and Bianchi (2009)
30 estimated the mesothelioma latency in 552 cases and reported mean latency periods of 35 years
31 among insulators, 46 years among various industries, and 49 years among shipyard workers.

32 The effect of insufficient length of follow-up for mesothelioma mortality would be to
33 underestimate the risk of exposure since there would be workers who may eventually die of
34 mesothelioma that are not counted in this current assessment. Because the risk of mesothelioma
35 mortality is evaluated as an absolute risk, the unit risk of mesothelioma mortality may reasonably

1 be expected to rise with time moderated by the increase in person-years of follow-up. According
2 to the results of Suzuki (2001) and of Bianchi and Bianchi (2009), a mean length of follow-up of
3 35 years may only have captured half of all eventual mesothelioma mortality cases among the
4 Libby workers hired after 1959. If this were so, then the unit risk of mesothelioma mortality
5 could be larger than was estimated from existing data, depending on the relationship between the
6 number of additional deaths and increase in person-years.

8 **5.4.6.1.9. *Uncertainty in use of life-tables to calculate cancer mortality IUR***

9 The life-table procedure computes the extra risk of death from birth up to 85 years of age,
10 in part, because this is how national cancer incidence and mortality rate data that are one basis of
11 the life-tables are made available (see 2003–2007 SEER Table 15.10, age-specific U.S. death
12 rates). Because the prevalence of cancer mortality is a function of increasing age, this cut-off at
13 age 85 ignores a small additional risk of lung-cancer mortality among a small percentage of
14 people who have the higher background risk. This has the effect of slightly underestimating the
15 IUR that would be derived if the life-table were extended for an additional period of time,
16 accounting for longer life spans. Extension of the life-table analysis to people over the age of
17 85 requires an additional assumption. Assuming that having attained the age of 85 years, the
18 additional life expectancy is 5 years, then the lung-cancer mortality unit risk based on the LEC_{01}
19 would be somewhat larger—on the order of 5–10%—slightly more than the additional
20 mesothelioma mortality risk if the life-tables were extended.

22 **5.4.6.1.10. *Uncertainty in combining of risk for composite cancer IUR***

23 For the purpose of combining risks, it is assumed that the unit risks of mesothelioma and
24 lung-cancer mortality are normally distributed. Since risks were derived from a large
25 epidemiological cohort, this is a reasonable assumption supported by the statistical theory, and
26 uncertainty related to it is low.

28 **5.4.6.1.11. *Uncertainty in extrapolation of findings in adults to children***

29 The analysis of lung-cancer mortality specifically tested and confirmed the assumption
30 that the relative risk of exposure is independent of age within the age range of the occupational
31 sub-cohort hired after 1959. However, no comparable data are available to estimate the lifetime
32 risk from early life exposures. The life-table procedure is conducted so as to initiate exposure at
33 age 16 to represent adult exposures. Then, the adult-only-exposure IUR estimates derived from
34 the life-table analysis need to be rescaled to a 70-year lifespan in order to yield the standard
35 lifetime IUR, allowing risk estimate calculations involving less-than-lifetime exposure scenarios,

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1 in the standard manner. After rescaling, the resulting “adult-based” IUR estimate (in contrast to
2 the unscaled “adult-only-exposure” IUR estimate obtained from the life-table calculations) can
3 be employed seamlessly by the end-user in the same manner as for an adult-based IUR estimate
4 derived from a rodent bioassay. Lack of published information on risks associated with Libby
5 Amphibole asbestos-specific exposure during childhood is the uncertainty associated with the
6 proposed extrapolation. If such information is subsequently published, the extrapolation
7 procedure can be updated.

8 9 **5.4.6.2. Summary**

10 In the discussion of the overall uncertainty in the IUR, it is important to distinguish
11 between uncertainty that encompasses both the direction and the magnitude from uncertainty
12 with known directional effects on the IUR but of unknown magnitude. In this summary, only the
13 latter uncertainties, which may result in underestimated or overestimated risk, are listed below.
14 Uncertainties that are not thought to alter the estimated magnitude of the risk in a systematic
15 direction are not included in this summary.

16 The sources of uncertainty that could lead to a likely underestimation of the cancer risk
17 value include the following:

- 18
19
- 20 • *Use of historical PCM exposure measurements.* Because asbestos was a
21 component of vermiculite that was the primary object of production, mine and dry
22 and old wet mill ambient air may have contained material other than asbestos that
23 could have contributed to fibers counted by PCM. Therefore, it is possible that
24 exposure estimates for some, or possibly a large portion of the cohort, are
25 overestimated, and, therefore, the resulting IUR may be underestimated.

 - 26 • *Measurement error in exposure assessment and assignment.* This current
27 assessment showed that unit risk results from analysis of the lung-cancer
28 mortality in the full cohort (see Table 5-21) compared to the sub-cohort hired
29 after 1959 may have been attenuated as much as 2–6 times (see Section
30 5.4.6.1.2.4). By excluding those cohort members hired before 1960 for whom
31 there was insufficient work history information to estimate their exposures, the
32 unit risk for lung cancer was less attenuated due to exposure measurement error.
33 However, exposure measurements from the 1960s are also imperfect and include
34 a lesser degree of exposure measurement error, which could have led to
35 underestimated risk even in the sub-cohort hired after 1959.

 - 36 • *Limited length of follow-up.* Absolute risk is used for mesothelioma; therefore,
37 the unit risk of mesothelioma mortality could be larger than was estimated from

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1 existing data, depending on the relationship between the number of additional
2 deaths and an increase in person-years.

- 3 • *Use of life-tables to calculate the IUR based on cancer mortality.* The
4 lung-cancer mortality unit risk based on the LEC_{01} would be somewhat larger,
5 about 5–10%, and the mesothelioma unit risk would be slightly less (about 3%)
6 than that if the life-tables were extended from 85 to 90 years to account for longer
7 life spans.
- 8 • *Small number of women and ovarian cancer.* While asbestos is causally
9 associated with increased risks of ovarian cancer (Straif et al., 2009), there were
10 only 84 women in the whole cohort, and there were no deaths from ovarian cancer
11 among 24 total deaths. To the extent that there was an increased risk of ovarian
12 cancer in the Libby workers cohort due to inhalation exposures that was
13 unobserved, then the IUR would be somewhat underestimated. However, it was
14 not possible to estimate the magnitude of this underestimation on the total cancer
15 risk.
- 16 • *Dependent competing risks.* Competing risk of mortality from other diseases
17 related to exposure may have resulted in underestimates of the risk of mortality
18 from either mesothelioma or lung cancer. The mean length of follow-up for the
19 Libby workers who died of mesothelioma was to 30.1 years, and evidence exists
20 (Suzuki, 2001; Bianchi and Bianchi, 2009) that early deaths from other
21 exposure-related causes could have precluded an individual's risk of death from
22 mesothelioma. However, it was not possible to estimate the magnitude of this
23 effect on the total cancer risk.

24
25
26 The sources of uncertainty that could lead to a likely overestimation of the cancer risk
27 value include the following:

- 28
29
30 • *Potential residual confounding and effect modification.* The unit risk of
31 lung-cancer mortality estimated herein, and the combined mesothelioma and
32 lung-cancer mortality IUR, would over-estimate the risk in any population that
33 had a lower prevalence of smoking than that of the Libby worker cohort. Since
34 the Libby worker cohort had a large prevalence of smokers and ex-smokers and
35 no known nonsmokers developed lung cancer, it is also possible that estimated
36 risk for lung cancer is actually risk for an interaction of lung cancer and smoking,
37 and effects of smoking and asbestos are known to be between additive and
38 multiplicative (see Section 4).

39
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1 exposures (both occupational and community), as well as the potential for ongoing exposures to
2 waste materials, contaminated soils and vegetation, and consumer products (e.g., vermiculite
3 attic insulation; see Section 2.3) (ATSDR, 2008, 2001).

4 There are many ways in which workers and residents in Libby, MT, and the surrounding
5 communities may have been exposed while the mining and milling operations were active.
6 Historical routes of exposure include (1) occupational exposure; (2) take-home exposure for
7 household contacts of the workers (including children); (3) dust/fiber emissions to the
8 community from the milling and exfoliating facilities; (4) distribution of waste material into the
9 community as fill (including yards and recreational areas); (5) use of vermiculite attic insulation
10 in homes; (6) use of vermiculite in gardening/horticulture; and (7) children playing in the waste
11 stoner rock piles (ATSDR, 2001). Other than documentation of dust and fiber exposure levels
12 for mine and mill workers, there are few data to inform the levels of exposure to household
13 contacts and community members during mine and mill operations. Although no historical
14 exposure measurements are available from the homes of the workers, the EPA has conducted
15 sampling to determine exposure levels from vermiculite and waste materials that remain in the
16 community (U.S. EPA 2006, 2001; see Appendix B). These data provide information useful to
17 understand what historical exposures might have been for similar activities. More recently, EPA
18 has characterized exposures for various exposure pathways in the community and continues to
19 evaluate exposure potential in the ongoing efforts for cleanup (U.S. EPA, 2010b).

20 Outside of Libby, MT, vermiculite concentrate and exfoliated product was shipped to
21 271 domestic sites that served as processing facilities (GAO, 2007). These sites included
22 exfoliation plants (e.g., for the production of vermiculite insulation) as well as nonexfoliation
23 facilities (e.g., production of gypsum wallboard). The vermiculite concentrate was exfoliated by
24 heat-induced expansion resulting in vermiculite produced for commercial purposes. Both the
25 commercial vermiculite and the waste stoner rock (i.e., residual waste stoner rock from
26 exfoliation) contained Libby Amphibole asbestos fibers. Potential exposure routes in these
27 communities located around the country parallel the exposures in Libby, MT, including
28 occupational exposures, take-home exposures from workers, and children playing in the piles of
29 waste stoner rock near the facility (ATSDR, 2008, 2005). Waste materials (expanded
30 vermiculite and waste stoner rock) from some of these facilities were also used for fill in local
31 communities, potentially creating additional exposure pathways based on an Agency for Toxic
32 Substances and Disease Registry (ATSDR) review of 28 facilities, and a survey of the Western
33 Minerals Plant, MN (ATSDR, 2008, 2003). Few historical samples are available from these
34 facilities that could be used to quantify the exposure potential for workers or for the surrounding
35 communities (ATSDR, 2008, 2005). Air modeling conducted for one exfoliating facility in

1 Minnesota does provide support for the potential of dust/fiber emissions from exfoliating plants
2 to impact ambient air quality in the vicinity of the plant (ATSDR, 2005).

3 While the mine was active, there was potential exposure to commercial products
4 containing vermiculite from Libby, MT, especially in gardening soils and vermiculite attic
5 insulation. No studies have evaluated the potential for consumer exposure when vermiculite
6 from Libby, MT, was employed as a soil amender, but air sampling at one facility where this was
7 produced (O.M. Scott facility in Marysville, OH) demonstrated that workers handling this
8 material during manufacture were exposed to Libby Amphibole asbestos fibers (see
9 Section 5.2.3.1). There is potential for exposure in homes that contain vermiculite attic
10 insulation from Libby, MT, where residents and workers might enter attics for various uses,
11 repairs, and renovations (see Section 2.3.3).

13 **6.1.2. Fiber Toxicokinetics**

14 There is no specific information available on the fiber toxicokinetics of Libby Amphibole
15 asbestos. However, as a mineral fiber, the characteristics that define the deposition, clearance,
16 and translocation of other amphibole fibers might apply to Libby Amphibole asbestos. As
17 discussed in Section 3, the specific fiber dimensions and density of Libby Amphibole asbestos
18 will determine the probable pattern of deposition in the respiratory tract and other tissues (e.g.,
19 pleura, peritoneum). Based on the fiber-size profile of airborne Libby Amphibole asbestos
20 fibers, deposition is expected throughout the respiratory tract including the alveolar regions.
21 Less is known about mineral fiber translocation to other target tissues in general, and, to date, no
22 studies have specifically examined translocation following exposure to Libby Amphibole
23 asbestos.

24 As with other mineral fibers, clearance is likely to occur via the mucociliary apparatus in
25 the upper respiratory tract and the mucociliary escalator for those fibers deposited in the trachea
26 and bronchioles. This clearance is enhanced by macrophage action, which may transport some
27 of the fibers from the alveolar sac to the mucociliary system. Fibers may also be dissolved in
28 lung fluids or through the more aggressive action of alveolar macrophages. In general,
29 amphibole asbestos is considered more persistent and less likely to dissolve than other natural
30 mineral fibers, including serpentine asbestos (i.e., chrysotile) fibers. However, no data are
31 available for Libby Amphibole asbestos specifically, and it is unknown if Libby Amphibole
32 asbestos fibers would split or break in the pulmonary compartment as has been shown with some
33 amphibole fibers (e.g., ferroactinolite) (Coffin et al., 1983).

34 Any fibers deposited in the respiratory tract and not cleared via the mucociliary system,
35 or not dissolved, can remain in the lung or can be transported to other tissues. Although data

1 specific to Libby Amphibole asbestos are not yet available, other asbestos fiber types can
2 translocate from the lung via macrophage action and transport through the lymph system, or
3 direct migration may occur through tissues from the mechanical action of the lung. Pleural and
4 peritoneal effects documented in Libby Amphibole asbestos-exposed individuals support the
5 potential for translocation of Libby Amphibole asbestos into the pleura.
6

7 **6.1.3. Noncancer Health Effects in Humans and Laboratory Animals**

8 Noncancer health effects identified in humans following inhalation exposure to Libby
9 Amphibole asbestos include pleural abnormalities, asbestosis, and reduced lung function as well
10 as increased mortality from noncancer causes. Two cohorts of workers exposed to Libby
11 Amphibole asbestos have been studied: workers at the mine and related operations in Libby, MT
12 and employees in the O.M. Scott plant in Marysville, OH, where the vermiculite product was
13 exfoliated and used as an inert carrier in lawn care products. Radiographic assessments of study
14 participants in both cohorts indicate radiographic abnormalities consistent with asbestos-related
15 disease, specifically pleural thickening (localized [LPT] and diffuse [DPT]) and small opacities
16 (indicative of interstitial fibrosis) (Rohs et al., 2008; Amandus et al., 1987b; McDonald et al.,
17 1986b; Lockey et al., 1984). These studies provided quantitative exposure estimates and were
18 considered suitable for exposure-response analysis to support an RfC derivation. Additionally,
19 five cohort mortality studies of Libby, MT workers identified increased risk of mortality from
20 noncancer causes, including nonmalignant respiratory disease (e.g., asbestosis) (McDonald et al.,
21 1986a; Amandus and Wheeler 1987; McDonald et al., 2004; Sullivan, 2007; Larson et al.,
22 2010a) and cardiovascular disease (Larson et al., 2010a).

23 ATSDR conducted health screening of community members in and around Libby, MT
24 (including past workers), and identified an increase in radiographic abnormalities with an
25 increased number of exposure pathways (ATSDR, 2001; Peipins et al., 2003; Peipins et al.,
26 2004). Other researchers have also used these data to identify the increased prevalence of
27 respiratory symptoms in children (Vinokoor et al., 2010) and to evaluate the prevalence of
28 radiographic abnormalities and reduced lung function in nonworker participants (Weill et al.,
29 2010). Radiographic abnormalities were more prevalent in mine/mill workers versus other
30 exposure categories (i.e., household contacts, dusty trades, and community-only exposures)
31 (Weill et al., 2010). Pleural thickening (LPT or DPT) increased with age, within each exposure
32 group. Decreased pulmonary function (as percent of the predicted forced vital capacity) are
33 reported for participants with radiographic abnormalities (small opacities, DPT, and LPT) with
34 greater effects seen in participants with small opacities and DPT (Weill et al., 2010). A nested
35 case-control study based on this study group also identified a potential for increased prevalence

1 of autoimmune disease (Pfau et al., 2006), although additional research is needed to explore this
2 potential health outcome.

3 Although laboratory animal data and experimental data on toxicity mechanisms are
4 limited for Libby Amphibole asbestos, the existing data are consistent with the health effects
5 observed in both workers and community members exposed to Libby Amphibole asbestos.
6 Experimental animal studies have demonstrated increased collagen deposition consistent with
7 fibrosis following intratracheal instillation of Libby Amphibole asbestos fibers in C57Bl6 mice
8 (Putnam et al., 2008; Smartt et al., 2009) and Fisher 344 rats (Padilla-Carlin et al., 2011) as well
9 as increased markers of pulmonary inflammation in a rat model for human cardiovascular
10 disease (Shannahan et al., 2011a, b). Pulmonary fibrosis, inflammation, and granulomas were
11 observed after tremolite, which comprises approximately 6% of the fiber mixture in Libby
12 Amphibole asbestos, inhalation exposure in specific-pathogen-free (SPF) male Wistar rats
13 (Bernstein et al., 2003, 2005), and intratracheal instillation in male albino Swiss mice (Sahu et
14 al., 1975). Davis et al. (1985) also reported pulmonary effects after inhalation exposure to
15 tremolite in SPF male Wistar rats including increases in peribronchiolar fibrosis, alveolar wall
16 thickening, and interstitial fibrosis.

18 **6.1.4. Carcinogenicity in Humans and Laboratory Animals**

19 There is convincing evidence of a causal association between exposure to Libby
20 Amphibole asbestos mesothelioma and lung cancer in workers from the Libby, MT vermiculite
21 mining and milling operations (Larson et al., 2010a; Moolgavkar et al., 2010; Sullivan, 2007;
22 McDonald et al., 1986a; 2004; Amandus et al., 1988; Amandus and Wheeler, 1987; NIOSH,
23 1986). No other occupational cohort with exposures to Libby Amphibole asbestos has been
24 studied with respect to mortality risks. Whitehouse et al. (2008) documented 11 mesothelioma
25 cases in nonworkers exposed to Libby Amphibole asbestos in Libby, MT. Increased lung cancer
26 and mesothelioma deaths are also reported for worker cohorts exposed to other forms of
27 amphibole fibers (amosite and crocidolite) (de Klerk, 1989; Seidman et al., 1986; Henderson and
28 Enterline, 1979). These findings are consistent with the increased cancers reported for
29 communities exposed to various rocks and soils containing tremolite fibers (Baris, 1987;
30 Yaziciglu, 1976; Yaziciglu et al., 1973; Langer et al., 1987; Baris et al., 1979; Sichletides et al.,
31 1992; Hasanoglu et al., 2006). Although potency, fiber dimension, and mineralogy differ
32 between amphiboles, these studies are supportive of the hazard identification of Libby
33 Amphibole asbestos fibers described in this assessment.

34 Although there is a limited laboratory animal database, the studies that are available
35 support the determination of carcinogenicity of Libby Amphibole asbestos fibers. Smith (1978)

1 demonstrated mesotheliomas in hamsters given a single intrapleural injection of Libby
2 Amphibole asbestos material (see Table 4-15). Tremolite is also carcinogenic in studies in rats,
3 hamsters, and mice, resulting in pleural mesothelioma, peritoneal mesothelioma, and lung cancer
4 depending on the route of exposure (see Table 4-16) (Davis et al., 1985, 1991; Stanton, 1981;
5 Roller et al., 1996; Bernstein et al., 2003, 2005). Although comparing the potency of the
6 tremolite used in these studies is difficult given the lack of information on fiber characteristics
7 and other study limitations, these results demonstrate an increased risk for lung cancer and
8 mesothelioma following exposure to tremolite asbestos.

9 10 **6.1.5. Susceptible Populations**

11 Certain populations could be more susceptible than the general population to adverse
12 health effects from exposure to Libby Amphibole asbestos. In general, factors that may
13 contribute to increased susceptibility from environmental exposures include lifestage, gender,
14 race/ethnicity, genetic polymorphisms, health status, and lifestyle. However, little data exist to
15 address the potential of increased susceptibility to cancer or noncancer effects from exposure to
16 the Libby Amphibole asbestos.

17 Most occupational studies of workers exposed to Libby Amphibole asbestos have
18 examined the effects only in men because this group represents the vast majority of workers in
19 these settings (Amandus and Wheeler, 1987; Amandus et al., 1987c, 1988; McDonald et al.,
20 1986a, 1986b, 2004; Sullivan, 2007; Moolgavkar et al., 2010). The analysis presented here
21 includes all workers, however, there were few women in the cohort, and therefore no
22 determination can be made regarding increased susceptibility to lung cancer or mesothelioma by
23 gender. Gender-related differences in exposure patterns, physiology, and dose-response are
24 some of the factors that may contribute to gender-related differences in risk from asbestos
25 exposure (Smith, 2002). The limited data available from community-based studies (ATSDR,
26 2000) do not provide a basis for drawing conclusions regarding gender-related differences in
27 carcinogenic effects from Libby Amphibole asbestos. Racial diversity among workers exposed
28 to Libby Amphibole asbestos is also limited, and data on ethnic groups are absent, precluding the
29 ability to examine racial and ethnicity-related differences in the mortality risks within the Libby,
30 MT worker cohort. Finally, the potential modifying effects of genetic polymorphisms,
31 pre-existing health conditions, nutritional status, and other lifestyle factors have not been studied
32 sufficiently to determine their potential contribution to variation in risk in the population.

1 **6.1.6. Mode-of-Action Information**

2 Due to the limited data that are available specific to Libby Amphibole asbestos, the mode
3 of action (MOA) of Libby Amphibole asbestos for lung cancer and mesothelioma following
4 inhalation exposure cannot be established. Laboratory animal studies of mice (Putnam et al.,
5 2008; Smartt et al., 2009), hamsters (Smith, 1978) or rats (Shannahan et al., 2011a,b;
6 Padilla-Carlin et al., 2011) exposed to Libby Amphibole asbestos suggest a similar type of
7 inflammatory response to that observed with other mineral fibers; however, no inhalation studies
8 were available in the published literature. In vivo studies in rats, hamsters, or mice exposed to
9 tremolite (McConnell et al., 1983a; Davis et al., 1991; Smith et al., 1979; Wagner et al., 1982;
10 Stanton et al., 1981; Roller et al., 1996, 1997) show results similar to other amphibole asbestos
11 fibers including lung cancer and mesothelioma, with limited inhalation studies (Davis et al.,
12 1985; Bernstein et al., 2003, 2005). In vitro studies demonstrate that the uptake of Libby
13 Amphibole asbestos fibers by macrophage, mesothelial, and lung epithelial cell lines may lead to
14 an increase in oxidative stress as measured by reactive oxygen species production, gene
15 expression changes or genotoxicity (Blake et al., 2007; Hillegass et al., 2010; Pietruska et al.,
16 2010). Thus, the available data indicate that Libby Amphibole asbestos induces biological
17 responses similar to other forms of asbestos such as oxidative stress, chronic inflammation,
18 genotoxicity, and increased cell proliferation. These biological effects following exposure to
19 Libby Amphibole asbestos and/or tremolite are demonstrated in a limited number of laboratory
20 animal and in vitro studies. Multiple key events for one particular toxicity pathway or MOA
21 have not been identified and adequately supported; therefore, the MOA for Libby Amphibole
22 asbestos carcinogenicity cannot be established.

24 **6.1.7. Weight-of-Evidence Descriptor for Cancer Hazard**

25 Under the EPA *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a), Libby
26 Amphibole asbestos is “carcinogenic to humans” following inhalation exposure based on
27 epidemiologic evidence that shows convincing evidence of a causal association between
28 exposure to Libby Amphibole asbestos fibers and increased lung cancer and mesothelioma
29 mortality (McDonald et al., 1986a, 2004; Amandus and Wheeler, 1987; Sullivan, 2007, Larson et
30 al., 2010b, Moolgavkar et al., 2010). These results are further supported by animal studies that
31 demonstrate the carcinogenic potential of Libby Amphibole asbestos fibers and tremolite fibers
32 in rodent bioassays. As a durable mineral fiber of respirable size, this conclusion is consistent
33 with the extensive published literature that documents the carcinogenicity of amphibole fibers.

34 U.S. EPA’s *Guidelines for Carcinogenic Risk Assessment* (U.S. EPA, 2005a) indicate
35 that for tumors occurring at a site other than the initial point of contact, the weight of evidence

1 for carcinogenic potential may apply to all routes of exposure that have not been adequately
2 tested at sufficient doses. An exception occurs when there is convincing information (e.g.,
3 toxicokinetic data) that absorption does not occur by other routes. Information on the
4 carcinogenic effects of Libby Amphibole asbestos via the oral and dermal routes in humans or
5 animals is absent. The increased risk of lung cancer and mesothelioma following inhalation
6 exposure to Libby Amphibole asbestos has been established by studies in humans, but these
7 studies do not provide a basis for determining the risk from other routes of exposure.
8 Mesothelioma occurs in the pleural and peritoneal cavities and, therefore, is not considered a
9 portal-of-entry effect. However, the role of indirect or direct interaction of asbestos fibers with
10 tissues at extrapulmonary sites is still unknown. There is no information on the translocation of
11 Libby Amphibole asbestos to extrapulmonary tissues following either oral or dermal exposure,
12 and limited studies have examined the role of these routes of exposure in cancer. Therefore,
13 Libby Amphibole asbestos is considered “carcinogenic to humans” by the inhalation route of
14 exposure.

16 **6.2. EXPOSURE RESPONSE**

17 This assessment contains a derivation of an RfC for noncancer effects and an IUR for
18 cancer based on epidemiologic data. It does not contain an RfD or OSF.

20 **6.2.1. Noncancer/Inhalation**

21 Of the observed noncancer health effects from exposure to Libby Amphibole asbestos,
22 data that provide exposure-response information are only available for increased pleural
23 thickening (localized and diffuse) and signs of interstitial fibrosis (i.e., small opacities) in the two
24 worker cohorts (i.e., Libby worker cohort and Marysville worker cohort). Both cohorts provide
25 individual exposure estimates, and document increased hazard of pleural and parenchymal
26 effects. As detailed in Section 5.2.1, each of the available studies has strengths and weaknesses.
27 The cohort of Marysville, OH workers (Lockey et al., 1984 and the follow-up by Rohs et al.,
28 2008) was selected as the principal cohort over the Libby worker cohort for five reasons: (1) lack
29 of confounding by residential and community exposure; (2) information on important covariates
30 (e.g. BMI); (3) exposure-response relationship defined for lower cumulative exposure levels (in
31 the post-1972 sub-cohort); (4) adequate length of follow-up; and (5) use of more recent criteria
32 for evaluating radiographs (ILO, 2000) (see Section 5.2.1 for details). Of the observed
33 radiographic abnormalities in exposed workers, localized pleural thickening (LPT) was selected
34 as the critical effect due to its higher prevalence relative to the other outcomes, minimal
35 adversity (compared with other effects), and specificity for durable mineral fiber exposure. LPT

1 is an irreversible pathological change associated with constricting chest pain, dyspnea, and
2 decreased pulmonary function and considered adverse (see Section 5.2.1.4). For an RfC
3 derivation, analyses focused on the cohort of Marysville, OH workers described by Rohs et al.
4 (2008). Specifically, the RfC was derived from the sub-cohort of the Marysville, OH workers
5 who started employment after 1972, due to the greater certainty in exposure assessment in this
6 group.

7 Benchmark dose (BMC) modeling, with a benchmark response of 10% extra risk, was
8 used to derive the point of departure (POD). A Michaelis-Menten regression model was the
9 best-fitting model for the sub-cohort and used to estimate the exposure-response relationship for
10 Libby Amphibole asbestos and LPT. Cumulative exposure with a lag of 10 years was selected as
11 the exposure metric, based on evidence for biological latency and model fit considerations. A
12 background rate of LPT of 1% was assumed based on a limited number of published estimates.
13 The resulting BMC_{10} under these modeling assumptions was 0.2642 fibers/cc-year; the
14 corresponding lower 95% confidence limit of the BMC_{10} ($BMCL_{10}$) is 0.1177 fibers/cc-year as a
15 cumulative lifetime exposure. The RfC is for continuous exposure (i.e., 24 hours/day,
16 365 days/year, with exposure beginning at birth and continuing for 70 years). Thus, the modeled
17 $BMCL_{10}$ as CE was adjusted to 70 years of exposure, lagged by 10 years (non-occupational,
18 lifetime exposure) resulting in a value of 60 years (see Section 5.2.4).

$$\begin{aligned} \text{POD} &= \text{BMCL}_{10} \div (\text{lifetime exposure duration}) \\ &= [0.1177 \text{ (fibers/cc)} \times \text{year}] \div [70 - 10 \text{ years}] \\ &= 1.96 \times 10^{-3} \text{ fibers/cc} \end{aligned}$$

25 The RfC is obtained by applications of uncertainty factors as needed. Two uncertainty
26 factors (UF) have been applied for a composite UF of 100 (interspecies uncertainty factor,
27 $UF_A = 10$; database uncertainty factor, $UF_D = 10$) (see Section 5.2.4). As shown below, the
28 chronic RfC is 2×10^{-5} fibers/cc for Libby Amphibole asbestos; it was calculated by dividing the
29 lifetime-POD by a composite UF of 100:

$$\begin{aligned} \text{Chronic RfC} &= \text{POD} \div \text{UF} \\ &= 1.96 \times 10^{-3} \text{ fibers/cc} \div 100 \\ &= 1.96 \times 10^{-5} \text{ fibers/cc, rounded to } 2 \times 10^{-5} \text{ fibers/cc} \end{aligned}$$

1
2 Modeling was also conducted in the full cohort of workers described in Lockey et al.
3 (1984) and Rohs et al. (2008). These analyses used a different modeling approach, due to the
4 wider range of exposures and time from first exposure. A modified Michaelis-Menten model
5 provided the best fit to the full cohort data, which incorporated time from first exposure via the
6 plateau term for the model. For a time from first exposure of 30 years and exposure lag of
7 10 years, the BMC and BMCL corresponding to a 10% extra risk of LPT were 0.1477 and
8 0.0580 fibers/cc-year, respectively. This BMC and BMCL are quite similar to the values
9 obtained in the analysis for the RfC and provide important support for the selected modeling
10 approach. When time from first exposure is set at 40 years, the calculated RfC is
11 4×10^{-6} fibers/cc.

12 Confidence in the principal study is considered medium. The data used are human,
13 epidemiological data which are preferred to animal bioassays, and the principal study is
14 conducted in a population of occupationally exposed workers with long-term, relatively low
15 intensity exposures. However, use of the sub-cohort resulted in a smaller data set, and fewer
16 cases to model. Additionally there are weaknesses in the primary study. Exposure estimates are
17 based on self-reported job histories. The study used a cross-sectional design and may be
18 negatively biased as individuals with more severe disease could have left employment or may
19 have died and not been included in the follow-up study, resulting in an underestimation of
20 overall toxicity. However, for a less severe effect, such as LPT, this bias should be minimal. As
21 discussed in Sections 4.1.3 and 5.2.1.3.2, there may have been potential for selection bias due to
22 exposure-dependent censoring in this population, based on information provided by Rohs et al.
23 (2008) regarding the higher average exposure in participants compared to nonparticipants. In
24 terms of sensitivity of the study to detect a health effect, it is known that high-resolution
25 computed tomography can identify mineral fiber-related lesions in the respiratory tract, which
26 cannot be identified by standard radiographs (ATS 2004; Staples et al., 1989; Muravov et al.,
27 2005). Thus, the technology employed for determining the prevalence of radiographic changes
28 in the Marysville cohort may underestimate the actual prevalence of localized pleural thickening.

29 Confidence in the database is low-to-medium. The database contains long-term mortality
30 and morbidity studies in humans exposed via inhalation to Libby Amphibole asbestos. The
31 morbidity studies do provide appropriate data for RfC derivation for pleural and lung
32 abnormalities. However, although decreased pulmonary function, a potential for autoimmune
33 effects, and cardiovascular disease are noted in exposed individuals, data do not provide an
34 exposure-response relationship. It is known that inhaled asbestos fibers migrate out of the lung
35 and into other tissues (see Section 3.1), lending uncertainty to any assumptions that other effects

1 would not be expected. There are no data in laboratory animals or humans on general systemic
2 effects. Therefore, overall confidence in the RfC is low-to-medium, reflecting medium
3 confidence in the principal study and low-to-medium confidence in the database.

4 ***Uncertainty and Sensitivity Analyses for RfC Derivation:*** It is important to consider the
5 sources of uncertainties in the derivation of the RfC for Libby Amphibole asbestos. These
6 include the following:

7 *Measurement error in exposure assessment and assignment.* The estimated exposure for
8 each individual relied on self-reported employment history, which may be subject to recall error.
9 Only data from 1972 and later were used for an RfC derivation, based on lack of fiber
10 measurements prior to this date; although better there remains some uncertainty in exposures
11 prior to installation of IH controls (1974). There is also uncertainty in the post-1972 data
12 regarding asbestos content in other ore sources (Virginia, South Carolina, and South Africa).
13 Although Libby Amphibole asbestos was not used in the facility after 1980, industrial hygiene
14 measurements collected after 1980 showed low levels of fibers. However, because the
15 concentration of fibers in the workplace was near background after 1980, this exposure makes
16 only a small contribution to an individual's cumulative exposure estimate. Similarly, any
17 exposure to Libby Amphibole asbestos outside of the workplace is not likely to contribute
18 significantly to cumulative exposure—~10% of workers reported bringing raw vermiculite
19 home, and the majority showered and changed clothes before leaving the workplace.

20 *Radiographic assessment of localized pleural thickening.* Conventional radiographs—
21 rather than the more sensitive high-resolution computed tomography—were used to determine
22 the health outcome. Localized pleural thickening may be difficult to detect on these radiographs,
23 leading to the potential for outcome misclassification. However, uncertainty in the detection of
24 LPT in each individual is considered minimal due to the use of a team of highly qualified chest
25 radiologists evaluating the radiographic films and the use of consensus diagnosis.

26 *Length of follow-up.* Time from first exposure to X-ray was 23.2–32.7 years in the
27 preferred sub-cohort (mean of 28.2 years). The literature suggests that the prevalence of LPT
28 may increase with time, beyond this observed range of time from first exposure. The lack of
29 observed data beyond ~30 years after first exposure (on average) is a source of uncertainty when
30 characterizing the exposure-response relationship for a full lifetime of exposure (e.g., 70 years).
31 This likelihood that the prevalence of localized pleural thickening may increase further with time
32 beyond 30 years after first exposure, and lack of data to support characterization of the
33 exposure-response curve outside this range, is a principal rationale cited for the selection of a
34 database UF of 10 for an RfC derivation.

1 *Background rate of localized pleural thickening.* In the derivation of the RfC, a
2 background rate of 1% for LPT was used. Previous studies have reported a range of prevalence
3 estimates (0.02 to 3.9%) in populations not known to be occupationally exposed to asbestos.
4 However, in statistical modeling of the Marysville, OH sub-cohort, uncertainty in the
5 background rate of localized pleural thickening is very low. The difference in the POD when the
6 background rate is fixed at 1% versus when it is estimated (estimated background rate of 3.12%)
7 is ~15% (0.1177 compared to 0.1349 fibers-year/cc), and it does not affect the proposed RfC
8 (after rounding to one significant digit).

9 *Model Form.* A number of model forms were explored in the initial stages of analysis
10 (see Appendix E) before selecting the Michaelis-Menten model. The BMC and the BMCL
11 estimated from other candidate models for the sub-cohort, as well as those obtained in modeling
12 from the full cohort were in a similar range to the selected model. A second model-based
13 uncertainty is the choice of lag for cumulative exposure. The RfC derivation is based on the
14 exposure lagged by 10 years, since this lag yielded the lowest Akaike Information Criterion
15 (AIC) value, and indication of superior fit. However, if other lags (with similar AICs) are used,
16 the difference in POD may fluctuate to be approximately 20% higher or approximately 55%
17 lower. However, the choice of lag does not affect the proposed RfC (after rounding to one
18 significant digit).

19 *Effect of smoking.* Information on ever/never smoking was available for the preferred
20 sub-cohort. This individual variable did not meet statistical significance in the best-fitting
21 model, although inclusion did improve model fit (see Appendix E). When including smoking in
22 the best-fitting model, BMCs and BMCLs estimated separately for smokers and nonsmokers
23 differed by approximately sixfold. Smoking was not included in the model selected for RfC
24 derivation due to the lack of statistical significance, limited sample size (only three cases were
25 never smokers out of a total of 12 cases), and lack of detailed information on smoking history,
26 but these sensitivity analyses indicate a need for further research on the effect of smoking in
27 relation to LPT risk among asbestos-exposed populations.

28 *Sensitivity analysis for the derivation of a POD for lifetime exposure from the CE metric*
29 *of the worker cohort.* Exposure-response modeling for LPT in the Marysville sub-cohort used
30 the cumulative exposure (CE) metric (represented as CHEEC, described in Section 5.2.3.1)
31 providing a POD in fibers/cc-years. In order to derive an RfC in the units of continuous air
32 concentration for a lifetime (i.e., fibers/cc), the POD from the CE metric was weighted across a
33 lifetime exposure. Thus, the lifetime BMCL₁₀ is 1.96×10^{-3} [0.1177 (fibers/cc)-years ÷ 60years].
34 This procedure is one way to account for the duration of exposure in the occupational study
35 being less than lifetime. There is some uncertainty as to whether—and how—to take account for

1 less-than-lifetime exposure in the occupational cohort. A sensitivity analysis was done to
2 consider other procedures for this averaging. The primary analysis assumes duration contributes
3 to risk and thus calculates a concentration across a lifetime that would yield the POD. The
4 second analysis is consistent with assuming duration contributes to risk but estimating the
5 concentration only for the mean duration in the observed database. The third analysis assumes
6 duration does not contribute to risk and models the average work duration continuous exposure
7 equivalent for each worker. This sensitivity analysis indicates that the approach taken to average
8 the POD based on the CE metric (CHEEC) across a lifetime was a reasonable approach, as
9 similar results are obtained using different approaches (i.e., within 4 fold).

10 *Choice of critical effect.* The critical effect selected for RfC derivation is localized
11 pleural thickening. Alternative endpoints were not modeled using the preferred sub-cohort due
12 to small numbers—there were five cases of bilateral LPT, only one case of diffuse pleural
13 thickening, and no individuals with interstitial changes. As a sensitivity analysis, these three
14 alternative endpoints (along with all LPT) were modeled among all Marysville workers not
15 previously exposed to other forms of asbestos, with X-rays performed in 2002–2005 ($n = 250$).
16 These analyses were performed using the Michaelis-Menten model with a background rate of 1%
17 and unlagged CHEEC as the exposure metric. BMRs of 1, 5, and 10% were investigated (see
18 Table 5-5). Use of the 10% BMR for these alternative endpoints allows for comparison to a
19 POD based on the selected critical effect of LPT. In this larger cohort, the POD for a
20 10% increase in LPT was 0.06 fibers/cc-years (in comparison with the POD derived from the
21 sub-cohort and used in RfC derivation of 0.1177 fibers/cc-years). Results for all pleural
22 thickening (LPT and DPT) did not differ from results for LPT. Bilateral localized pleural
23 thickening was included as a rough indication of increased severity within LPT, and as expected
24 results in higher PODs at each BMR than LPT. The resulting BMCLs for DPT and small
25 opacities (1.17 and 2.89 fibers/cc-years respectively, 10% BMR) are higher than the POD for
26 LPT (0.06 fibers/cc-years). Thus, use of an alternative endpoint at the same BMR would provide
27 a higher POD, and corresponding higher RfC.

28 However, a 10% BMR is not appropriate for more severe endpoints and BMCLs are
29 calculated at 1 and 5% BMRs as well. If DPT is used as a critical effect, PODs of 0.081 and
30 0.473 fibers/cc-years would be calculated for a 1% and 5% BMR respectively. If small opacities
31 are used as a critical effect, the PODs are higher at both a 1% and a 5% BMR (i.e., 0.243 and
32 1.32, respectively). In summary, the use of more severe alternative endpoints (with appropriate
33 BMRs) results in PODs higher than that estimated using the critical effect of LPT (i.e.,
34 0.06 fibers/cc-year, BMR 10%), and all are higher than the POD used in RfC derivation, with the
35 exception of DPT at a 1% BMR (0.0814 fibers/cc-year). BMCLs for these more severe

1 endpoints using a 1% BMR were within ~2-fold of the preferred POD (0.0814 and
2 0.2425 fibers/cc-year for diffuse pleural thickening and interstitial changes, respectively). There
3 is uncertainty associated with these estimates due to the inclusion of individuals hired before
4 1972, when no quantitative exposure measurements were available. Thus, a choice of alternative
5 critical effects—even with lower BMRs—would not result in an RfC appreciably lower than the
6 proposed RfC based on LPT and a 10% BMR.

7 8 **6.2.2. Cancer/Inhalation**

9 **6.2.2.1. Background and Methods**

10 The most appropriate data set for deriving quantitative cancer risk estimates based on
11 Libby Amphibole asbestos exposure in humans is the cohort of workers employed at the
12 vermiculite mining and milling operation near Libby, MT (see Section 4.1). No data were
13 available pertaining to cancer incidence or mortality in the Marysville, OH cohort, and mortality
14 and exposure data for other populations exposed to Libby Amphibole asbestos are very limited.
15 Whitehouse et al. (2008) provided detailed information on 11 mesothelioma cases among
16 nonworkers, but this information could not be used in exposure-response analyses for this
17 assessment, because there is no quantitative exposure information for these cases and no
18 information on the population from which these cases arose.

19 The Libby, MT worker cohort has been the focus of two epidemiologic investigations by
20 National Institute for Occupational Safety and Health (NIOSH) scientists. A database created by
21 NIOSH in the 1980s contains demographic data, work history, and vital status at the end of May
22 of 1982 for 1,881 workers at the vermiculite mine, mill, and processing plant in Libby, MT (see
23 Section 4.1.1.1). Vital status follow-up was completed by NIOSH through 2006 using the
24 National Death Index (NDI-Plus; Bilgrad, 1995). Nearly 54% of workers in the cohort
25 ($n = 1,009$) had died by December 31, 2006. The data from this update (provided by NIOSH) is
26 the basis of the EPA exposure-response modeling.

27 EPA does not have sufficient biological information to select models for the
28 epidemiology data on the basis of biological mechanism (see Section 5). In this situation, EPA's
29 practice is to investigate a range of model forms to determine how to best empirically model the
30 exposure-response relationship in the range of the observed data. In this case, different exposure
31 metrics were explored for model fit in the analytic models. The exposure metric options were
32 selected to provide a range of shapes that was sufficiently flexible to allow for a variety of ways
33 that time and duration might relate to cancer risk in the data being modeled. EPA then evaluated
34 how well the models and exposure metric combinations fit the data being modeled. Metrics that
35 did not fit the data well were rejected. For purposes of calculating a reasonable upper-bound on

1 the risk per exposure EPA accounted for uncertainty in the choice of exposure metrics by using
2 the exposure metric (among those of reasonable fit) that estimated the highest risk. This is
3 explained in more detail below and in Sections 5.4.3–5.4.5. However, there are other
4 uncertainties in the modeling of the epidemiological data that may impact the IUR and these are
5 described in detail in Section 5.4.6.

6 Cumulative exposure has been the traditional method of measuring exposure in
7 epidemiologic analyses of many different occupational and environmental exposures and was the
8 exposure metric applied for to the risk of lung-cancer mortality in the EPA general asbestos
9 evaluation (U.S. EPA, 1988). Two alternative approaches to developing exposure metrics to
10 describe the effects of air concentrations of asbestos dust in the air on the risks of mortality have
11 also been proposed. The first alternative was proposed by Jahr (1974) who studied
12 silica-induced pneumoconiosis. He also suggested that exposures to occupational dusts could be
13 weighted by the time since exposure yielding an exposure metric which gives greater weight to
14 earlier exposures. Berry et al. (1979) subsequently suggested the application of exposure metrics
15 that allowed for the clearance of dust or fibers by using a decay term on exposures. For the
16 evaluation of mortality risk from mesothelioma, U.S. EPA (1988) used a different exposure
17 metric than was used for lung-cancer mortality, which factored in the time since first exposure.
18 It is important to note that different characterizations of ambient exposures may be reasonably
19 expected to be associated with different endpoints (i.e., lung cancer or mesothelioma).

20 In the Libby, MT worker cohort data developed by NIOSH and used by the EPA in this
21 assessment, detailed work histories, together with job-specific exposure estimates, allowed for
22 the reconstruction of each individual’s occupational exposure experience over time to define
23 multiple exposure metrics. From this information-rich individual-level data set from NIOSH, the
24 EPA constructed a suite of the different metrics of occupational exposure which had been
25 proposed in the asbestos literature or used in the EPA health assessment on general asbestos
26 exposures (U.S. EPA, 1988). This suite of models was defined a priori to encompass a
27 reasonable set of proposed exposure metrics to allow sufficient flexibility in model fit to these
28 data. These exposure metrics were evaluated in analytic-regression models to test which
29 exposure metrics were the best empirical predictors of observed cancer mortality and the better
30 fitting models were advanced for consideration as the basis of the exposure-response relationship
31 for the IUR. The types of exposure metrics evaluated were intended to allow for variations of
32 the classic metric of cumulative exposure, allowing for more or less weight to be placed on
33 earlier or later exposures. These simulated exposure metrics were derived mathematically to
34 approximate underlying processes that are not well understood, and their fit is evaluated on the

1 basis of maximizing the likelihood for the workers cohort and estimated parameters does not
2 necessarily have biological interpretation (see Section 5.4.2.5 for details).

3 Exposure estimates for all exposure metrics were adjusted to account for the time period
4 between the onset of cancer and mortality. The lag period defines an interval before death, or
5 end of follow-up, during which, any exposure is excluded from the calculation of the exposure
6 metric. Modeling of mesothelioma mortality included two additional exposure metrics: duration
7 of exposure and the exposure metric including a cubic function of time (see Eq. 5-5), originally
8 proposed in Peto et al. (1982) and employed in derivation of the IUR for asbestos (U.S. EPA,
9 1988).

10 Analyses of mesothelioma mortality were conducted using a Poisson model with a
11 Markov chain Monte Carlo (MCMC) Bayesian approach, whereas analyses of lung-cancer
12 mortality were conducted using the Cox proportional hazards model with time-varying
13 exposures. There was one important limitation of the NIOSH job exposure matrix (JEM). Of
14 the 991 workers hired before 1960, 706 workers with unknown department code and unknown
15 job assignments hired between 1935 and 1959 were assigned the same average estimated
16 exposure intensity. The lack of information on specific job assignments for such a large portion
17 of these early workers when exposures were higher resulted in the misclassification of the
18 exposure and effectively yielded exposure metrics that were differentiated only by the duration
19 of each worker's employment. For this reason and because there was little measured fiber
20 exposure data during the earlier period, identifying an adequate exposure-response model fit was
21 unsuccessful. The two biggest problems were that the duration of employment was the
22 best-fitting metric for modeling mesothelioma and that the Cox model assumptions were violated
23 in modeling lung-cancer mortality (see Section 5.4.3.5). As a result, this assessment developed a
24 sub-cohort analysis by dividing the whole cohort into two groups: those hired prior to 1960 and
25 those hired after 1959. This removed all but nine cohort members with missing department code
26 and job category information and lessened the effect of estimates of early exposures where no air
27 sampling data were available. For the sub-cohort of those hired after 1959, those two biggest
28 problems were resolved: the assumptions of the Cox model were satisfied, and a lagged
29 cumulative exposure with a decay (rather than duration of exposure, as for the full cohort) was
30 the best-fitting metric for mesothelioma.

31 Of the 880 workers hired after 1959, 230 (26%) had died by December 31, 2006. The
32 number of mesothelioma deaths in the sub-cohort is relatively small ($n = 7$, 2 deaths coded in
33 ICD-10 and 5 deaths coded in ICD-9), but the rate of mesothelioma mortality was very similar in
34 the subcohort (24.7 per 100,000 person-years vs. 26.8 per 100,000 person-years for the full
35 cohort [18 mesothelioma deaths], a difference of less than 10%).

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6.2.3. Modeling of Mesothelioma Exposure Response

A Poisson model is employed for estimating the absolute risk of mesothelioma following exposure to Libby Amphibole asbestos, 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, 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 (diffuse) 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 Deviance Information Criterion (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.

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. In the sub-cohort hired after 1959, the DIC value for mesothelioma using the IRIS IUR (U.S. EPA, 1988) metric (see Eq. 5-5) is substantially higher (DIC = 98.4) than for any of the metrics in Table 5-10, where the lowest DIC is 70.6. This difference of over 20 DIC units, is an indication that the model used for mesothelioma in the U.S. EPA (1988) IUR derivation (see Eq. 5-5), does not fit these data from the Libby, MT work cohort, compared to other exposure metrics presented (see Table 5-10). It should be noted that the data modeled here are very different from the data on which the IRIS assessment for asbestos (U.S. EPA, 1988) is based—and one does not necessarily expect the same model to fit different data sets—this is why EPA goes through a process to determine the best-fitting model in each case. One difference with the IRIS IUR (U.S. EPA, 1988) modeling is that the analysis in this assessment is based on individual-level data, whereas the IRIS IUR (U.S. EPA, 1988) application was to aggregate data. Also, cohorts used in the IRIS IUR (U.S. EPA, 1988) did not include cohorts exposed to Libby Amphibole asbestos and Libby Amphibole asbestos may be different from other types of asbestos. Alternately, the relative fit of this model may have been affected by uncertainties in the estimated exposure described in detail in Section 5.4.6.

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. All eight models retained for derivation of IUR include a decay half-life in the exposure metric. For the sub-cohort hired after 1959, the best-fitting exposure metric was

1 cumulative exposure with a 5 year half-life and a 15 year lag time with a central estimate for the
2 β of 2.07×10^{-4} with 95% upper confidence limit (UCL) of 3.42×10^{-4} .

3 4 **6.2.4. Unit Risk Estimates for Mesothelioma Mortality**

5 The increased risk of mesothelioma mortality attributable to continuous fiber exposure
6 was estimated using a life-table procedure based on the general U.S. population. The life-table
7 procedure involved the application of the estimated Libby Amphibole asbestos toxicity to a
8 structured representation of the general U.S. population in such a manner as to yield age-specific
9 risk estimates for cancer mortality in the presence or absence of exposure to Libby Amphibole
10 asbestos (see Section 5.4.5; Appendix G).

11 A default linear low-dose extrapolation below the POD was used because the mode of
12 action by which Libby Amphibole asbestos causes mesothelioma cannot be established. The
13 lower limit on the effective concentration (LEC_{01}) for adult-only exposures was determined to be
14 0.245 fibers/cc, which yielded an adult-based unit risk for mesothelioma mortality of 0.053 per
15 fiber/cc (POD of 1% divided by the LEC_{01}).

16 The value of the effective concentration (EC) that would correspond to the measure of
17 central tendency is the EC_{01} . This value is used in the derivation of a combined risk of
18 mesothelioma and of lung cancer. The EC_{01} was determined to be 0.406 per fiber/cc, which
19 when divided into a POD of 1% and scaled (by 70/54) to encompass the whole lifespan, gives a
20 lifetime central estimate value of 0.032 per fiber/cc.

21 For mesothelioma, the undercounting of cases (underascertainment) is a particular
22 concern given the limitations of the International Classification of Diseases (ICD) classification
23 systems used prior to 1999. In practical terms, this means that some true occurrences of
24 mortality due to mesothelioma are missed on death certificates and in almost all administrative
25 databases such as the National Death Index. Even after introduction of special ICD code for
26 mesothelioma with introduction of ICD-10 in 1999, detection rates are still imperfect (Pinhiero et
27 al., 2004; Camidge et al., 2006) and the reported numbers of cases typically reflect an
28 undercount of the true number. Kopylev et al. (2011) reviewed the literature on this
29 underascertainment and developed methods to account for the likely numbers of undocumented
30 mesothelioma deaths.

31 To compensate for mesothelioma underascertainment attributable to ICD coding, the
32 mesothelioma mortality unit risk was further adjusted following the analysis of Kopylev et al.
33 (2011). The adjusted mesothelioma central (i.e., maximum likelihood estimate) risk,
34 corresponding to the best-fit metric, was 0.044 per fiber/cc, and the adjusted mesothelioma
35 mortality unit risk was 0.074 per fiber/cc. The adjusted mesothelioma mortality unit risks from

1 all eight exposure parameterization models with adequate fit produced a range of unit risk values
2 (see Table 5-17) from 0.044 to 0.122. Thus, there is uncertainty in mesothelioma risks generated
3 from similar-fitting models from different exposure metrics (see details in Section 5.4.6.1.3).
4

5 **6.2.5. Modeling of Lung Cancer Exposure Response**

6 All multivariate extended Cox models were fit to the sub-cohort hired after 1959 with
7 covariates for sex, race, and date of birth, and exposure. Exposure for each of the 40 exposure
8 parameterizations was calculated independently and fit of these exposure metrics was evaluated
9 one at a time. As the exposure-response models cannot strictly be considered to be nested, a
10 standard measure of fit, the AIC (Burnham and Anderson, 2002), was used for comparison of
11 model fit with smaller values of AIC, indicating better goodness of fit. Of the
12 40 exposure-response metrics, 14 demonstrated an adequate fit to the data as measured by the
13 overall model fit with the likelihood ratio test ($p < 0.05$) as well as having statistically significant
14 exposure metrics ($p < 0.05$). However, only the nine models that demonstrated adequate model
15 and exposure metric fit and incorporated a lag period to account for cancer latency were
16 considered further in the development of the IUR (see Table 5-18).

17 Lagging exposure by 10 years was a better predictor of lung-cancer mortality compared
18 to other lags. As it is less likely that exposure during the last few years before death were
19 contributory to the development of the cancer and cancer mortality, the zero lag metrics were
20 dropped from further consideration. The residence time-weighted cumulative exposure, both
21 with and without decay of the exposure metric, did not fit these lung-cancer mortality data well
22 compared to the other models (see Table 5-12); this form of exposure metric does not
23 demonstrate evidence of an empirical fit to these epidemiologic data.

24 The model with the smallest AIC was for cumulative exposure with a 10-year half-life for
25 decay and a 10-year lag for cancer latency. The extended Cox model estimated a slope (beta) of
26 1.26×10^{-2} per fiber/cc-year based on a 365-day year, and the 95th percentile upper bound was
27 1.88×10^{-2} per fiber/cc-year. The p -value for the Libby Amphibole asbestos regression
28 coefficient (slope) was <0.001 . The slopes and confidence interval for the other exposure
29 metrics, which had similar fits to these data are reported in Table 5-13. Uncertainty in the choice
30 of the exposure metric (cross-metric uncertainty) is considered in the derivation of the final unit
31 risk (see details in Section 5.4.5.3), representing the range of unit risks that are derived from
32 these similarly fitting metrics. The model results that were ultimately selected to reflect the
33 upper-bound among the range of results were based on the cumulative exposure with a 10-year
34 lag exposure metric (CE10). The extended Cox model estimated a slope (beta) of

1 5.28×10^{-3} per fiber/cc-year based on a 365-day year, and the 95th percentile upper bound was
2 1.00×10^{-2} per fiber/cc-year.

4 **6.2.6. Unit Risk Estimates for Lung-Cancer Mortality**

5 The increased risk of lung-cancer mortality attributable to continuous fiber exposure was
6 estimated using a life-table procedure based on the general U.S. population. The life-table
7 procedure involved the application of the estimated Libby Amphibole asbestos-specific toxicity
8 to a structured representation of the general U.S. population in such a manner as to yield
9 age-specific risk estimated for cancer mortality in the presence or absence of exposure to Libby
10 Amphibole asbestos (see Section 5.4.5; Appendix G).

11 The nine exposure-response models retained in Table 5-13 all had reasonably similar
12 goodness of fits. No single model stands out as clearly statistically superior; however, there is a
13 range of quality of fit within the set that could be considered to have adequate fit. The
14 lung-cancer mortality unit risks are shown in Table 5-18.

15 Using the results of the exposure model with the lowest AIC value (i.e., cumulative
16 exposure with a 10-year half-life for decay and a 10-year lag for cancer latency) alone, the LEC_{01}
17 for the adult-only exposures was determined to be 0.333 fibers/cc. This yields an adult-based
18 unit risk of lung-cancer mortality of 0.0300 (POD of 1% divided by the LEC_{01}). This estimate
19 was then scaled by 70/54 to encompass the whole lifespan; it yielded a lifetime unit risk of
20 0.0389 per fiber/cc. The value of the concentration that would correspond to the measure of
21 central tendency was based on the EC_{01} rather than LEC_{01} . The EC_{01} for the adult-only
22 exposures was determined to be 0.499 per fiber/cc, which, when divided into a POD of 1%,
23 yielded an adult-based central estimate for lung-cancer mortality of 0.0200. This estimate was
24 then scaled by 70/54 to encompass the whole lifespan to, yielded a lifetime central estimate of
25 0.0260 per fiber/cc.

26 Using the results of the exposure model based on cumulative exposure with a 10-year lag
27 for cancer latency, the LEC_{01} for the adult-only exposures was determined to be 0.191 per
28 fibers/cc, yielding an adult-based unit risk of lung-cancer mortality of 0.0524 (POD of 1%
29 divided by the LEC_{01}). When scaled by 70/54 to encompass the whole lifespan, it yielded a
30 lifetime unit risk of 0.0679 per fiber/cc. The value of the risk that would correspond to the
31 measure of central tendency involves the EC_{01} rather than the LEC_{01} . The EC_{01} for the
32 adult-only exposures was determined to be 0.325 per fiber/cc, which, when divided into a POD
33 of 1%, yielded an adult-based central estimate for lung-cancer mortality of 0.0308. This estimate
34 was then scaled by 70/54 to encompass the whole lifespan to, yielded a lifetime central estimate
35 of 0.0399 per fiber/cc.

1 The resulting unit risks in Table 5-18 ranged from 0.0260 to 0.0679 per fibers/cc, for a
2 lifetime continuous exposure. This shows that the unit risk based on the exposure metric with
3 the lowest AIC value (i.e., cumulative exposure with a 10-year half-life for decay and a 10-year
4 lag for cancer latency) is in the center of this range (i.e., 0.0389 per fiber/cc). This estimate is in
5 the middle of the range of possible unit risks and does not capture the uncertainty across metrics
6 with similar goodness of fit (see details in Section 5.4.6.1.3).

7 The model results selected to represent the upper bound risk among the range of
8 reasonable results are based on CE10 metric with a 10-year lag. The model results selected to
9 reflect the upper-bound among the range of results are based on the CE10 exposure metric with a
10 10-year lag, providing an IUR of 0.0679 per fibers/cc.

11 12 **6.2.7. IUR Derivation Based on Combined Mesothelioma and Lung-Cancer Mortality from** 13 **Exposure to Libby Amphibole Asbestos**

14 When risks are combined, it is important to understand several concepts that are pertinent
15 to the evaluation and comparison of the cancer-specific mortality unit risks that will be
16 combined. First, there is statistical uncertainty in the potency estimate within the exposure
17 response model defined by each exposure metric. This within metric uncertainty is accounted
18 for in the confidence interval on slope. Next, there is an uncertainty in the choice of metrics for
19 developing IUR (cross-metric uncertainty). Finally, when unit risks corresponding to metrics are
20 chosen accounting for uncertainty, these are statistically combined into IUR. Details are
21 provided in Section 5.4.5.3.

22 Table 6-1 shows cancer-specific unit risks as well as combined risk of mesothelioma and
23 lung cancer. The IUR value of 0.17 per fiber/cc, continuous lifetime exposure, accounts for
24 important quantitative uncertainties in the selection of the specific exposure metric that may have
25 remained in an IUR that might have been based on the best-fitting exposure models alone.
26 Additional uncertainties are discussed in detail in Section 5.4.6.

27 28 **6.2.7.1. Comparison with Other Published Studies of Libby, MT Workers Cohort**

29 Several published studies have previously evaluated risk of mesothelioma and lung
30 cancer (i.e., Sullivan, 2007; Berman and Crump, 2008; Larson et al., 2010a; Moolgavkar et al.,
31 2010) in Libby, MT workers cohort.

Table 6-1. Reasonable upper bound and lowest information criteria estimates of central risks and unit risks, for mesothelioma mortality, lung-cancer mortality, and the IUR for the combined mortality risk from mesothelioma and lung cancer (IURs are presented in the units of excess cancers per fibers/cc, continuous lifetime exposure)

Model	Mesothelioma		Lung cancer		Combined mesothelioma and lung cancer	
	Central estimate	Unit risk	Central estimate	Unit risk	Central estimate	IUR
Reasonable upper bound ^a	0.075	0.122	0.040	0.068	0.115	0.169
Lowest information criteria ^b	0.044	0.074	0.026	0.040	0.070	0.103

^aFor mesothelioma, the selected model parameterized exposure as cumulative exposure with exponential decay half-life of 5 years and a 15-year lag. For lung cancer, the selected model parameterized exposure as cumulative exposure without decay and a 10-year lag.

^bFor mesothelioma, the selected model parameterized exposure as cumulative exposure with exponential decay half-life of 5 years and a 10-year lag. For lung cancer, the selected model parameterized exposure as cumulative exposure with exponential decay half-life of 10 years and a 10-year lag.

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 fibers/cc continuous lifetime exposure. Therefore, utilization of the exposure response modeling of Moolgovkar 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 number 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 risk from these studies are computed from life-table analyses (see Table 5-20). The lung cancer IURs 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).

1 **6.2.8. Sensitivity Analysis**

2 **6.2.8.1. Sensitivity Analysis of Influence of High Exposures in Early 1960s on Model Fit**

3 Although data do not exist to evaluate biological bases for model fit, other potential
4 factors can be explored where data allow. For example, because of concerns that very high
5 (>100 fibers/cc) early (1960–1963) 8-hour Libby Amphibole asbestos TWA exposures (see
6 Table 5-7) could have influenced the relative fit of the various exposure metrics, EPA conducted
7 a sensitivity analysis of the impact on the relative model fit of reducing all estimated exposure
8 intensities for 1960–1963 by 50%.

9 For modeling mesothelioma and lung-cancer mortality on this revised data set, there was
10 very little difference in the order of the relative fits of the exposure models as was seen for the
11 subcohort of workers hired after 1959 and included the exposures as estimated by Amandus et al.
12 (1987a) during 1960–1963 (see Tables 5-14 and 5-15). The models based on the revised data set
13 fit approximately as well for mesothelioma and for lung cancer.

14

15 **6.2.8.2. Analysis of Potential Confounding of Lung Cancer Results by Smoking in the**
16 **Sub-cohort**

17 EPA used three approaches to address the confounding issue, including restriction of the
18 cohort and two analytic evaluations of the potential for confounding by smoking including the
19 method described by Richardson (2010). Richardson (2010) describes a method to determine if
20 an identified exposure relationship with lung cancer is confounded by unmeasured smoking in an
21 occupational cohort study. EPA implemented this methodology to model the potential effects of
22 Libby Amphibole asbestos on the risk of COPD mortality on the subcohort of workers hired after
23 1959 (see Section 5.4.3.6.5). Summarizing these findings, EPA used the method described by
24 Richardson (2010) to evaluate whether exposures to Libby Amphibole asbestos predicted
25 mortality from COPD as an indication of potential confounding by smoking and found a
26 nonsignificant negative relationship, which was inconsistent with confounding by smoking.

27

28 **6.2.9. Uncertainty in the Cancer Risk Values**

29 It is important to consider the uncertainties in the derivation of the mesothelioma and
30 lung-cancer mortality risks in this assessment in the context of uncertainties in animal-based
31 health assessments. This assessment does not involve extrapolation from high dose in animals to
32 low dose in humans. The current assessment is based on a well-documented and well-studied
33 cohort of workers with adequate years of follow-up to evaluate mesothelioma and lung-cancer
34 mortality risks with PODs within the range of the data. The discussions in Section 5.4.6 explore

1 uncertainty in the derivation of the IUR in order to provide a comprehensive and transparent
2 context for the resulting cancer mortality risk estimates.

3 The summary below includes likely one-sided uncertainties (biases) associated with the
4 derivation of the IUR in order to provide a context for the resulting cancer risk estimates.

5 The sources of uncertainty that could lead to a likely underestimation of the cancer risk
6 value include the following:

- 7
8
9 • *Use of historical phase contrast microscopy (PCM) exposure measurements.* As asbestos
10 was a contaminant of vermiculite that was the primary object of production, mine and dry
11 and old wet mill ambient air may have contained material other than asbestos that could
12 have contributed to fibers counted by PCM. Therefore, it is possible that exposure
13 estimates for some or possibly a large portion of the cohort are overestimated, and,
14 therefore, the resulting IUR may be underestimated.
- 15 • *Measurement error in exposure assessment and assignment.* This current assessment
16 showed that unit risk results from analysis of the lung-cancer mortality in the full cohort
17 (see Table 5-21) compared with the sub-cohort hired after 1959 may have been
18 attenuated as much as 2–6 times (see Section 5.4.6.1.2.4). By excluding those cohort
19 members hired before 1960 for whom there was insufficient work history information to
20 estimate their exposures, the unit risk for lung cancer was less attenuated due to exposure
21 measurement error. However, exposure measurements from the 1960s are also imperfect
22 and include a lesser degree of exposure measurement error, which could have led to
23 underestimated risk—even in the sub-cohort hired after 1959.
- 24 • *Limited length of follow-up.* The IUR for mesothelioma mortality could be larger than
25 was estimated from existing data, since latency of mesothelioma can be as long as
26 60 years. The maximum length of follow-up was 46 years in this cohort. The magnitude
27 of underestimation would depend on the relationship between the number of additional
28 deaths and the increase in person-years.
- 29 • *Use of life-tables to calculate the IUR based on cancer mortality.* The life-table
30 procedure computes the extra risk of death from birth up to 85 years of age. This cut-off
31 at age 85 ignores a small additional risk of lung-cancer mortality among a small
32 percentage of people who have a higher background risk because of the increase in lung
33 cancer risk that is seen with increasing age. The lung-cancer mortality unit risk based on
34 the LEC₀₁ would be somewhat larger, on the order of 5–10%. On the other hand, the
35 additional mesothelioma mortality risk, if the life-tables were extended to account for
36 longer life spans, would be about 3%.
- 37 • *Small number of women and ovarian cancer.* While asbestos is causally associated with
38 increased risks of ovarian cancer (Straif et al., 2009), there were only 84 women in the
39 whole cohort, and there were no deaths from ovarian cancer among 24 total deaths. The
40 lack of observed ovarian cancer in this cohort may be a function of the limited number of

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1 female deaths in the cohort allowing for the possibility that exposure to Libby Amphibole
2 asbestos could result in increased risk of ovarian cancer. However, it was not possible to
3 estimate the magnitude of this underestimation on the total cancer risk.

- 4 • *Dependent competing risks.* Competing risk of mortality from other diseases related to
5 exposure may have resulted in underestimates of the risk of mortality from either
6 mesothelioma or lung cancer. The mean length of follow-up for the Libby, MT workers
7 who died of mesothelioma was to 30.1 years, and evidence exists (Suzuki, 2001; Bianchi
8 and Bianchi, 2009) that early deaths from other exposure-related causes could have
9 precluded an individual's risks of death from mesothelioma. However, it was not
10 possible to estimate the magnitude of this effect on the total cancer risk.

11
12
13 The source of uncertainty that could lead to a likely overestimation of the cancer risk
14 value:

- 15
16
17 • *Potential residual confounding and effect modification.* The unit risk of lung-cancer
18 mortality estimated herein, and the combined mesothelioma and lung-cancer mortality
19 IUR, would over-estimate the risk in any population that had a lower prevalence of
20 smoking than that of the Libby worker cohort. Because the Libby worker cohort had a
21 large prevalence of smokers and ex-smokers and no known nonsmokers developed lung
22 cancer, it is also possible that estimated risk for lung cancer is actually risk for an
23 interaction of lung cancer and smoking, and effects of smoking and asbestos are known
24 to be between additive and multiplicative (see Section 4). However, the company
25 imposed smoking ban, and the observation that there were many ex-smokers in the
26 cohort, would tend to lessen risks that would have occurred if these individuals continued
27 smoking.

30 **6.3. APPLICATION OF THE LIBBY AMPHIBOLE ASBESTOS RFC AND IUR**

31 **6.3.1. Sites and Materials**

32 This Libby Amphibole asbestos specific assessment is based on the evaluation of worker
33 cohorts, exposed to asbestos from a single mine in Libby, MT, and it is intended to allow for
34 estimates of the risk due to exposure to the asbestos fibers from that mine, or exposures to
35 asbestos fibers that arise from the management or use of the vermiculite ore and exfoliated
36 vermiculite from this mine. Therefore, it is appropriate to apply the Libby Amphibole
37 asbestos-specific RfC and/or IUR to sites which are believed to have been contaminated by these
38 materials when assessing risk from the amphibole fibers present from this contamination. This
39 may include sites where the ore was shipped or handled, where the vermiculite was exfoliated
40 and further processed, facilities which in other ways shipped or handled the exfoliated

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1 vermiculite, where products containing the raw or exfoliated vermiculite were present, the
2 consumer products themselves (e.g., vermiculite attic insulation) and any waste streams from the
3 above processes which contain vermiculite and the related Libby Amphibole asbestos-fibers.
4 The assessment was derived from PCM measurements taken at the Libby, MT occupational sites
5 and the mixture of minerals found in those measurements. It does not estimate the risk
6 attributable to specific subsets of those fibers whether based on size, shape, or mineral
7 composition other than the limitations on size and shape reflected in the PCM methodology and
8 counting rules. As detailed in Section 2, the amphibole asbestos present in the mine, ore and
9 expanded vermiculite, does not fit cleanly into a single category of nomenclature for amphibole
10 minerals. Most Libby Amphibole fibers are classified as winchite (84%), with lesser amounts of
11 richterite (11%) and tremolite (6%), based on the nomenclature proposed by Leake et al. (1997)
12 (Meeker et al., 2003). There are also trace amounts of magnesioriebeckite, edenite, and
13 magnesio-arfvedsonite present in Libby Amphibole asbestos (Meeker et al., 2003). Within the
14 30 samples taken from the mine the proportion of these minerals differed between samples
15 (Meeker et al., 2003) and the relative proportions of these species may have varied over time (as
16 ore from different locations was processed). This assessment estimates the risk of exposure to
17 the varying range of mineral fiber mixtures that result from material originating from the
18 geological deposit, recognizing there is variation and uncertainty as to variations in the exposure
19 to the underlying cohort and complex variation in settings to which these estimates will be
20 applied.

21

22 **6.3.2. Exposure Units for Libby Amphibole Asbestos**

23 As with the IRIS assessment for asbestos (U.S. EPA, 1988), the RfC and IUR specific to
24 Libby Amphibole asbestos are presented here as fibers/cc exposure continuous lifetime exposure,
25 where exposure measurements are based on analysis of air filters by PCM. Early PCM analytical
26 techniques did not have the same resolution as current analytical methods, and it is understood
27 that PCM data for the majority of the exposures characterized for the Libby, MT workers and
28 Marysville, OH workers would likely have a width resolution of 0.4–0.44 μm (Skinke, 1980;
29 Amandus et al., 1987a; WHO, 1980). Therefore, as with the IRIS assessment for asbestos
30 (U.S. EPA, 1988), the dimensions of the PCM fibers for the Libby Amphibole asbestos unit risk
31 are defined as fibers $\geq 5 \mu\text{m}$ in length with an aspect ratio of 3:1 or greater and a width $>0.4 \mu\text{m}$.

32 Environmental air sampling for asbestos is now often analyzed by transmission electron
33 microscopes (TEM) to confirm that the fibers viewed are asbestos, and often it is used to identify
34 the mineralogy of the fiber. Although some historical data do exist providing TEM analysis of
35 airborne fibers from the Libby, MT mill operation (McDonald et al., 1986a; Langer et al., 1974),

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1 these data are not sufficient to provide an alternative set of exposure measurements in TEM units
2 for the Libby, MT worker cohort, or provide a PCM to TEM conversion across the various work
3 environments.

4 Different sampling environments and varied site conditions may pose the potential for
5 airborne fibers from various materials. Because of that, it is expected that for many
6 environmental risk assessments conducted now and in the near future, measures of exposure may
7 be done with methods such as TEM and then adjusted through fiber-counting rules to estimate
8 the number of PCM-countable asbestos fibers. Site-specific environmental conditions should be
9 considered in determining how to best identify PCM-countable asbestos fibers in relevant air
10 samples for exposure assessments used in conjunction with this health assessment to yield
11 estimates of risk.

13 **6.3.3. Applications to Early Lifetime and Partial Lifetime Environmental Exposure** 14 **Scenarios for IUR**

15 The Libby Amphibole asbestos-specific unit risk derived in this assessment is a combined
16 risk of lung cancer and mesothelioma, each with its own adjustment for uncertainty in metrics.
17 The life-table analyses for Libby Amphibole asbestos do not predict greater risk from early-life
18 exposures. Thus, this assessment recommends that estimates of the risks of less-than-lifetime
19 exposures be computed by simple calculations of average lifetime exposure concentration
20 multiplied by IUR. This recommendation is consistent with standard Superfund guidance
21 (U.S. EPA, 1986b), where exposures are estimated, averaged across a lifetime exposure, and the
22 IUR simply applied to calculate excess cancer risk (U.S. EPA, 2005). The weight of evidence
23 does not support a mutagenic mode of action for Libby Amphibole asbestos carcinogenicity.
24 Therefore, according to EPA's *Supplemental Guidance for Assessing Susceptibility from*
25 *Early-Life Exposure to Carcinogens* (U.S. EPA, 2005b), the application of the age-dependent
26 adjustment factors are not recommended.

28 **6.3.4. Applications to Lifetime and Partial Lifetime Environmental Exposure Scenarios for** 29 **RfC**

30 The Libby Amphibole asbestos specific RfC should be used to derive estimates of hazard
31 from exposure to airborne materials containing Libby Amphibole asbestos as described above.
32 The Libby Amphibole asbestos RfC was derived from an evaluation of the O.M. Scott,
33 Marysville, OH worker cohort (Rohs et al., 2008; Lockey et al, 1984). Exposure-response
34 modeling of cumulative Libby Amphibole asbestosis exposure with the best-fitting model
35 (Michaelis-Menten with 10-year lagged exposure) resulted in a BMCL₁₀ of 0.1177 fibers/cc-year

1 yielding an RfC for a 70-year lifetime of 2×10^{-5} fibers/cc by calculating the average
2 concentration over a 60-year averaging period (70 years minus 10-year lag).

3 The estimate of hazard should be calculated by dividing the average daily exposure
4 concentration using an averaging period of 60 years by the reference concentration outlined in
5 *Superfund Guidance* (U.S. EPA, 1986b) to yield a quotient representing hazard. The use of the
6 reference concentration in risk assessment is further clarified in *RAGs, Part F, Supplemental*
7 *Guidance for Inhalation risk Assessment* (U.S. EPA, 2009). The guidance provides for
8 addressing hazard for children and adults by estimating time-dependent average daily exposures.

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**APPENDIX A. SUMMARY OF EXTERNAL PEER-REVIEW AND PUBLIC
COMMENTS AND DISPOSITION**

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

July 14, 2010

**Prepared by:
U.S. Environmental Protection Agency
Region 8
Denver, CO**



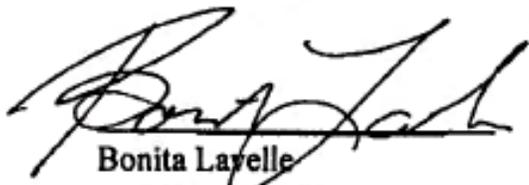
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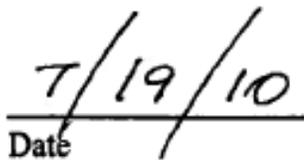
**SRC, Inc.
Denver, CO**



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 Layelle
U.S. EPA, Region 8


Date

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

1.0 INTRODUCTION

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

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

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

2.0 METHODS

2.1 Data Overview

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

Most of the samples that have been collected have been analyzed for asbestos by transmission electron microscopy (TEM) using either ISO 10312 (ISO 1995) or AHERA (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 (USEPA 2008b) 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 date¹ 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:

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:

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

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	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.

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 or 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.

5.0 REFERENCES

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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-00016

LB-00031

Table 1. Air Sample Collection Programs

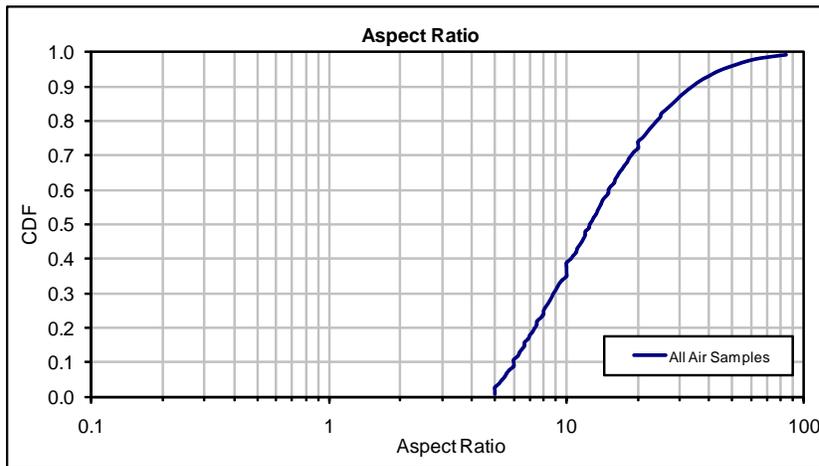
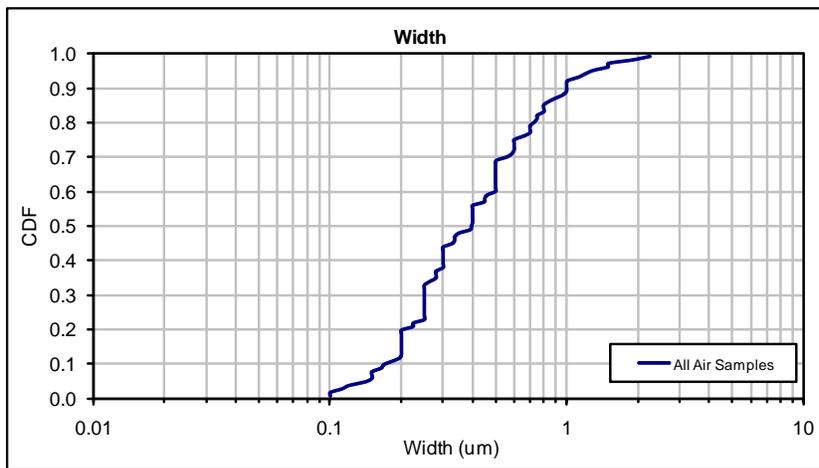
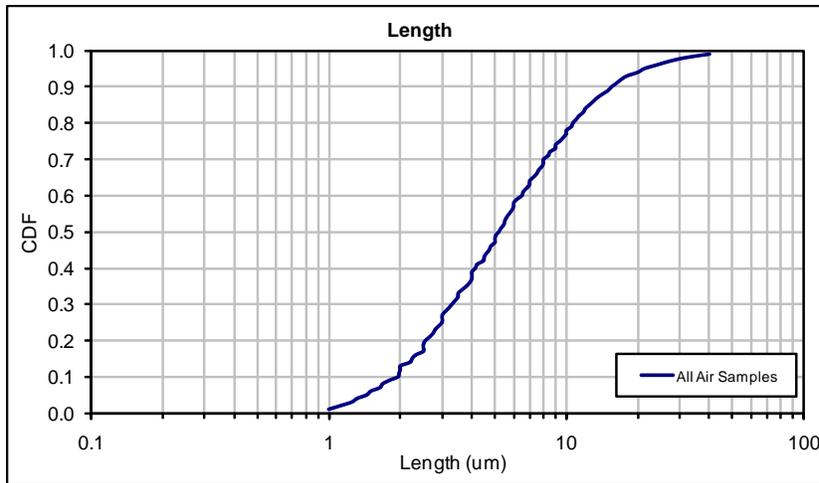
Program	Program Description	Program Date Range	Sampling and Analysis Plan (s)	Number of LA Structures ^(a)
Phase 1	Initial investigation sampling to assess nature and extent of potential contamination. Includes source areas (e.g., screening plant, export plant), commercial buildings, and residential properties.	Dec 1999 - present	USEPA 2000	328
Phase 1R	Monitoring and confirmation sampling as part of clean-up activities.	Jun 2000 - present	USEPA 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	USEPA 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	USEPA 2002	3
SQAPP	Sampling to address risk assessment data gaps. Included indoor ABS (routine activities) and outdoor ABS (raking, mowing, playing), as well as clean-up evaluation samples.	Jun 2005 - Oct 2006	USEPA 2005	1,456
Ambient Air (AA)	Ambient air monitoring program for 14 stations in OU4, 2 stations in OU2, 2 stations in OU6. Samples represent long-term (continuous 5-day) collection periods.	Oct 2006 - Jun 2008	USEPA 2006, USEPA 2007a	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	USEPA 2007b, USEPA 2007c	5,603
Indoor Schools	Stationary air sample collection from within Libby public schools	Dec 2008	USEPA 2008d	2
Outdoor Schools	Outdoor ABS sampling from Libby public schools simulating exposures to students and maintenance staff.	Jul - Sept 2009	USEPA 2009b	5
Phase 2 (OU3)	Ambient air sampling. Samples represent long-term (continuous 5-day) collection periods.	July - Oct 2008	USEPA 2008c	67
Phase 3 (OU3)	ABS air sampling of ATV riding, hiking, camp fire construction	Aug - Nov 2009	USEPA 2009a	59
Clean-up Evaluation	Sampling to monitor air and dust levels after completion of clean-up activities at 31 properties.	Nov 2003 - Feb 2004	USEPA 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

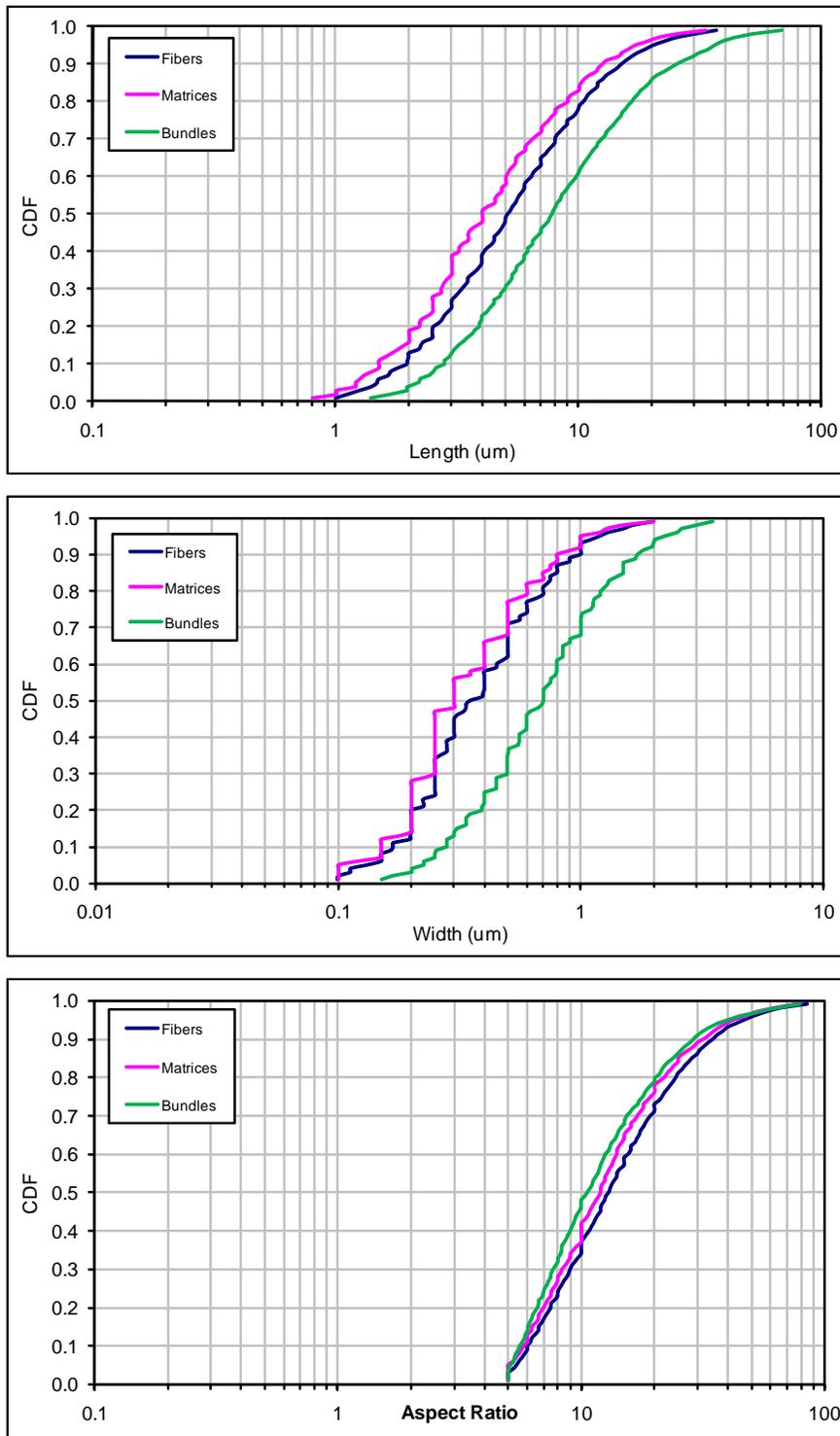


Data are based on a download of Libby 2DB performed on 12-8-09 and the Libby OU3 DB on 2-9-10.

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

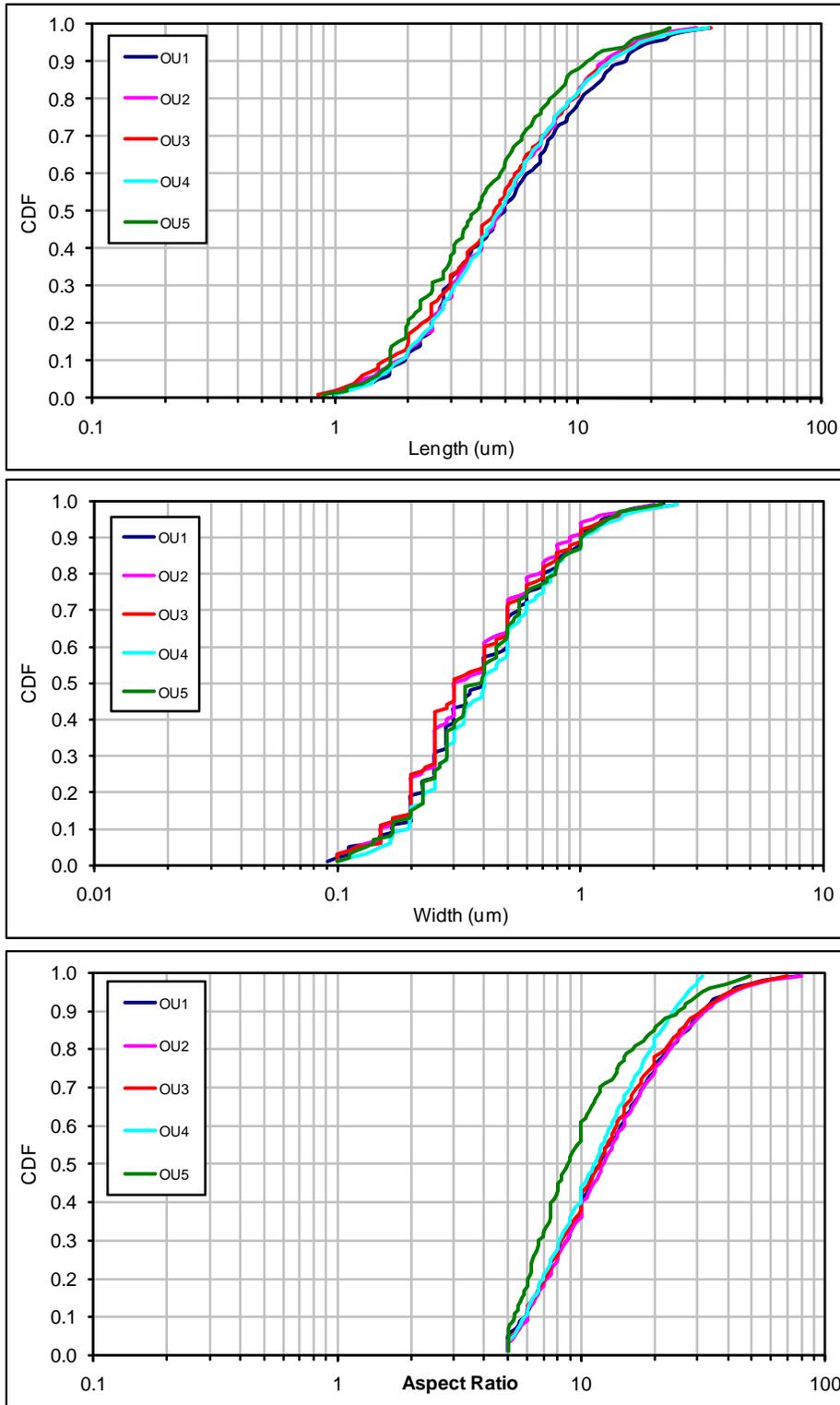


Data are based on a download of Libby 2DB performed on 12-8-09 and the Libby OU3 DB on 2-9-10.

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 is not believed to be a sufficient number of structures.

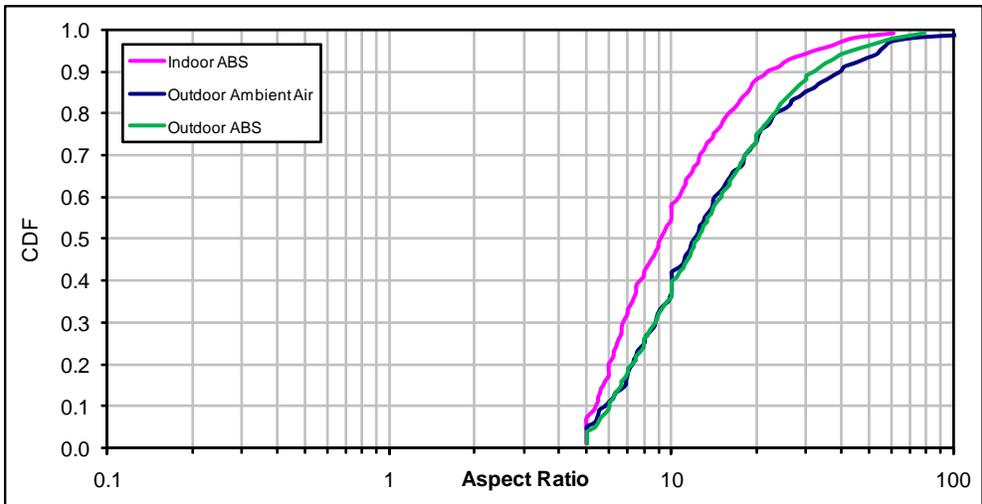
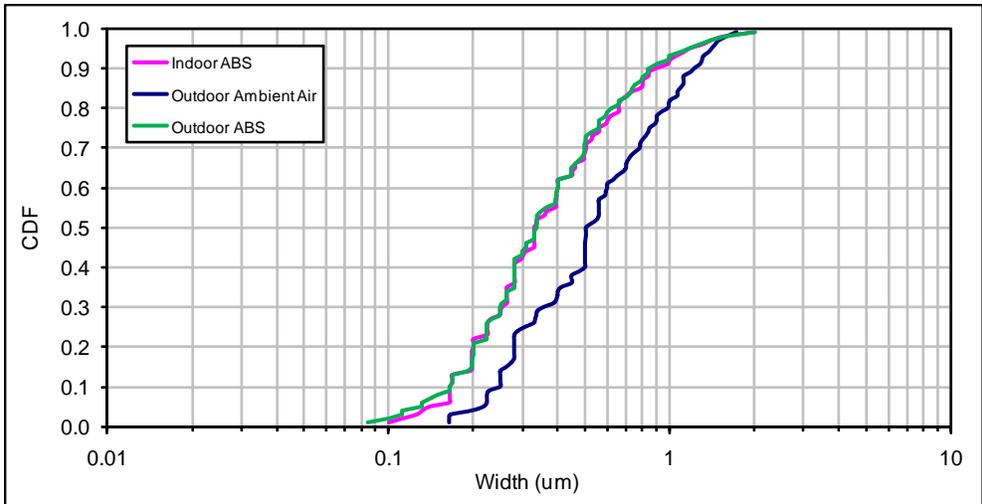
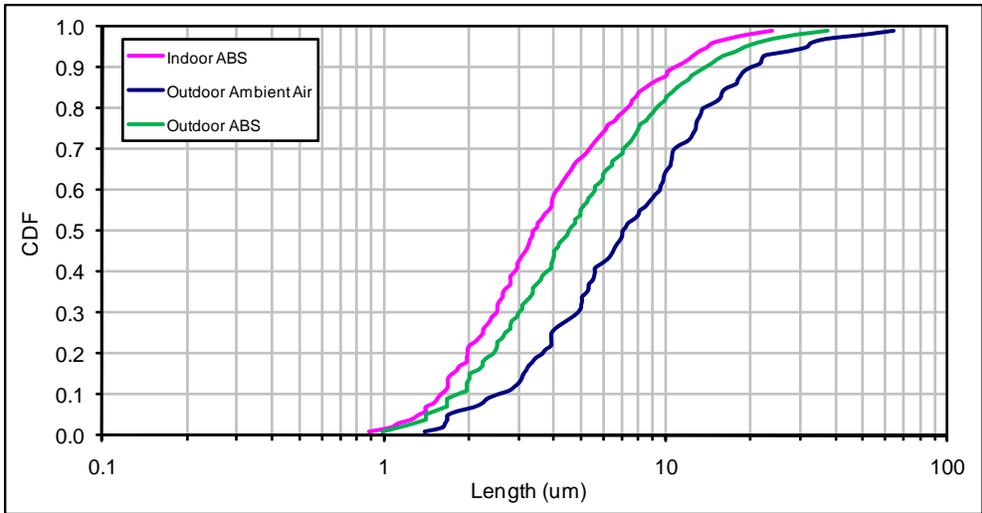
Figure 3-3. Particle Size Distributions of LA Particles in Libby Air Samples by Operable Unit (OU)



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

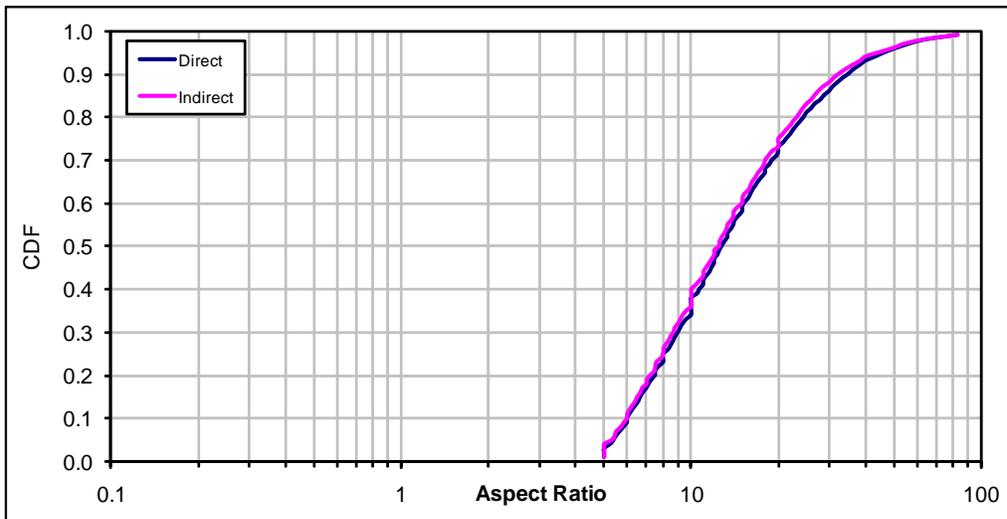
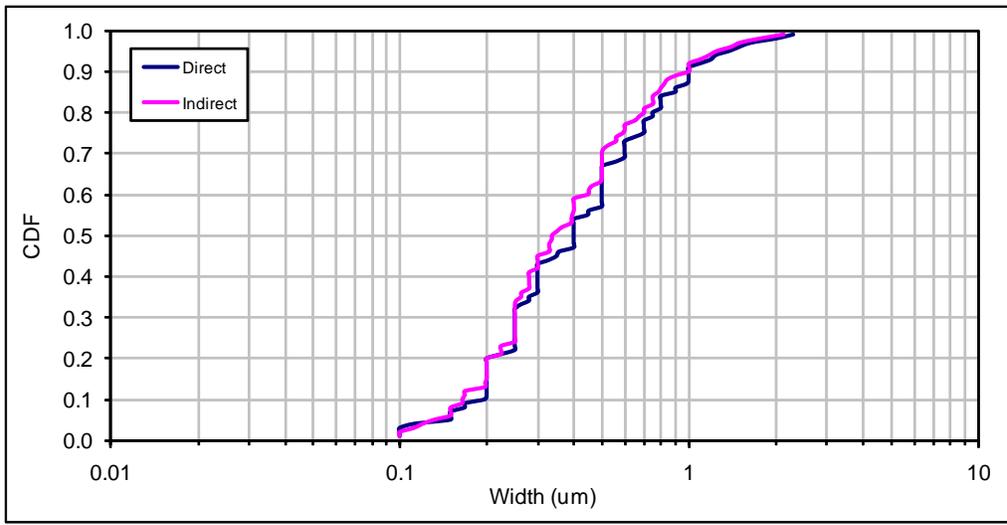
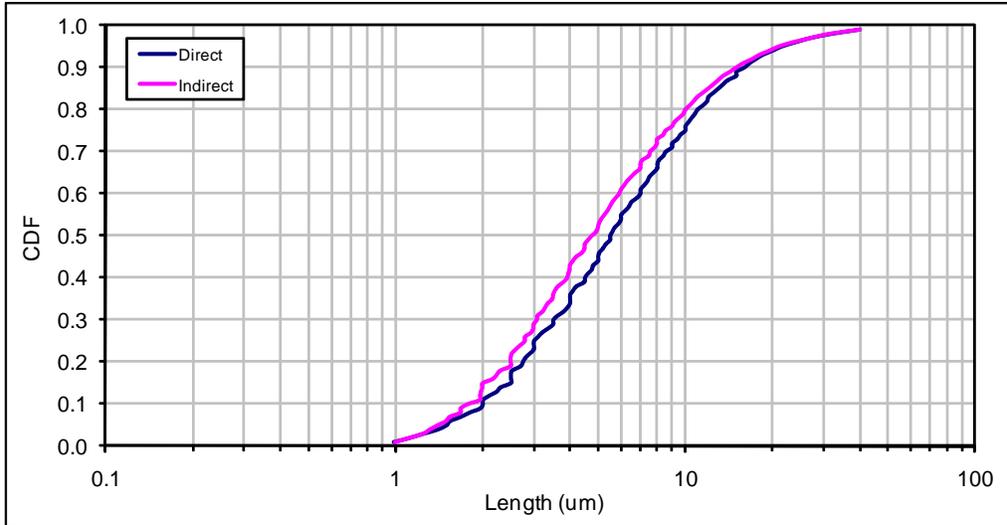
Figure 3-4. Particle Size Distributions of LA Particles in Libby Air Samples by Air Type



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

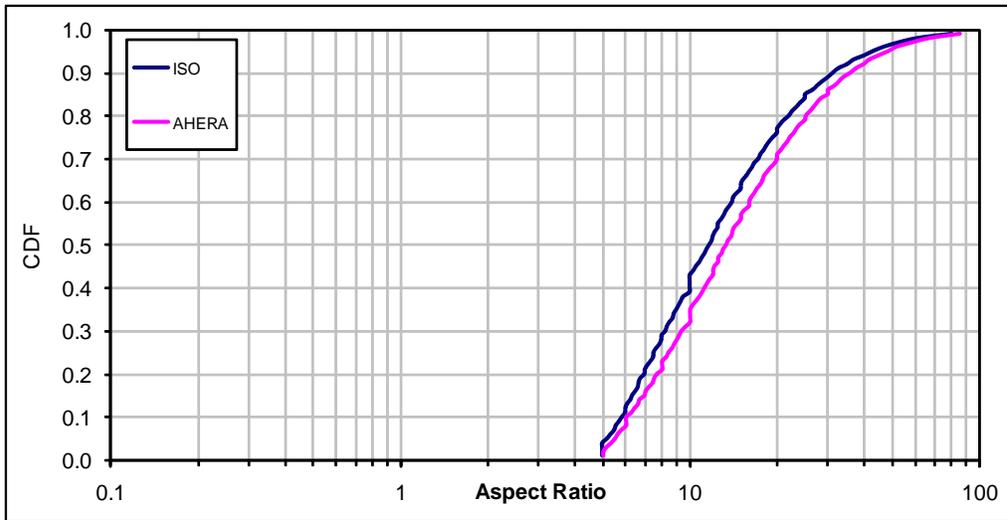
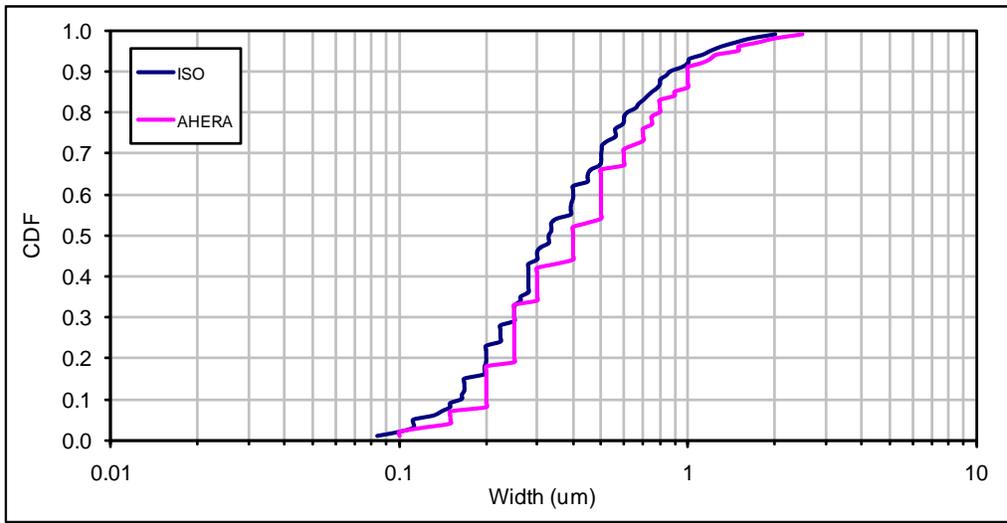
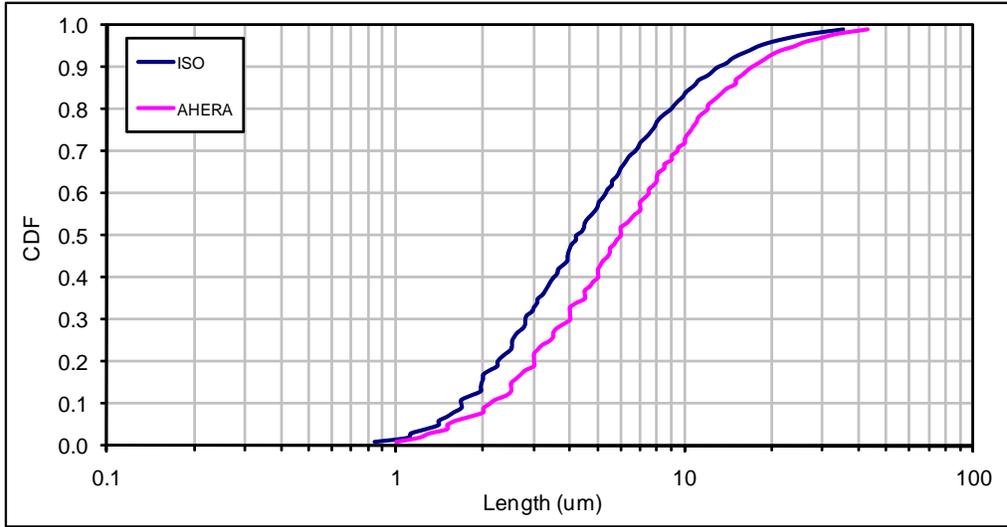
Figure 3-5. Particle Size Distributions of LA Particles in Libby Air Samples by Preparation Method



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

1 **APPENDIX C. CHARACTERIZATION OF AMPHIBOLE FIBERS FROM ORE**
2 **ORIGINATING FROM LIBBY, MT; LOUISA COUNTY, VA; AND PALABORA,**
3 **REPUBLIC OF SOUTH AFRICA**

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This document is a draft for review purposes only and does not constitute Agency policy.

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

10 The U.S. Environmental Protection Agency (EPA) Region 8 obtained samples of ore
11 from Libby, MT, South Africa, and Virginia from Dr. James Lockey, University of Cincinnati,
12 and analyzed the samples to determine mineralogy and particle size distribution (length, width,
13 and aspect ratio) using transmission electron microscopy (TEM) and energy dispersive
14 spectroscopy (EDS) to identify the nature of the amphibole fibers. Dr. Lockey obtained the
15 South African and Virginia ore samples from the Marysville, OH facility in 1980 and the Libby,
16 MT ore (Libby #3 ore) from an expansion plant in Salt Lake City, UT, in 1981. Region 8 was
17 unable to obtain vermiculite or ore from the Enoree, SC mine complex.

18 The ore from the Rainey Creek complex (Vermiculite Mountain Mine, Libby, MT)
19 resides in large ultramafic intrusive bodies that are rich in biotite, pyroxenite, and biotitite, a rock
20 comprised of almost pure biotite. The ultramafic intrusions are cut by deposits of syenite and
21 carbonatite, and much of the biotite has been hydrothermally altered to hydrobiotite and
22 vermiculite (Frank and Edmond, 2001; Meeker et al., 2003). The pyroxenite has been altered to
23 fibrous soda-rich amphiboles, and contacts with pyroxenite surrounding the biotitite contain the
24 vermiculite ore zone containing diopside, hydrobiotite, and apatite. Fibrous and nonfibrous
25 amphiboles are located in both veins and disseminated throughout the intrusive rock along
26 cleavage planes of pyroxene. Amphiboles from Vermiculite Mountain had been referred to as
27 soda tremolite, richterite, soda-rich tremolite, tremolite asbestos, and richterite asbestos by a
28 number of investigators. In 2000, Wylie and Verkouteren (2000) identified winchite as the
29 principal amphibole in the Vermiculite Mountain deposit based on chemical investigation
30 referencing the classification system of Leake et al. (1997) and optical properties. Meeker et al.
31 (2003) investigated amphibole types from the mine complex using electron probe microanalysis
32 and X-ray diffraction analysis and reported the presence of winchite, richterite, tremolite, and
33 magnesioriebeckite. Magnesio-arfvedsonite and edenite were detected in low abundance. The
34 amphibole composition of the Libby Amphiboles is roughly winchite, richterite, tremolite,
35 magnesio-riebeckite, magnesio-arfvedsonite, and edenite (84:11:6:<1:<1:<1). The O.M. Scott

1 facility received ore from the Vermiculite Mountain mine complex, Libby, MT from 1959
2 through 1980.

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

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

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

22 There is limited information on the asbestos content of the ores from the Louisa County
23 deposit. Rohl and Langer (1977) reported both chrysotile and amphibole fibers in six ore
24 samples from the Louisa County deposit. The chrysotile was reported as fibers and bundles
25 while the amphiboles fibers were classified as actinolite. Moatamed et al. (1986) analyzed a
26 Virginia ore sample collected at a processing plant in Salt Lake City, UT and reported traces of
27 fibrous amphibole asbestos identified as actionlite in the form of cleavage fragments having low
28 aspect ratios. Amphibole content for both unexfoliated and exfoliated ores ranged up to 1.3%
29 amphibole asbestos.

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

This document is a draft for review purposes only and does not constitute Agency policy.

1 As previously noted, EPA Region 8 obtained samples of ore from Libby, MT, South
2 Africa, and Virginia from Dr. James Lockey, University of Cincinnati, and analyzed the samples
3 to determine the particle-size distribution (length, width, and aspect ratio), using transmission
4 electron microscopy and energy dispersive spectroscopy to identify the mineral composition of
5 the amphibole fibers. Region 8 was unable to acquire a sample of ore from the South Carolina
6 Enoree mine complex for analysis. Region 8 conducted analysis of the ore and exfoliated
7 materials to connect the exposures of workers to mineral fibers in Marysville, OH, to the ore
8 originating in Libby, MT. The connection is based on fiber morphology, mineralogy, and
9 fiber-size similarities.

10 In order to analyze the fibers from the ore and vermiculite bulk material, the fibers must
11 be loaded onto filters and prepared for analysis by TEM. Three potential methods were
12 considered for transferring the fibers from the bulk material to filters: water elutriation,
13 glove-box transfer, and the fluidized bed asbestos segregator (FBAS). Of these three methods,
14 only the glove-box and FBAS involved physical disturbance of the bulk material to elutriate
15 fibers into the air that might be similar to handling and processing of ore in the Marysville, OH
16 plant. Due to the limited quantity of test material available for analysis, Region 8 employed the
17 FBAS as an analytical instrument to load the mineral fibers onto filters for TEM analysis

18 Briefly, samples of ore and vermiculite were prepared following the procedure outlined
19 by Bern et al. (2002). Samples were dried, ground with a Wylie mill and mortar and pestle, and
20 sieved through a 230- μm (60 mesh) sieve. Samples (exactly 2.0 g) were mixed with 18 g of
21 analytical silica sand and placed in a fluidized bed asbestos segregator vessel to load 25-mm
22 mixed cellulose ester air sampling filters (0.8- μ pore size). The fluidized bed asbestos segregator
23 was run for 3 minutes to load the filter cassettes with sufficient fibers for analysis by
24 transmission electron microscopy. Five filters were loaded for each of the ore and vermiculite
25 samples. After loading, the filters were prepared for TEM analysis by mounting on copper grids,
26 carbon coating, and subjected to TEM analysis (TEM-ISO 10312 method).

27 The laboratory followed fiber counting rules detailed in the Quality Assurance Project
28 Plan for the specific study using Libby-specific laboratory modifications. Total amphibole fibers
29 and Phase Contrast Microscopy equivalent (PCMe) fibers were counted for each of the
30 ore/vermiculite samples as described in Appendix B. A total of 1.0 mm^2 area or a total of
31 200 asbestos structures were counted to achieve the desired analytical sensitivity (1/g; 1.5×10^4).
32 Energy dispersive spectroscopy was performed on selected samples from each of the
33 vermiculite/ore samples to provide mineral characterization of individual fibers. Fiber counts
34 were recorded on National Asbestos Data Evaluation Sheet data sheets for further analysis. Only

1 the Libby, MT vermiculite and Libby, MT ore samples had sufficient fibers detected to construct
2 a fiber-size distribution.

3 Fiber counts were determined by counting fiber numbers for a specific area of the filter
4 grid or a specific number of grid openings (whichever was achieved first) to determine total
5 fibers present. As shown in Table C-1, the number of fibers for the test materials varied greatly
6 depending on the source, and the grid area measurement was exceeded prior to the fiber count
7 metric (167 grid openings ~1.0 mm²).
8

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

Sample type	Grid openings	Structures counted			Concentration (s/g)		
		LA	OA	C	LA	OA	C
Virginia Ore	167	0	0	0	0	0	0
Virginia Expanded	167	1	0	0	13,008	0	0
South Africa Ore	167	2	0	2	26,403	0	26,403
South Africa Expanded	167	0	0	0	0	0	0
Libby # 3 Ore	167	320	0	0	1,393,873	0	0
Libby Expanded	167	100	0	0	468,213	0	0

9
10 LA = Libby Amphibole, OA = Other amphibole, C = Chrysotile. Note: the designation of fibers as Libby Amphibole
11 in this instance reflects only a qualitative morphological comparison to amphiboles of the Libby, MT series.
12
13

14 The Libby #3 ore and the Libby #3 expanded material contained the greatest number of
15 fibers both in fiber counts on the filters and in calculated structures per gram of bulk material.
16 Virginia expanded and South African ore contain amphibole structures represented by low fiber
17 counts. South African ore also contained chrysotile fibers as determined by morphology and
18 EDS analysis. The absence of fibers detected in the Virginia ore and the South African-
19 expanded materials probably represents actual low fiber content of the ore and is a function of
20 the detection limit for the structure analysis. The estimation of structures per gram of material
21 indicated that there were 13,000 to 26,000 fibers per gram of bulk material, which was
22 approximately 18 times lower than the Libby, MT ore samples. The decrease in fibers found in
23 the Marysville, OH facility after 1980 when only ore from Virginia, Palabora, and South
24 Carolina was used (see Appendix F) is consistent with the findings of low fiber counts for the
25 Virginia and Palabora materials. In addition, numerous nonasbestiform minerals were also

1 detected including biotite, micas, and pyroxenes in the bulk materials from Virginia and South
2 Africa.

3 Amphiboles are a complex group of minerals characterized by double chains of silicate
4 tetrahedrons and the generic chemical formula of $A_{0-1}B_2C_5T_8O_{22}[OH]_2$ where A , B , C , and T
5 represent the various cations. The modern classification system of amphiboles is described in
6 Leake et al. (1997). To classify the mineral species of the amphibole, it is not sufficient to
7 determine its composition; the various cations must be assigned to the specific A , B , C , and T
8 sites. The cutoffs of the compositional ranges allowed for each amphibole mineral species are
9 based on the number of the cations in the various sites. The methodology to classify an
10 amphibole is to first determine its elemental compositions (e.g., as expressed as weight percent
11 oxide for each element or as atomic percent for each element). Then a normalized routine is
12 applied to the raw elemental measurements to calculate the number of each of the cations
13 contained in one formula unit. (This is a simple arithmetic calculation since the cation percents
14 have been measured, and the stoichiometry must balance the charges of the cations and anions.)
15 Generally, one formula unit is assumed to contain 23 oxygens. Next, the sites are filled up by
16 assigning cations to them subsequently, specifically:

17
18

- 19 T : Si^{4+} , Al^{3+} , and Ti^{4+}
- 20 C : Al^{3+} and Ti^{4+} (only after the T sites are filled first) and then Mg^{2+} , Fe^{2+} , Fe^{3+} , and
21 then Mn^{2+}
- 22 B : Any remaining Mg^{2+} , Fe^{2+} , and Mn^{2+} (after the C sites are filled), all Ca^{2+} , then
23 Na^+ if there is any room left
- 24 A : Na^+ and K^+ only
- 25
26

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

29 The Libby Amphibole asbestos¹ group of minerals is a complex group of amphiboles
30 consisting of six minerals:

31
32

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.

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- 1 • Winchite, $\text{CaNa}[\text{Mg}, \text{Fe}^{2+}]_4[\text{Al}, \text{Fe}^{3+}]\text{Si}_8\text{O}_{22}[\text{OH}]_2$
- 2 • Richterite, $\text{NaCaNa}[\text{Mg}, \text{Fe}^{2+}, \text{Mn}, \text{Fe}^{3+}]_5\text{Si}_8\text{O}_{22}[\text{OH}]_2$
- 3 • Tremolite, $\text{Ca}_2\text{Mg}_5\text{Si}_8\text{O}_{22}[\text{OH}]_2$
- 4 • Magnesio-riebeckite, $\text{Na}_2[\text{Mg}_3, \text{Fe}^{3+}]_2\text{Si}_8\text{O}_{22}[\text{OH}]_2$
- 5 • Magnesio-arfvedsonite, $\text{NaNa}_2[\text{Mg}_4, \text{Fe}^{3+}]\text{Si}_8\text{O}_{22}[\text{OH}]_2$
- 6 • Edenite, $\text{NaCa}_2\text{Mg}_5\text{Si}_7\text{AlO}_{22}[\text{OH}]_2$

7
8
9 Libby Amphibole is characterized by a low amount of Al in the *T* site—and a
10 correspondingly high Si content—so, according to Leake’s classification, if the Si (expressed as
11 atoms per formula unit, apfu) is at least 7.5, and Al content in the *T* site is <0.5, all 6 Libby
12 Amphibole types can be plotted on a graph of Na content of the *B* site versus the (Na + K)
13 content in the *A* site. This approach was described by Meeker et al. (2003) for the Rainy Creek
14 complex.

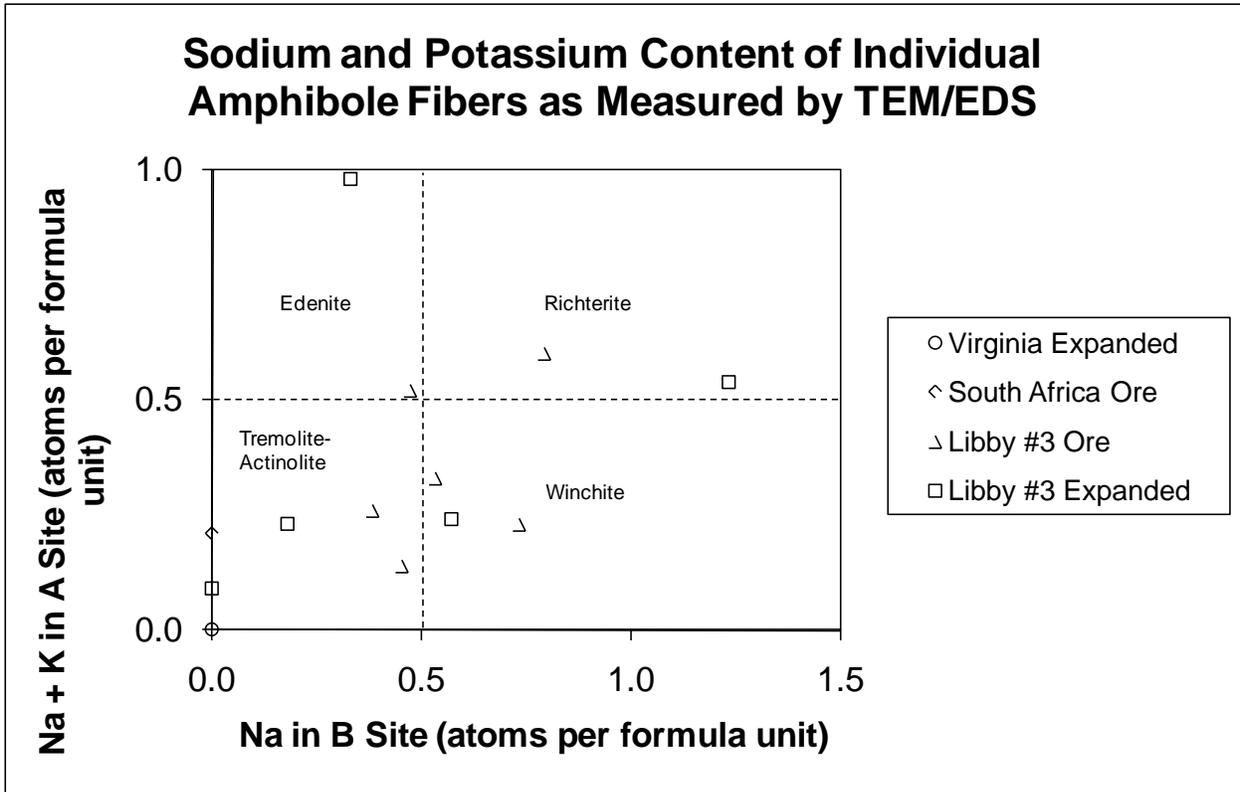
15 EDS spectra (TEM/EDS) were collected from all amphibole fibers found in the South
16 Africa and Virginia samples, and six randomly selected Libby Amphibole asbestos fibers in each
17 of the Libby, MT ore and Libby, MT expanded samples. Two bundles of asbestiform serpentine
18 (chrysotile) were found in the South African ore sample. EDS spectra were collected for one of
19 the bundles. The chemical formula of serpentine is $\text{Mg}_3\text{Si}_2\text{O}_5[\text{OH}]_4$. The EDS software package
20 collected and summarized each spectrum to determine the atomic percent of each element of
21 interest.

22 Several assumptions were made in the treatment of the TEM/EDS data:

- 23
24
25 1. Numbers of cations per formula unit are calculated on the basis of 23 oxygens. This may
26 or may not be correct because an [OH] site in the amphibole crystal can be occupied by
27 either OH^- , F^- , Cl^- , or O^{2-} . The calculated cation numbers will be affected if a significant
28 quantity of O^{2-} is in the OH site.
- 29 2. A persistent problem with amphiboles is that they can contain both ferric [3+] and ferrous
30 [2+] iron in the same crystal. For the purposes of this report all Fe was assumed to be
31 Fe^{2+} . A method for calculating the ratio of Fe^{2+} to Fe^{3+} is described in Leake et al.
32 (1997), but it is very complex, applies to polished sections, and was not attempted for this
33 report.
- 34 3. For the purposes of this report, the *T* sites were assumed to be filled completely full to
35 8 apfu, and the *C* sites were assumed to be completely full to 5 apfu. All Ca and any Mg,
36 Fe, and Mn remaining after the *C* site was full were then assigned to the *B* site. Next, Na
37 was assigned to the *B* site until it was full (2 apfu), then any remaining Na and all K were
38 assigned to the *A* site.

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1 Applying these assumptions to the TEM/EDS data produces a useable graph of the Na and K
 2 content of the amphibole fibers. As shown in Figure C-1, Libby #3 ore and Libby #3 Expanded
 3 amphiboles were characteristic of winchite and tremolite. Virginia Expanded and South African
 4 ore both contained amphibole fibers characteristic of non-Libby (Na and K⁻) in the tremolite
 5 series.
 6



7
8

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

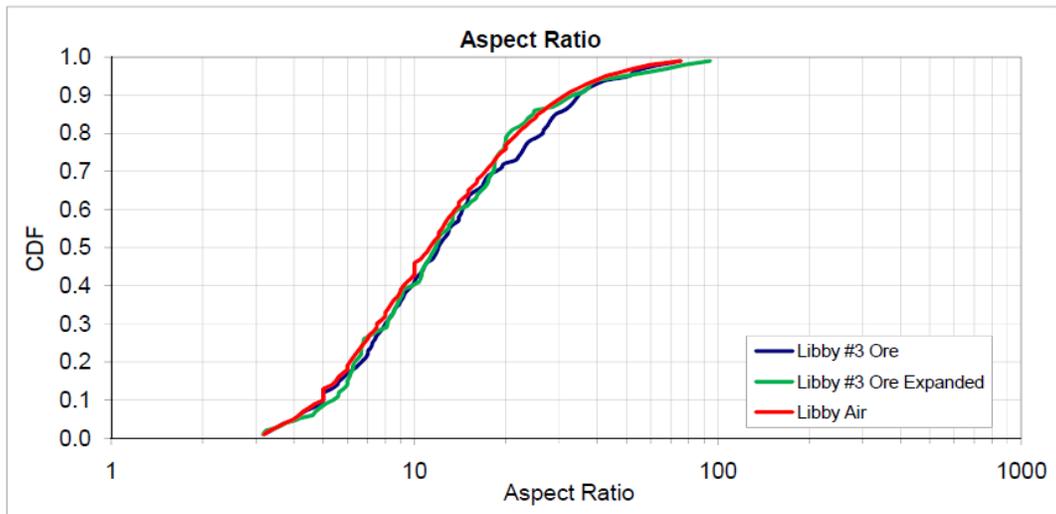
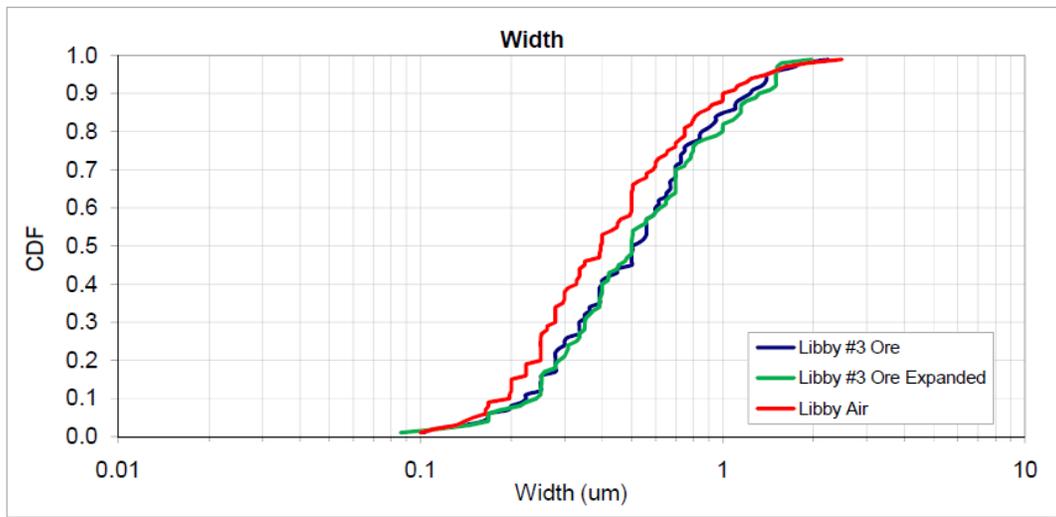
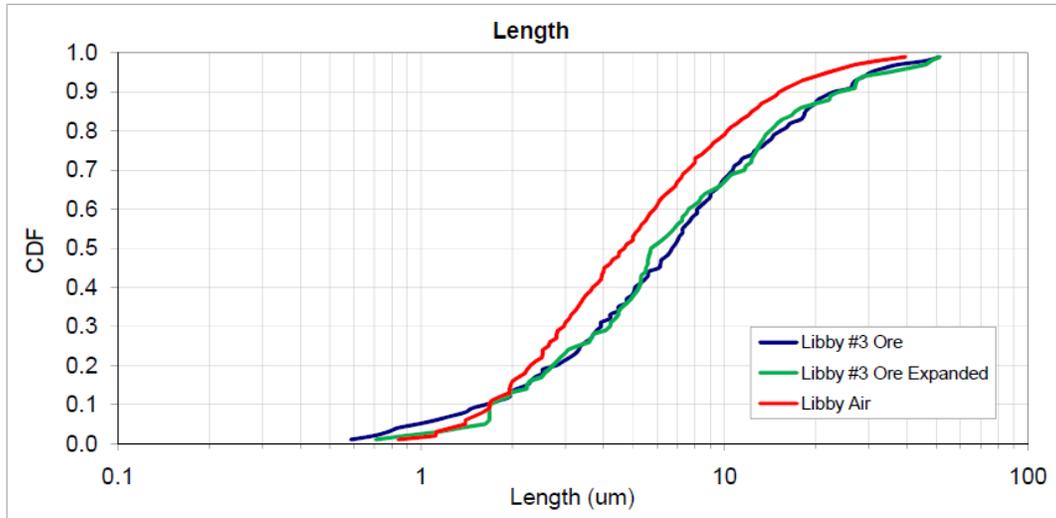
11
12

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

16
17
18
19

- The single Virginia amphibole asbestos fiber is an actinolite
- Both of the South African amphibole fibers are tremolite

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1
2

Figure C-2. Fiber-size distribution of Libby Amphibole asbestos amphiboles

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- 8 of the Libby Amphibole asbestos fibers from Libby, MT are winchite
- 4 of the Libby Amphibole asbestos fibers from Libby, MT are tremolite

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. Due to the low fiber count detected in the Virginia and South Africa sources, it was not possible to develop a fiber-size distribution for these fibers. The Libby Amphibole asbestos fiber-size data were plotted as a cumulative distribution frequency for fiber length, fiber width, and aspect ratio. These data were compared to Libby Amphibole asbestos fibers collected in Libby, MT as part of EPA's ongoing ambient air monitoring program and the Libby Asbestos Superfund site (see Appendix B). The Libby, MT ore and expanded material showed an increased frequency of longer and wider fibers than the fibers from the Libby, MT 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 Libby Amphibole asbestos fibers and were consistent with fiber-size distributions for soil activity-based-sampling data from Libby, MT.

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, MT (see also Appendix B). 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 as reported in Appendix F.

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1 **APPENDIX D. ANALYSIS OF SUBCHRONIC AND CHRONIC STUDIES AND**
2 **CANCER BIOASSAYS IN ANIMALS AND MECHANISTIC STUDIES**

3 **D.1. SUBCHRONIC AND CHRONIC STUDIES AND CANCER BIOASSAYS**

4 **D.1.1. Oral**

5 McConnell et al. (1983a) describe part of a National Toxicology Program study (NTP,
6 1990a) performed to evaluate the toxicity and carcinogenicity of ingestion of several minerals.
7 This study examined chrysotile and amosite in both hamsters and rats, and crocidolite and
8 tremolite only in rats. This chronic bioassay was designed to encompass the lifetime of the
9 animal, including exposure of the dams from which the test animals were derived. Although the
10 study examined chrysotile, amosite, crocidolite, and tremolite, for the purposes of this
11 assessment, the focus is on the results from exposure to tremolite. The tremolite (Gouverneur
12 Talc Co., Gouverneur, NY) used was not fibrous. Instead, the material was crystalline, as this
13 form was a common contaminant in talc at the time of these studies (McConnell et al., 1983a)
14 (see Table D-1). Citing the Stanton (1981) paper, McConnell et al. (1983a) stated that crystalline
15 tremolite can become fibrous upon grinding. Tremolite was incorporated by 1% weight into
16 NIH-31 feed and given to 250 male and female F344 rats from birth until death (118 male and
17 female controls).

18
19
20 **Table D-1. Fiber characteristics and distribution of fibers analyzed in feed**
21 **studies in F344 rats**
22

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

23
24 ^aAverage groups, more detailed in primary paper.

25
26 Source: McConnell et al. (1983a).

27
28
29 No significant tumor induction was observed in the animals with oral exposure to
30 tremolite animals. Although nonneoplastic lesions were observed in many of the aging rats,
31 these were mostly in the stomach and occurred in both controls and exposed animals. The
32 lesions included chronic inflammation, ulceration, and necrosis of the stomach (McConnell et al.,

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1 1983a). McConnell et al. (1983a) suggested that nonfibrous tremolite could account for the lack
 2 of toxicity following exposure in this group of animals. Also, oral studies of asbestos, in general,
 3 show decreased toxicity and carcinogenicity as compared to inhalation and
 4 implantation/injection studies.

5
 6 **D.1.2. Inhalation**

7 Davis et al. (1985) performed a chronic inhalation study examining response to tremolite
 8 asbestos. Groups of 48 specific-pathogen-free (SPF) male Wistar rats were exposed in a
 9 chamber to 10 mg/m³ (~1,600 fibers/mL, >5 µm) of commercially mined tremolite (South
 10 Korea) for a total of 224 days (7 hours per day, 5 days per week) over a 12-month period. The
 11 tremolite sample contained approximately 50% fibers 10–100-µm long, using a fiber definition
 12 of length = >5 µm, diameter = <3 µm, and aspect ratio = >3:1. The results of the inhalation
 13 study produced very high levels of pulmonary fibrosis, as well as 16 carcinomas and
 14 2 mesotheliomas, among the 39 tremolite-exposed animals (see Tables D-2 and D-3). No
 15 pulmonary tumors were observed in the controls.

16
 17 **Table D-2. Pulmonary fibrosis and irregular alveolar wall thickening**
 18 **produced by tremolite exposure**
 19

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)

20
 21 ^aPercentage of 100 squares counted in lung tissue area.

22 ^bPercentage of total lung tissue area.

23
 24 SD = standard deviation.

25
 26 Source: Adapted from Davis et al. (1985).
 27

Table D-3. Tumors (benign and malignant) produced by tremolite exposure

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

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

Although Davis et al. (1985) did not describe the 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-2). 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-3 and appear to be unrelated to exposure. Although a method for an injection study is described in Davis (1985), only the inhalation results are presented. This same tremolite was used in later intraperitoneal injection experiments (Davis et al., 1991) and might be what the authors are referring to in this article.

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-4). The long-term effects from the same exposure were described in Bernstein et al. (2005) (6 hours per day, 5 days per week). This study describes the full results through 1 year after cessation of tremolite exposure in Wistar rats (*n* = 56). The tremolite samples were chosen to have 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, or a total of 1,000 fibers and nonfibrous particles were recorded (Bernstein et al., 2003). Lung tissue and associated lymph nodes were examined by

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1 histopathology following tissue digestion. Associated lymph nodes showed erythrophagocytosis
2 (minimal severity) in one animal at all time points, compared to chrysotile and control, which
3 showed erythrophagocytosis (minimal severity) only at 180 days.

4
5 **Table D-4. Chrysotile and tremolite fiber characteristics of fibers used in**
6 **inhalation exposure studies in rats**
7

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

8
9 Source: Bernstein et al. (2003).

10
11
12 Table D-4 shows the comparison of number, concentration, and mean size distribution of
13 fibers used in this study. Note that the mean tremolite fiber diameter and length are much greater
14 than those of chrysotile, but the size ranges do overlap somewhat (Bernstein et al., 2003). The
15 long tremolite fibers, once deposited in the lung, remain throughout the rat's lifetime. Even the
16 shorter fibers, following early clearance, remain with no dissolution or additional removal. At
17 365 days postexposure, the mean lung burden was 0.5 million tremolite fibers >20-µm long and
18 7 million fibers 5–20-µm long with a total mean lung burden of 19.6 million tremolite fibers.
19 The tremolite-exposed rats showed a pronounced inflammatory response in the lung as early as
20 1 day postexposure, with the rapid development of granulomas (1 day postexposure) followed by
21 the development of pulmonary fibrosis characterized by collagen deposition within the
22 granulomas. Increases in alveolar macrophages and granulomas were observed at all time points
23 (1, 2, 14, 90, and 180 days) measured except 365 days. Pulmonary fibrosis increased starting at
24 14 days and continued to be observed for up to 365 days. Slight interstitial fibrosis also was
25 observed, but only at 90 and 180 days postexposure. This study demonstrates that tremolite
26 exposure leads to pronounced inflammation and fibrosis (Bernstein et al., 2006). Tumors were
27 not observed in this study, which is a consistent observation with the time frame observed in
28 other studies (i.e., 1-year postexposure) (Smith, 1978).

29 30 **D.1.3. Intratracheal Instillation**

31 A recent study by Putnam et al. (2008) was designed to explore gene-environment
32 interactions in the development of asbestos-related diseases. C57Bl/6 mice were exposed once

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1 to either Libby Amphibole asbestos¹ (Six Mix) (100 µg via intratracheal instillation); crocidolite
2 (100 µg via intratracheal instillation); or saline (30 µL via intratracheal instillation).
3 Characteristics of fibers are described in Table D-5. Animals were sacrificed, and the lungs were
4 harvested 6 months postinstillation. The left lung was used for ribonucleic acid (RNA) isolation,
5 and the right lung was used for histology (personal communication, e-mail from E. Putnam
6 [University of Montana] to M. Gwinn [U.S. EPA] 02/26/09). Histology on mouse lungs from
7 each treatment group demonstrated an increase in fibrosis, as viewed by Gomori’s trichrome
8 staining, following exposure to crocidolite and, to a lesser extent, Libby Amphibole asbestos.
9 Histologic tissue was also exposed to Lucifer Yellow stain to further analyze variability in
10 collagen following exposure. Lucifer Yellow staining revealed an increase in collagen following
11 exposure to both crocidolite and Libby Amphibole asbestos, but only crocidolite exposure led to
12 a statistically significant increase ($p < 0.05$). RNA was isolated from homogenized lungs and
13 purified for use in microarray analysis. Pooled RNA samples from mice in each exposure group
14 were analyzed on a 0K-element mouse oligonucleotide array (MWG Biotech), and expression
15 was compared to a mouse reference standard RNA. Gene-expression results were analyzed by
16 GO Miner, and genes exhibiting at least 1.25-fold up- or down-regulation in treated lungs were
17 described. These included genes involved in membrane transport, signal transduction, epidermal
18 growth factor signaling, and calcium regulation for both crocidolite and Libby Amphibole
19 asbestos exposures, which support the increase in collagen observed above. Some limitations to
20 this study are the use of a standard reference for gene-expression comparisons (as opposed to the
21 saline controls), the practice of describing genes only if a greater than twofold difference in
22 expression is observed, and the use of pooled samples of homogenized whole lung that in some
23 cases could dilute variability between different areas of exposed lung (different lobes, fibrotic
24 versus nonfibrotic).

25
26 **Table D-5. Fiber characteristics for intratracheal instillation studies in mice.**

Material	Diameter	Length	Aspect Ratio
Libby Amphibole asbestos (Six Mix)	0.61 ± 1.22 µm	7.21 ± 7.01 µm	22.52 ± 22.87
Crocidolite	0.16 ± 0.09 µm	4.59 ± 4.22 µm	34.05 ± 43.29

28
29 Source: Blake et al. (2007, 2008); Putnam et al. (2008); Smartt et al. (2009).
30
31

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.

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1 A follow-up paper to Putnam et al. (2008), prepared by Smartt et al. (2009), examined the
2 increase of collagen in C57Bl/6 mouse lung following exposure to crocidolite or Libby
3 Amphibole asbestos and also examined a few specific gene alterations by quantitative reverse
4 transcription polymerase chain reaction (RT-PCR). Animals ($n = 3$ to 6 mice per group) were
5 dosed with the same samples (see Table D-5) as described above (Putnam et al., 2008) but were
6 euthanized at 1 week, 1 month, and 3 months postinstillation. Treated mice were then divided
7 into two groups, with the left lung from the first group used for RNA isolation and the right lung
8 used for histology. The lungs from the second group were used for protein isolation and
9 hydroxyproline assay (personal communication, e-mail from E. Putnam [University of Montana]
10 to M. Gwinn [U.S. EPA] 02/26/09). Similar to results from Putnam et al. (2008), Gomori's
11 staining demonstrated increased collagen and inflammation at the airways in lungs of mice
12 exposed to either Libby Amphibole asbestos or crocidolite. These results were similar following
13 exposure to both amphiboles, with crocidolite effects appearing more severe at all time points
14 examined. No changes in the pleura of the lungs that were indicative of potential mesothelioma
15 were observed; such changes, however, would not be expected in such a short time-frame. This
16 study also examined severity of inflammation and found that, on average, crocidolite-exposed
17 animals demonstrated minimal inflammation at 1 week postinstillation, which then progressively
18 worsened at 1 and 3 months postinstillation. Although both asbestos exposures led to increased
19 inflammation, Libby Amphibole asbestos exposure demonstrated minimal inflammation that did
20 not progress in the time points examined. Gene-expression alterations were measured by
21 quantitative RT-PCR for genes involved in collagen accumulation and scar formation (Col1A1,
22 Col1A2, Col3A1). Although exposure to both forms of asbestos at 1 week and 1 month
23 postinstillation led to increased Col gene expression, the levels and subtypes altered varied.
24 Libby Amphibole asbestos exposure led to increased gene expression of Col1A2 at 1 week
25 postinstillation and Col3A1 at 1 month postexposure, while crocidolite led to no significant
26 alterations in the expression of these genes. Both crocidolite and Libby Amphibole asbestos
27 exposure led to increased Col1A1 gene expression as compared to saline control at 1 week and
28 1 month postexposure. Due to these differences in expression, the authors also examined the
29 collagen protein levels in the lungs to compare to the gene-expression changes. Total collagen
30 content was determined by measuring the hydroxyproline content in the caudal aspect of the left
31 lung. As compared to saline-exposed mice, a significant increase in hydroxyproline was
32 observed at 1 week and 1 month following exposure to both crocidolite and Libby Amphibole
33 asbestos; however, only lungs from crocidolite-exposed animals demonstrated a significant
34 increase at 3 months postexposure. These studies demonstrate that exposure to Libby

1 Amphibole asbestos lead to inflammation and fibrosis, although with differences in the time and
2 level of response.

3 Shannahan et al. (2011a) exposed two rat models of human cardiovascular disease to
4 Libby Amphibole asbestos² to determine if the preexisting cardiovascular disease in these
5 models would impact lung injury and inflammation following exposure. Healthy Wistar Kyoto
6 (WKY) rats were compared to spontaneously hypertensive (SH) and spontaneously hypertensive
7 heart failure (SHHF) rats following exposure. These rat models demonstrate pulmonary iron
8 homeostasis dysregulation (Shannahan et al., 2010). All rats (male only) were exposed to
9 0, 0.25, or 1.0 mg/rat via intratracheal instillation and were examined at 1 day, 1 week and
10 1 month postexposure. No changes were observed histopathologically, however, changes were
11 observed in markers of homeostasis, inflammation, and oxidative stress. Bronchoalveolar lavage
12 fluid (BALF) protein was significantly increased in both the SH and SHHF rat models as
13 compared to controls as early as 1 week postexposure. γ -glutamyl transferase (GGT) activity was
14 increased in a concentration-dependent manner with exposure to Libby Amphibole asbestos at
15 the earliest time point measured (1 day), and was more pronounced in WKY rats as compared to
16 SH and SHHF rats. Lactic dehydrogenase (LDH) activity was also elevated in all strains but was
17 more pronounced in the SHHF rat model. Neutrophil increases were observed following
18 exposure in all strains, peaking at 1 day postexposure in all strains and persisting in the SH and
19 SHHF rats until 1 month postexposure. Macrophages showed similar results but persisted only
20 in the SH rat model until 1 month postexposure. In order to determine any impact of exposure
21 on iron homeostasis, BALF ferritin and transferrin levels were measured in the lung. Increases
22 in ferritin and transferrin were observed in both SH and SHHF rats as compared to WKY
23 controls. Nonheme iron was also observed to be increased in only the SH rats at 1 days and
24 1 week postexposure. Markers of inflammation (MIP-2) and oxidative stress (heme
25 oxygenase-1, HO-1) were elevated in both SH and SHHF as compared to WKY rats at baseline,
26 but limited exposure-related differences were observed. Limited changes were also observed in
27 ascorbate and glutathione levels in BALF and lung tissue. While inflammation and cell injury
28 were observed in all strains, no strain-related differences were observed following exposure to
29 Libby Amphibole asbestos (Shannahan et al., 2011a). In conclusion, this study showed the
30 potential for population variability related to cardiac disease in response to exposure to Libby
31 Amphibole asbestos, including markers of cellular injury, iron homeostasis, and inflammation.

32 Shannahan et al. (2011b) tested the hypothesis that Libby Amphibole asbestos³ will bind
33 iron and increase the inflammogenic activity of fibers in vitro and acute lung injury and

²Median fiber dimensions as determined by TEM: length = 3.59 μ m; width = 0.23 μ m; aspect ratio \geq 5.

³ Median fiber dimensions as determined by TEM: length = 3.59 μ m; width = 0.23 μ m; aspect ratio \geq 5.

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1 inflammation in vivo. The authors examined the ability of Libby Amphibole asbestos to bind
2 exogenous iron in an acellular system and evaluated iron-related alterations in the production of
3 reactive oxygen species (ROS). The authors also investigated the role of iron in the acute
4 inflammogenic response in vitro, using human bronchiolar epithelial cells, and in vivo using SH
5 rats by modulating fiber-associated iron concentrations. In a cell-free medium, Libby
6 Amphibole asbestos bound about 16 µg of iron/mg of fiber and increased ROS generation about
7 3-fold. Generation of ROS was reduced by treatment with deferoxamine (DEF), an iron
8 chelator. To determine the role of iron in Libby Amphibole asbestos ROS generation and
9 inflammation, BEAS2B cells (bronchiolar epithelial cell line) were exposed to Libby Amphibole
10 asbestos (50 µg), iron-loaded Libby Amphibole asbestos, or Libby Amphibole asbestos treated
11 with DEF. No conditions altered HO-1 or ferritin mRNA expression. Libby Amphibole
12 asbestos by itself markedly increased IL-8 gene expression, which was significantly reduced by
13 iron loaded Libby Amphibole asbestos, but increased with Libby Amphibole asbestos treated
14 with DEF. To determine the role of iron in Libby Amphibole asbestos-induced lung injury in
15 vivo, spontaneously hypertensive rats were exposed intratracheally to either saline (300 µl), DEF
16 (1 mg), ferric chloride (21 µg), Libby Amphibole asbestos (0.5 mg), iron loaded Libby
17 Amphibole asbestos (0.5 mg), or Libby amphibole asbestos plus DEF (0.5 mg). Neither ferric
18 chloride nor DEF increased bronchoalveolar lavage fluid (BALF) neutrophils compared to saline
19 at 24 hours after treatment. Libby Amphibole asbestos exposure led to a statistically significant
20 increase in BALF neutrophils ($p < 0.05$). Loading of iron on Libby Amphibole asbestos, but not
21 chelation, slightly decreased inflammation (Libby Amphibole asbestos + DEF > Libby
22 Amphibole asbestos > iron loaded Libby Amphibole asbestos). At 4 hours after exposure, Libby
23 Amphibole asbestos-exposed lung mRNA expression of MIP-2 was significantly reduced in rats
24 exposed to iron loaded Libby Amphibole asbestos, but increased by DEF (Libby Amphibole
25 asbestos + DEF > Libby Amphibole asbestos > iron loaded Libby Amphibole asbestos). Ferritin
26 mRNA expression was elevated in rats exposed to iron loaded Libby Amphibole asbestos
27 compared to the Libby Amphibole asbestos control. HO-1 expression was unchanged following
28 treatment with Libby Amphibole asbestos. The authors concluded that the acute inflammatory
29 response following exposure to Libby Amphibole asbestos might be modified by the fiber's
30 ability to complex iron, rather than redox cycling of fiber associated iron. The authors further
31 concluded that iron overload conditions may influence susceptibility to Libby Amphibole
32 asbestos-induced pulmonary disease.

33 Padilla-Carlin et al. (2011) investigated pulmonary and histopathological changes in a
34 male Fischer 344 rats following exposure to Libby Amphibole asbestos⁴. The rats were

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

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1 administered a single dose of either saline, amosite (0.65 mg/rat), of Libby Amphibole asbestos
2 (0.65 or 6.5 mg/rat) by intratracheal instillation. At time from 1 day to 3 months after exposure,
3 bronchoalveolar lavage (BAL) was performed and the right and left lung was removed for
4 Rt-PCR and histopathological analysis, respectively. The results showed that amosite exposure
5 (0.65 mg/rat) resulted in a higher degree of pulmonary injury, inflammation, and fibrotic events
6 than the same mass dose of Libby Amphibole. Both amosite and Libby Amphibole resulted in
7 higher levels of cellular permeability and injury, inflammatory enzymes, and iron-binding
8 protein in both BAL fluid and lung tissue compared to saline controls. In addition
9 histopathological examination showed notable thickening of interstitial areas surrounding the
10 alveolar and terminal bronchioles in response to amosite and Libby Amphibole. However,
11 mRNA levels for some growth factors (e.g., PDGF-A and TGF-1 β), which contribute to fibrosis,
12 were down regulated at several time points. The authors concluded that on a mass basis amosite
13 produced greater acute and persistent lung injury in this study.

14 In an early study, Sahu et al. (1975) described histological changes in the lungs of mice
15 exposed individually to amosite, anthophyllite, and tremolite. Fibers were described only as
16 <30- μ m long. Groups of 20 male albino Swiss mice were exposed to amosite, anthophyllite, and
17 tremolite at a single dose of 5 mg, and two animals from each group were sacrificed at 1, 2, 7,
18 15, 30, 60, 90, 120, and 150 days postexposure. Microscopic results following exposure to
19 tremolite showed acute inflammation of the lungs at 7 days postexposure, including macrophage
20 proliferation and phagocytosis similar to that observed with amosite and anthophyllite. Limited
21 progression of fibrotic response was observed at 60 and 90 days postexposure, with no further
22 progression of fibrotic response.

23 Blake et al. (2008) and Pfau et al. (2008) examined the role of asbestos in autoimmunity.
24 Blake et al. (2008) performed in vitro assays with Libby Amphibole asbestos, and both studies
25 performed the in vivo assays with tremolite. C57BL/6 mice were instilled intratracheally for a
26 total of two doses each of 60- μ g saline and wollastonite or Korean tremolite sonicated in sterile
27 PBS, given 1 week apart in the first 2 weeks of a 7-month experiment. Detailed fiber
28 characteristics were described in Blake et al. (2007) for wollastonite and Libby Amphibole
29 asbestos, but not for Korean tremolite (see Table D-5; wollastonite and Korean tremolite not
30 shown).

31 Blake et al. (2008) described autoantibody production, monitored biweekly with blood
32 samples from saphenous vein bleeds and then by cardiac puncture following euthanization.
33 Specific autoantibodies were identified by immunoblotting with known nuclear antigens. These
34 autoantibodies were then incubated with murine macrophage cells previously exposed to Libby
35 Amphibole asbestos, wollastonite, or vehicle control (binding buffer containing 0.01 M Hepes,

1 0.14 M NaCl and 2.5 mM CaCl₂). Only sera from mice exposed to tremolite showed antibody
2 binding colocalized with SSA/Ro52 on the surface of apoptotic blebs (Blake et al., 2008).

3 In Pfau et al. (2008), collected serum samples, and urine were checked for protein
4 bi-weekly for 7 months. By 26 weeks, the tremolite-exposed animals had a significantly higher
5 frequency of positive antinuclear antibody tests compared to wollastinate and saline. Most of the
6 tests were positive for dsDNA and SSA/Ro52. Serum isotyping showed no major changes in
7 immunoglobulin subclasses (IgG, IgA, IgM), but serum IgG in tremolite-exposed mice decreased
8 overall. Further, IgG immune complex deposition in the kidneys increased, with abnormalities
9 suggestive of glomerulonephritis. No increased proteinuria was observed during the course of
10 the study. Local immunologic response was further studied on the cervical lymph nodes.
11 Although total cell numbers and lymph-node size were significantly increased following
12 exposure to tremolite, percentages of T- and B-cells did not significantly change. Because
13 tremolite is part of the makeup of Libby Amphibole asbestos (6%), using tremolite-exposed mice
14 might yield a similar response to Libby Amphibole asbestos-exposed mice. This same effect has
15 been demonstrated following exposure to ultraviolet radiation in skin cells, suggesting a similar
16 mechanism (Saegusa et al., 2002).

18 **D.1.4. Injection/Implantation**

19 LVG:LAK hamsters were intrapleurally injected with tremolite obtained from the Libby,
20 MT mine in an unpublished study by Smith (1978) prepared for W.R. Grace & Company. These
21 samples were identified as tremolite (22260p5; Sample 60) and 50% tremolite + 50% vermiculite
22 (22263p2, Sample 63). Both fiber samples were measured by optical phase microscopy, and
23 fibers were described as amorphous, irregularly shaped particles of about 5–15 µm diameter,
24 with Sample 60 (tremolite) also containing the occasional fiber up to 30 µm long. Fiber size for
25 Sample 60 (tremolite) also was measured by scanning electron microscopy (SEM) and was
26 determined to have a geometric mean length of 2.07 µm, a geometric mean diameter of 0.2 µm,
27 and an average aspect ratio of 10.36. Twenty-five milligrams of each of the two samples were
28 individually injected intraperitoneally into the pleural cavity of LVG:LAK hamsters. Pathology
29 was examined at approximately 3 months postexposure in 10 animals from each group, with the
30 remaining animals observed until death, or 600 days postexposure, depending on the health of
31 the animal. Average survivorships were 410, 445, and 421 days in groups exposed to Sample 60,
32 Sample 63, and saline, respectively (see Table D-6). Pleural fibrosis was observed 3 months
33 postexposure, and mesothelioma was observed in both treatment groups between 350 and
34 600 days postexposure, with no mesotheliomas in control groups.

1 **Table D-6. Pleural adhesions and tumors following intraperitoneal injection**
 2 **exposure in LVG:LAK hamsters (25 mg)**
 3

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

4
 5 ^aAs analyzed in first group sacrificed (between 41 and 92 days postexposure).

6 ^bRating for pleural adhesions: 0 = no adhesions; 1 = minimal adhesions; 4 = extensive adhesions.

7 ^cThese include adrenal adenoma, adrenal adenocarcinoma, lymphoma, pulmonary adenocarcinoma, adrenal
 8 and salivary carcinoma, mesothelioma, rhabdomyosarcoma, hepatoma, thyroid carcinoma, subcutaneous
 9 carcinoma, and malignant melanoma.

10
 11 Source: Smith (1978).
 12
 13

14 The Smith et al. (1979) study was designed to determine whether mesothelioma is a
 15 nonspecific result of mesothelial cells trapped in fibrous pleural adhesions, occurring regardless
 16 of fiber type. Earlier studies by this group suggested that fibrosis and tumors resulting from fiber
 17 exposure (chrysotile or glass) were related to fiber dimensions (>20- μ m long, >0.75- μ m
 18 diameter) (Smith, 1974). Injected fibrous talc (FD-14) was used as a negative control in earlier
 19 studies and led to limited fibrosis and no tumor formation. The characteristics of the FD-14
 20 sample are described in the proceedings of Smith (1974). No further information could be found
 21 on the characteristics of the samples used in this study.⁵ Because the talc contained
 22 50% tremolite, 35% talc, 10% antigorite, and 5% chlorite, it was considered a tremolite sample
 23 by Smith (1978). When the sample was later analyzed independently by Wylie et al. (1993),
 24 only 64 (12.8%) of 500 tremolite particles measured met the National Institute for Occupational
 25 Safety and Health definition of a fiber ($\geq 3:1$ aspect ratio). Wylie et al. (1993) note, however,
 26 that very long fibers of the mineral talc, with narrow widths and fibrillar structure, occur in this
 27 sample. A second tremolite sample (Sample 275) used by Smith et al. (1979) was described as
 28 similar to FD-14, although no details were given. The last two samples were prepared from a

⁵This fiber is also analyzed in Wylie et al. (1993) and Stanton et al. (1981).

1 deposit of tremolitic talc from the western United States (Sample 31) and from a specimen of
 2 asbestiform tremolite (Sample 72),⁶ respectively.

3 Each of the four samples was examined microscopically, although the data were not
 4 reported in the paper by Smith et al. (1979). The average fibers in Sample 72 were long, thin,
 5 crystalline fibers (>20- μm long, 0.4- μm diameter). Sample 31 appeared to have fewer long, thin
 6 fibers than Sample 72, and many of the fibers in this sample were acicular. The characteristics
 7 of the FD-14 sample were determined by phase microscopy (Smith, 1974), but no
 8 characterization method was reported for the other three samples in this study. Other samples
 9 used by this group have been analyzed by both optical and electron microscopy (Smith, 1974;
 10 Smith, 1978). The limited information on the fiber characteristics of the samples used in these
 11 studies is provided in Table D-7. Note that no information was provided confirming the
 12 presence or absence of particles or fibers less than 5 μm in length in any of the three papers by
 13 Smith (1974) or Smith et al. (1978, 1979). These data deficiencies limit the interpretation of
 14 results from this study.

15
 16 **Table D-7. Fiber characteristics and numbers of resulting tumors following**
 17 **intrapleural injection of 10- or 25-mg fiber samples into Syrian hamsters**
 18

Sample	Average length ^a (μm)	Average diameter ^a (μm)	Tumors/survivors at 10 mg ^b			Tumors/survivors at 25 mg ^b		
			350 days	500 days	600 days	350 days	500 days	600 days
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

19
 20 ^aAlthough average length and diameter are reported, what range of fibers was counted is unclear. Smith, 1978
 21 (unpublished) states that only fibers greater than 5 μm long are included. No other information is provided for
 22 these samples.

23 ^bNumerator = cumulative number of animals with tumors; denominator = number of survivors.

24
 25 N/D = not described.

26
 27 Source: Smith et al. (1979); Smith (1978); Smith (1974).
 28
 29

30 Following analysis of Syrian hamsters intrapleurally injected with 10 or 25 mg of each of
 31 the four samples of tremolite, Smith (1978) reported tumors at 350 days postexposure (25 mg) or

⁶Although the source of this material is not reported, these studies parallel those in the unpublished studies performed by Smith et al. for W.R. Grace that used material from Libby, MT. Whether Sample 72 is material from Libby, MT, or another location is unknown.

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1 600 days postexposure (10 mg) for Samples 31 and 72 (see Table D-7). Although number of
2 animals was not provided by Smith et al. (1979), previous studies by these authors reported using
3 50 animals per exposure group (Smith et al., 1978; Smith, 1974). The results in Table D-7
4 Present the cumulative number of tumors (numerator) at each time point analyzed over the
5 remaining survivors (denominator). The survival rate without tumor presentation was decreased
6 for animals exposed to Samples 72, 31, and 275. Smith et al. (1979) concluded that the FD-14
7 and 275 samples were noncarcinogenic, and Sample 31 was less carcinogenic than Sample 72.
8 Hamsters exposed to Sample 72 had extensive pleural fibrosis, which was observed to a lesser
9 degree in hamsters exposed to the other samples (Sample 72 > Sample 31 > Sample
10 275 = FD – 14). No statistical information was reported for these results, and because the
11 number of background tumors in control animals was not provided, no statistical analysis can be
12 performed.

13 Both studies demonstrate that intrapleural injections of Libby Amphibole asbestos⁷ leads
14 to an increase in pleural fibrosis and mesothelioma in hamsters compared to controls or animals
15 injected with less fibrous materials. The use of doses of equal mass for both studies makes it
16 difficult to compare potency between samples, as each sample could have vastly different fiber
17 number and total surface area. Although these studies clearly show the carcinogenic potential of
18 Libby Amphibole asbestos fibers, intrapleural injections bypass the clearance and dissolution of
19 fibers from the lung after inhalation exposures.

20 Stanton et al. (1981) also examined tremolite and describe a series of studies on various
21 forms of asbestos. Fibers, embedded in hardened gelatin, were placed against the lung pleura.
22 As an intrapleural exposure, results might not be comparable to inhalation exposures, as the
23 dynamics of fiber deposition and pulmonary clearance mechanisms are not accounted for in the
24 study design. Studies using two tremolite asbestos samples from the same lot were described as
25 being in the optimal size range for carcinogenesis; the fibers were distinctly smaller in diameter
26 than the tremolite fibers that Smith et al. (1979) used. These samples both had a high number of
27 fibers in the Stanton et al. (1981) -size range (>8- μ m long and <0.25- μ m diameter). Exposure to
28 both tremolite samples led to mesotheliomas in 21 and 22 of 28 rats exposed. The Stanton et al.
29 (1981) study also used talc that did not lead to mesothelioma production. This talc was found to
30 be the same as that used by Smith et al. (1979) and later by Wylie et al. (1993). Wylie et al.
31 (1993) stated that, although the two tremolites were consistent by size with commercial
32 amphibole asbestos, the talc used contained fibers that were much thinner and shorter, which is
33 not typical of prismatic tremolite fibers.

⁷Assuming Smith et al. (1979) used Libby Amphibole asbestos.

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1 Wagner et al. (1982) examined three types of tremolite (California talc, Greenland, and
 2 Korea) using SPF Sprague-Dawley ($n = 48$) and Wistar ($n = 32$) rats, then followed up with a
 3 range of in vitro tests using the same fiber samples. Rats were injected intrapleurally
 4 (20-mg tremolite) at 8–10 weeks of age and allowed to live out their lives. Median survival
 5 times after injections were 644 days (California talc), 549 days (Greenland tremolite), and
 6 557 days (Korean tremolite). Positive controls had a decreased survival time due to an infection,
 7 which limits the interpretation of these data. Also, this study was performed separately using
 8 different rat strains for the three tremolite samples. The authors state that, although the
 9 decreased control survival time and use of different rat strains limit the usefulness of the study
 10 for quantitative analysis, the results can be described qualitatively. Of the three tremolites, only
 11 the Korean tremolite showed carcinogenic activity producing mesothelioma (14/47 rats, 30%).
 12 Analysis of the fiber characteristics showed the Korean sample had fibers that were longer than 8
 13 μm and a diameter of less than 1.5 μm . The California talc and Greenland tremolite had
 14 little-to-no fibers in this size range (see Table D-8). Follow-up in vitro assays in the sample
 15 publication (Wagner et al., 1982) confirmed the in vivo results, with the exposure to Korean
 16 tremolite resulting in increased LDH and β -glucuronidase (BGL) release, cytotoxicity, and
 17 giant-cell stimulation.

18

19 **Table D-8. Fiber characteristics of three tremolite samples analyzed by in**
 20 **vivo and in vitro methods (TEM measurements)**

21

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

22

23 TEM = transmission electron microscopy.

24

25 Source: Wagner et al. (1982).

26

27

28 Davis et al. (1991) examined six tremolites with differing morphologies through
 29 intraperitoneal injections with male SPF Wistar rats. Four of the tremolites were from
 30 Jamestown, California; Korea; Wales; and Italy; and two were from Scotland. Of these, the three
 31 from California, Korea, and Wales were asbestiform, and the other three were fiber bundles or
 32 prismatic (see Table D-9). Rats were exposed ($n = 33$ or 36) with one intraperitoneal injection

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1 with samples that were 10 mg/2 mL-sterile phosphate buffered saline (PBS). Animals were
 2 allowed to live out their full life spans or until signs of debility or tumor formation developed.
 3 Although exposure was performed based on sample weight, each sample was analyzed to
 4 determine the number of expected fibers per milligram and, therefore, per exposure. These
 5 samples also were characterized further by counting fibers versus particles. Data were collected
 6 for all fibers (aspect ratio >3:1) and particles (aspect ratio <3:1) of total fibers. A fiber was
 7 defined as any component $\geq 8\text{-}\mu\text{m}$ long and $< 0.25\text{-}\mu\text{m}$ diameter as measured by SEM (i.e.,
 8 Stanton fibers).

10 **Table D-9. 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 $\geq 8\text{-}\mu\text{m}$ long, $< 0.25\text{-}\mu\text{m}$ 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

12 ^aStanton fibers.

13 Source: Davis et al. (1991).

14
 15
 16
 17
 18 The authors' overall conclusions were that all materials studied could cause
 19 mesothelioma by this method of exposure, and the number of Stanton fibers was not sufficient to
 20 explain the differences in response. Mesothelioma incidence was not correlated to Stanton
 21 fibers, total particles, or mass of dust. The best predictor of mesothelioma incidence was total
 22 fibers (see Table D-9). Although three samples were considered asbestiform (California,
 23 Swansea, Korea), all samples had <1% of counted fibers defined as Stanton fibers. The highest
 24 mesothelioma incidence was observed for the California sample, which contained the most
 25 Stanton fibers (121 fibers per mg dust). The tremolite from Swansea, resulted in 97%
 26 mesothelioma incidence yet contained only eight Stanton fibers per milligram (more than 90%
 27 less than in the California sample). In contrast, the Italy tremolite, although containing only
 28 0.08% Stanton fibers, resulted in 67% mesothelioma incidence. Little is known, however, about
 29 the characteristics of particles or fibers $< 5\text{-}\mu\text{m}$ long. This study highlights two issues associated

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1 with all fiber studies: the limits of analytical techniques and the variability in response based on
 2 the metric used to measure exposure. This study also supports the premise that asbestos samples
 3 containing fibers that are not long and thin can be carcinogenic.

4 The Roller et al. (1996) study was designed to provide data on the dose response of
 5 various fiber types in relation to their fiber dimensions (as measured by SEM). Fibers were
 6 defined in this study as having an aspect ratio of >5:1 for all lengths and widths. Female Wistar
 7 rats ($n = 40$) were given either one intraperitoneal injection of 3.3 mg or 15 mg of tremolite.
 8 Rats were examined for tumors in the abdominal cavity following a lifetime (up to 30 months) of
 9 observation. This paper described the fiber dimensions in depth (see Table D-10), while limited
 10 discussion is focused on the exposure results. This table shows the characteristics of the fibers
 11 sorted first by aspect ratio and diameter, and the fiber size distribution binned by the length and
 12 diameter for those fibers with a length >5 μm . Results were described in this study in a table as
 13 “positive rats” being those with histologically confirmed mesothelioma or macroscopically
 14 supposed mesothelioma. No information was provided on how these determinations were made.
 15 Exposure to 3.3-mg and 15-mg tremolite resulted in 9 mesotheliomas in 29 animals (64 weeks
 16 postexposure) and 30 mesotheliomas in 37 animals (42 weeks postexposure), respectively. This
 17 study demonstrates that intraperitoneal injection of tremolite led to mesothelioma in Wistar rats.
 18 Analysis of other tissues was not described.

19
 20 **Table D-10. Characteristics of tremolite fibers intraperitoneally injected into**
 21 **Wistar rats**
 22

Fiber number per ng dust and mass fraction (%)													
Aspect Ratio (L/D) >5/1; D <2 μm (Roller study)							Aspect Ratio (L/D) <3/1; D <3 μm (WHO, 1985)						
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					

23 SEM = scanning transmission microscopy.

24
 25 Source: Roller et al. (1996).
 26
 27

28 *This document is a draft for review purposes only and does not constitute Agency policy.*

1 **D.2. MECHANISTIC DATA AND OTHER STUDIES IN SUPPORT OF THE MODE OF** 2 **ACTION**

3 **D.2.1. In Vitro Studies—Libby Amphibole Asbestos**

4 Hamilton et al. (2004) examined the potential for fibers, including Libby Amphibole
5 asbestos, to modify the function of antigen-presenting cells (APC). Analysis was performed at
6 24 hours with two forms of asbestos (crocidolite [25 or 50 µg/mL] and Libby Amphibole
7 asbestos obtained from Site No. 30, Libby, MT [25 or 50 µg/mL]) and ultrafine particulate
8 matter (PM_{2.5} [particulate matter 2.5 microns diameter or less] [50 or 100 µg/mL]). Limited
9 information is provided by Hamilton et al. (2004) on fiber characteristics. Samples from Site
10 No. 30, however, are described as predominantly richterite and winchite by Meeker et al. (2003).
11 Primary human alveolar macrophages were incubated for 24 hours with Libby Amphibole
12 asbestos (25 or 50 µg/mL), crocidolite (25 or 50 µg/mL), or ultrafine particulate matter (50 or
13 100 µg/mL). Following incubation, cells were isolated from remaining particles and nonviable
14 cells, after which 0.25×10^6 macrophages were cocultured with autologous lymphocytes
15 (1×10^6 cells) in an 11-day APC assay. This assay analyzes the antigen-presenting function of
16 the pretreated macrophages by stimulating the lymphocytes using tetanus toxoid as the antigen.
17 The supernatant was assayed for cytokines on Day 11, and Hamilton et al. (2004) found that
18 pretreatment with either asbestos or PM_{2.5} significantly upregulated both T_{H1} and T_{H2} cytokines
19 (interferon gamma [IFN γ]; interleukin-4 [IL-4]; and interleukin-13 [IL-13]) ($p < 0.05$).
20 Therefore, pre-exposure to either fibers or particles increased APC function, as reflected in
21 increased cytokine release after tetanus challenge. No significant differences, however, were
22 discernable between asbestos and PM_{2.5} pretreatment. The authors speculated that the variability
23 in response between samples assayed—presumably due to the use of primary cells—obscures
24 statistical significance. Although this study supports a role for fibers and PM_{2.5} in potentiating
25 immune response, the implications of these findings to human health are unclear because many
26 agents can activate macrophages prior to antigen challenge.

27 Recent studies (Blake et al., 2007, 2008) compared the response of murine macrophages
28 (primary and cell line RAW264.7) to Libby Amphibole asbestos fibers and crocidolite asbestos
29 fibers. The Libby Amphibole asbestos fibers (7.21 ± 7.01 -µm long, 0.61 ± 1.22 -µm diameter)
30 used in these studies were obtained from the U.S. Geological Survey and were chemically
31 representative of the Libby, MT mine (Meeker et al., 2003). The crocidolite fibers
32 (4.59 ± 4.22 µm-long, 0.16 ± 0.09 µm-diameter) used in these studies were provided by Research
33 Triangle Institute, NC, and the noncytotoxic control fiber (wollastonite, 4.46 ± 5.53 µm-long,
34 0.75 ± 1.02 µm-diameter) was provided by NYCO Minerals, NY. Cells were exposed for
35 24 hours to fiber samples measured by relative mass ($5 \mu\text{g}/\text{cm}^2$), after which the cells were

1 analyzed by transmission electron microscopy to measure internalization. The results of the first
2 study (Blake et al., 2007) indicate that Libby Amphibole asbestos fibers can both attach to the
3 plasma membrane and be internalized by macrophages, similar to the crocidolite fibers. These
4 internalized fibers were primarily less than 2- μm long and were found localized in the
5 cytoplasm, in cytoplasmic vacuoles, and near the nucleus following 3-hour exposure,
6 62.5 $\mu\text{g}/\text{cm}^2$. This same concentration (62.5 $\mu\text{g}/\text{cm}^2$) was selected for the remaining studies
7 because cell viability was not decreased at this concentration for the Libby Amphibole asbestos
8 (92%); cell viability was decreased for crocidolite (62%), however, at this concentration. As a
9 result, the remaining assays would be expected to have decreased viability following exposure to
10 crocidolite, which may impact the levels of various responses. For example, the reactive oxygen
11 species (ROS) measurement would increase with increased cell number; therefore, some of the
12 quantitative results would be difficult to compare between fiber types unless normalized to cell
13 number.

14 Oxidative stress was measured by the induction of ROS and the reduction in glutathione
15 (GSH) levels. These two measurements generally complement each other, as GSH is used in
16 cells to maintain intracellular redox balance in cells in response to increased ROS levels. Both
17 Libby Amphibole asbestos and crocidolite fiber internalization generated a significant increase
18 ($p < 0.05$) in intracellular ROS as quantified by the oxidation of 2,7-dichlorodihydrofluorescein
19 to dichlorofluorescein with hourly readings on a fluorescent plate reader. Libby Amphibole
20 asbestos exposure significantly increased ROS in a dose-dependent manner (6.25, 32.5, and
21 62.5 $\mu\text{g}/\text{cm}^2$), as early as 1 hour postexposure at the highest dose ($p < 0.05$), as compared to a
22 no-treatment group. Only the highest concentration of crocidolite was tested. The lower
23 concentrations of Libby Amphibole asbestos were not compared to crocidolite and wollastonite,
24 but a comparison of the highest exposure concentrations (62.5 $\mu\text{g}/\text{cm}^2$) of Libby Amphibole
25 asbestos, crocidolite, and wollastonite revealed greater ROS production following Libby
26 Amphibole asbestos exposure (1 hour, $p < 0.05$). Blake et al. (2007) stated that similar results
27 were seen in the primary cell line but did not report the data. To differentiate the type of ROS
28 produced, dehydroergosterol (DHE) fluorescence intensity levels were used, revealing that
29 superoxide anion was significantly increased following exposure to Libby Amphibole asbestos
30 as compared to controls. This observation was further confirmed with use of a free radical
31 scavenger (PEG-SOD [polyethylene glycol-superoxide dismutase]) specific to superoxide anion.
32 This coexposure of Libby Amphibole asbestos and PEG-SOD led to a significant decrease in
33 ROS as compared to cells exposed only to Libby Amphibole asbestos ($p < 0.05$). Total
34 intracellular superoxide dismutase (SOD) activity also was measured following exposure to
35 Libby Amphibole asbestos and showed a decrease in activity at 3 hours postexposure as

1 compared to controls ($p < 0.05$). Crocidolite appears to increase intracellular SOD activity at
2 24 hours postexposure. These three assays demonstrate that Libby Amphibole asbestos exposure
3 leads to increased superoxide anion in macrophages, most likely by suppressing activity of
4 intracellular SOD.

5 GSH levels were found to be decreased in response to Libby Amphibole asbestos and
6 crocidolite exposure in the macrophage cell line as compared to unexposed cells ($p < 0.05$). The
7 decreased GSH levels were more prominent following crocidolite exposure as compared to
8 Libby Amphibole asbestos. Crocidolite exposure has been shown in other studies to lead to
9 increased hydrogen peroxide but not superoxide anion (Kamp et al., 1992; Kamp and Weitzman,
10 1999). The increased hydrogen peroxide from crocidolite exposure can then lead to increased
11 hydroxyl radical production (through interactions with endogenous iron), and potentially,
12 deoxyribonucleic acid (DNA) adduct formation. DNA adduct formation
13 (8-hydroxy-2' deoxyguanosine, 8-OHdG), 8-oxoguanine-DNA-glycosylase 1 (Ogg1) levels, and
14 DNA damage (comet assay) also were measured. A significant increase in DNA damage in
15 exposed macrophages, as measured by increases in both 8-OHdG formation and expression of
16 Ogg1, a DNA repair enzyme that excises 8-OHdG from DNA following oxidative stress, was
17 observed following exposure to crocidolite but not Libby Amphibole asbestos. Increased
18 superoxide anion following Libby Amphibole asbestos exposure does not appear to yield
19 oxidative damage similar to crocidolite. These results suggest a chemical-specific response to
20 each type of amphibole that yields varied cellular responses. Therefore, the mechanism of action
21 following response to Libby Amphibole asbestos might be different than that of crocidolite, also
22 an amphibole fiber.

23 To determine if the ROS production was related to fiber number for both Libby
24 Amphibole asbestos and crocidolite, cell-fiber interactions and fiber internalization were
25 measured following exposure to equal concentrations of crocidolite, Libby Amphibole asbestos,
26 and wollastonite ($62.5 \mu\text{g}/\text{cm}^2$, 3 hours). With phase contrast light microscopy, the number of
27 cells interacting with one or more fibers was counted (100 cells counted for each treatment). All
28 murine macrophages bound or internalized at least one fiber from the Libby Amphibole asbestos
29 sample (mean \pm SD, 4.38 ± 1.06 internalized) or the crocidolite sample (3.28 ± 1.58 internalized)
30 but not the wollastonite sample (Blake et al., 2007). No significant differences were observed in
31 the responses to Libby Amphibole asbestos or crocidolite samples, suggesting that the
32 differences in measured ROS were not related to cell number. Fiber sizes varied between the
33 two samples, with the crocidolite sample containing a more homogeneous mixture of long fibers
34 (exact size not given), while the Libby Amphibole asbestos sample contained a mixture of sizes

1 and widths. These characteristics were not analyzed to determine what, if any, role they might
2 play in the varied response.

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

13 The role of reactive oxygen species in chromosomal damage from asbestos was examined
14 in a recent study of Libby Amphibole asbestos and Union for International Cancer Control
15 (UICC) crocidolite in XRCC1-deficient human lung epithelial H460 cells (Pietruska et al.,
16 2010). XRCC1 is involved in the repair mechanisms for oxidative DNA damage, particularly
17 single-strand breaks. This study examined the effect of XRCC1 deficiency (induced in cells by
18 shRNA knockdown) following exposure to genotoxic (crocidolite and Libby Amphibole
19 asbestos) and nongenotoxic compounds (wollastonite, titanium dioxide) on micronucleus
20 formation. Cells were exposed to chemicals with known oxidants hydrogen peroxide (0–60 μM)
21 or bleomycin (0–10 $\mu\text{g/ml}$) for 1 and 3 hrs, or the nonoxidant paclitaxel (0–5 nM, 24 hours) to
22 confirm the clonogenic survival of the knockout cells, and as positive and negative controls.
23 Fiber-size distribution for crocidolite and Libby Amphibole asbestos is shown in Table D-11.
24 Micronuclei induction was measured following treatment of cells by controls as described above,
25 and by 5- $\mu\text{g/cm}^2$ fibers or TiO_2 particles for 24 hours. Following treatment, cells were fixed,
26 permeabilized, and blocked before being exposed to anticentromere antibodies, and micronuclei
27 were counted and scored as centromere negative arising from DNA breaks (clastogenic) or
28 centromere positive arising from chromosomal loss (aneugenic). Spontaneous micronuclei
29 induction was increased in XRCC1-deficient cells as compared to control. Wollastonite and
30 titanium dioxide did not induce micronuclei in either cell type. Crocidolite and Libby
31 Amphibole asbestos induced dose-dependent increases in micronuclei formation in both cell
32 types including an increase in the proportion of micronuclei in XRCC1-deficient cells (see
33 Table D-12). Libby Amphibole asbestos exposure led to a decreased amount of micronuclei as
34 compared to crocidolite. Specifically in relation to clastogenic versus aneugenic micronuclei,
35 crocidolite exposure led to mainly clastogenic micronuclei while Libby Amphibole asbestos

1 exposure led to a mixture of aneugenic and clastogenic micronuclei. Nuclear bud formation was
 2 also observed but only with exposure to crocidolite and bleomycin. Western blot analysis was
 3 performed to analyze protein expression related to DNA damage repair (XRCC1) and cell cycle
 4 progression (p53, p21) (data not shown in publication). The differences observed between
 5 crocidolite and Libby Amphibole asbestos are most likely related to their physicochemical
 6 differences, particularly related to their iron content. However, these results support a genotoxic
 7 effect of exposure to both crocidolite and Libby Amphibole asbestos.

8
 9 **Table D-11. Size distribution of UICC crocidolite and Libby Amphibole**
 10 **asbestos used in Pietruska et al. (2010)^a**
 11

Length (µm)	% fibers in size range	
	Crocidolite	Libby Amphibole Asbestos
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

12
 13 ^aDistribution by diameter also given in original manuscript.
 14 Source: Adapted from Supplemental Material of Pietruska et al. (2010).
 15
 16

17 **Table D-12. Percent clastogenic micronuclei following exposure to Libby**
 18 **Amphibole asbestos or crocidolite.**
 19

	H460 cells	XRCC1-deficient
Libby Amphibole Asbestos (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

20
 21 ^a*p* < 0.05 as compared to control cells.
 22

23 Source: Pietruska et al. (2010).
 24
 25

26 Mechanisms of oxidative stress following exposure to Libby Amphibole asbestos were
 27 also studied in human mesothelial cells (Hillegass et al., 2010). Gene-expression changes were
 28 measured with Affymetrix U133A microarrays (analysis with GeneSifter) following exposure to

1 15×10^6 - $\mu\text{m}^2/\text{cm}^2$ Libby Amphibole asbestos⁸ as compared to the nonpathogenic control
2 (75×10^6 - $\mu\text{m}^2/\text{cm}^2$ glass beads) in the human mesothelial cell line LP9/TERT-1 for 8 and
3 24 hours. Gene expression of only one gene (manganese superoxide dismutase [*MnSOD*;
4 *SOD2*]) was altered following exposure to Libby Amphibole asbestos for 8 hours, while
5 111 genes had an altered gene expression following exposure to Libby Amphibole asbestos for
6 24 hours (altered by at least twofold as compared to control).

7 The gene for *MnSOD*; *SOD2* was observed to be significantly upregulated at both time
8 points ($p < 0.05$) as compared to nonpathogenic controls. This gene was confirmed in normal
9 human pleural mesothelial cells (HKNM-2) by quantitative RT-PCR at 24 hours following
10 exposure to the nontoxic dose of Libby Amphibole asbestos. Upregulation of three genes from
11 this and previous studies by these authors was confirmed by quantitative RT-PCR (*SOD2*, *ATF*,
12 and *IL8*) in HKNM-2 cells exposed to both Libby Amphibole and crocidolite asbestos. Gene
13 ontology of these results demonstrated alterations related to signal transduction, immune
14 response, apoptosis, cellular proliferation, extracellular matrix, cell adhesion and motility, and in
15 only one gene related to reactive oxygen species processing. Follow-up studies at both the
16 nontoxic dose' ($15 \times 10^6 \mu\text{m}^2/\text{cm}^2$) and the toxic dose ($75 \times 10^6 \mu\text{m}^2/\text{cm}^2$) exposure levels in
17 LP9/TERT-1 cells examined SOD protein and activity, reactive oxygen species production, and
18 glutathione (GSH) levels. At 24 hours, SOD2 protein levels were increased following exposure
19 to the toxic dose of Libby Amphibole asbestos ($p < 0.05$) but not at 8 hours. Cells exposed to all
20 doses of Libby Amphibole and crocidolite asbestos had increased copper-zinc superoxide
21 dismutase (Cu/ZnSOD; SOD1) protein at 24 hours ($p < 0.05$) but not at 8 hours. Although total
22 SOD activity remained unchanged, a dose-related SOD2 activity was observed following
23 exposure to both doses of Libby Amphibole asbestos for 24 hours, but this appeared to be
24 minimal and was not statistically significant (8 hours was not examined). Oxidative stress was
25 measured by dichlorodihydrofluorescein diacetate fluorescence staining detected by flow
26 cytometry and was observed as both dose- and time-dependent in cells exposed to Libby
27 Amphibole asbestos but was increased following exposure to the toxic dose of Libby Amphibole
28 asbestos (statistical analysis not possible). Oxidative stress was further supported by analysis of
29 gene expression of heme oxygenase 1 (HO-1) following exposure to Libby Amphibole asbestos
30 in both LP9/TERT-1 and HKNM-2 cells for 8 and 24 hours. HO-1 was significantly increased
31 following exposure to the toxic dose of Libby Amphibole asbestos in both cell lines (p -value not
32 given). GSH levels were transiently depleted following 2–8 hours exposure to

⁸Libby Amphibole asbestos 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 as either nontoxic ($15 \times 10^6 \mu\text{m}^2/\text{cm}^2$) or toxic ($75 \times 10^6 \mu\text{m}^2/\text{cm}^2$).

1 75×10^6 - $\mu\text{m}^2/\text{cm}^2$ -levels of Libby Amphibole asbestos, with a gradual recovery up to 48 hours in
2 LP9/TERT-1 cells (HKNM-2 not analyzed). Exposure to crocidolite asbestos at the toxic dose
3 led to a significant GSH decrease at all times points up to 24 hours ($p < 0.05$). These studies
4 demonstrate that Libby Amphibole asbestos exposure leads to increases in oxidative stress as
5 measured by ROS production, gene expression, protein and functional changes in oxidative
6 stress proteins (SOD), and GSH-level alterations in human mesothelial cells.

7 The relative toxicity of Libby Amphibole asbestos was measured by gene-expression
8 changes of interleukin-8 (*IL-8*), cyclooxygenase-2 (*COX-2*), heme oxygenase (*HO-1*) as well as
9 other stress-responsive genes as compared to amosite (Research Triangle Institute, NC) in
10 primary human airway epithelial cells (HAEC) in vitro. Comparisons were made with both
11 fractionated (aerodynamic diameter $\leq 2.5 \mu\text{m}$) and unfractionated fiber samples (Duncan et al.,
12 2010). Crocidolite fibers (UICC) were also included in some portions of this study for
13 comparison. Fractionation was performed using the water elutriation method (Webber et al.,
14 2008) and characterized as described in Lowers and Bern (2009). Primary HAECs were exposed
15 to 0, 2.64, 13.2, and 26.4 $\mu\text{g}/\text{cm}^2$ of crocidolite, amosite (AM), AM2.5 (fractionated), Libby
16 Amphibole asbestos, or LA2.5 (fractionated) for 2 or 24 hours in cell culture. Confocal
17 microscopy was used to determine fiber content in cells exposed for 4 or 24 hours to
18 26.4- $\mu\text{g}/\text{cm}^2$ AM2.5 or LA2.5 only. At 4 hours postexposure, fibers were mainly localized on
19 the periphery of the cell with some fibers internalized. By 24 hours postexposure, most fibers
20 appeared to be internalized and localized by the nucleus. Cytotoxicity was determined by
21 measurement of LDH from the maximum dose (26.4 $\mu\text{g}/\text{cm}^2$) of both amosite and Libby
22 Amphibole asbestos samples, with less than 10% LDH present following exposure to all
23 four samples. Cytotoxicity was also determined for just the fractionated samples of amosite and
24 Libby Amphibole asbestos by measuring intracellular calcein fluorescence emitted by live cells
25 and showed 95% and 99% viability for AM2.5 and LA2.5, respectively. These results support a
26 limited cytotoxicity of both amosite and Libby Amphibole asbestos under these concentrations
27 and time frames.

28 Gene-expression changes in specific inflammatory markers (*IL-8*, *COX-2*, *HO-1*) were
29 analyzed by quantitative RT-PCR for AM, AM2.5, Libby Amphibole asbestos, LA2.5, and CRO
30 at both 2 and 24 hours postexposure (all doses). Minimal increases in gene expression of *IL-8*,
31 *COX-2*, or *HO-1* were observed at 2 hours postexposure to all five fiber types; at 24 hours
32 postexposure, however, a dose response was observed following exposure to all fiber types. The
33 smaller size fractions resulted in differences in magnitude of gene-expression changes between
34 AM2.5 and LA2.5, with AM2.5 leading to greater induction of *IL-8* and *COX-2* as compared to
35 LA2.5. *HO-1* levels were comparable between the two samples (see Table D-13). Gene

1 expression of transforming growth factor (*TGF*)-*BI* was also quantified but only following
 2 exposure to AM2.5 and LA2.5 (all doses; data not shown in publication). Levels of IL-8 protein
 3 were also measured following 24 hours exposure to AM2.5 and LA2.5 (all doses) and were
 4 statistically significant at the two highest exposures (13.2 and 26.4 $\mu\text{g}/\text{cm}^2$). Gene-expression
 5 changes were also examined for 84 genes involved in cellular stress and toxicity using a 96-well
 6 RT-PCR array format following 24 hours exposure to 13.2- $\mu\text{g}/\text{cm}^2$ AM, Libby Amphibole
 7 asbestos, AM2.5, or LA2.5 or to 26.4- $\mu\text{g}/\text{cm}^2$ LA2.5 only. The results show a pro-inflammatory
 8 gene-expression response. Gene-expression profiles were similar between AM and Libby
 9 Amphibole asbestos, but differences were observed between AM2.5 and LA2.5.

10
 11 **Table D-13. Gene-expression changes following exposure to 26.4- $\mu\text{g}/\text{cm}^2$**
 12 **amphibole asbestos for 24 hours^a**
 13

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

14
 15 ^aAll results in fold change as compared to untreated control cells.

16
 17 Source: Duncan et al. (2010).
 18
 19

20 To determine if surface iron on the fibers played a role in the inflammatory response,
 21 Duncan et al. (2010) also examined surface iron concentrations by two methodologies:
 22 inductively coupled plasma optical emission spectroscopy (ICP-OES) and
 23 citrate-bicarbonate-dithionite (CBD). Both assays determined AM2.5 appeared to have the
 24 measured by thiobarbituric acid (TBA)-reactive product formation following exposure to AM,
 25 AM2.5, Libby Amphibole asbestos, and LA2.5. Both AM samples were found to generate the
 26 greatest amount of hydroxyl radicals compared to the two Libby Amphibole asbestos samples,
 27 with the fractionated AM2.5 and LA2.5 exhibiting small increases in ROS produced compared to
 28 the unfractionated samples.
 29

1 **D.2.2. In Vitro Studies—Tremolite**

2 In general, all fibrous tremolite samples were shown to be carcinogenic, with those
3 containing more of the longer, thinner fibers (>10- μ m-length, <1- μ m-diameter) being more
4 potent carcinogens. Most studies described here used weight as the measurement of fibers for
5 exposure, with the doses ranging from 0 to 40 mg/animal. One set of studies did expose animals
6 with fibers measured by number (100 fibers/cm³) (Bernstein et al., 2005, 2006).

7
8 **D.2.2.1. Cytotoxicity**

9 Wagner et al. (1982) examined the in vitro cytotoxicity of three forms of tremolite (see
10 Table D-8) used in their in vivo studies. LDH and BGL were measured in the medium following
11 incubation of unactivated primary murine macrophages to 50, 100, and 150 μ g/mL of each
12 sample for 18 hours. Cytotoxicity of Chinese hamster lung fibroblasts V79-4 was measured by
13 methylene blue staining (fiber concentrations not given). Giant-cell formation in A549 human
14 basal alveolar epithelial cell cultures was measured, using 100 and 200 μ g/mL of each sample for
15 5 days. Crocidolite fibers were used as the positive control.

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

24 In a study to further elucidate the role of ROS following exposure to asbestos, Suzuki and
25 Hei (1996) examined the role of heme oxygenase (HO) in response to asbestos. HO is induced
26 in response to oxidative stress and functions to degrade heme; it might, therefore, prevent
27 iron-mediated hydroxyl radical production. All fibers tested led to an increase in HO, though
28 chrysotile (UICC) and crocidolite (UICC) led to a greater increase than tremolite (Metsovo,
29 Greece) and erionite (Rome, Oregon). No statistics, however, are described for these results.
30 This study focused on responses to 20 and 40 μ g/mL of chrysotile and then used doses that
31 yielded 0.5 and 0.3 relative survival fractions for all other fibers (crocidolite, 20 and 40 μ g/mL;
32 tremolite, 150 and 300 μ g/mL; erionite, 200 and 400 μ g/mL). Fibers were not characterized in
33 this paper. When normalized by survival fraction, the inductions of HO above control were
34 3.89-, 3.86-, 2.75-, and 2.78-fold above background for chrysotile, crocidolite, tremolite, and
35 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) 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. Cells were exposed to fibers by weight, number, and surface area (see Table D-14).

Table D-14. 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/cm²) 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/cm², *p* < 0.05) (Wylie et al., 1997).

1 No proliferation was observed for either chrysotile or crocidolite asbestos fibers in RPM
2 cells, but cytotoxicity was observed at concentrations greater than $0.05 \mu\text{g}/\text{cm}^2$ ($p < 0.05$). All
3 talc samples were less cytotoxic in both cell types. Comparing results of these samples when
4 exposure is measured by fiber number, the same number of crocidolite asbestos fibers $>5\text{-}\mu\text{m}$
5 long leads to proliferation in HTE cells, but proliferation did not occur for FD14 fibers. The
6 other two talc samples showed both insignificant cytotoxicity (SI57) and significant cytotoxicity
7 (CPS183, $p < 0.05$). Therefore, when measured by fiber number, the results show differential
8 responses for the fibers analyzed, suggesting the mineralogy of the fibers is more important in
9 determining the biological response to fibers. In the RPM cells, however, similar responses were
10 seen for all fibers analyzed, except for the slight cytotoxicity of FD14 at $2.6 \text{ fibers}/\text{cm}^2$. This
11 suggests that fiber number does play a role in biological response in this cell type.

12 Data analysis by surface area of these samples is shown in Table D-14. The results of
13 these samples in both cell lines demonstrated that the cellular responses seemed unrelated to the
14 surface area, which demonstrates the impact of the dose metric on data. Analyzing the data for
15 cytotoxicity and proliferation based on the exposure measurement demonstrated differences in
16 response depending solely on how the fibers were measured (e.g., by mass, number, or surface
17 area). These results show variability in interpreting the same assay based on the defined unit of
18 exposure. Most early studies used mass as the measurement for exposure, which can impact how
19 the results are interpreted. When possible, further analysis of fiber number and surface area
20 might help elucidate the role of these metrics, particularly for in vivo studies.

21 22 **D.2.2.2. Genotoxicity**

23 Athanasiou et al. (1992) performed a series of experiments to measure genotoxicity
24 following exposure to tremolite, including the Ames mutagenicity assay, micronuclei induction,
25 chromosomal aberrations, and gap-junction intercellular communication. Although a useful test
26 system for mutagenicity screening for many agents, the Ames assay is not the most effective test
27 to detect mutations induced by mineral fibers. Mineral fibers can cause mutation through
28 generation of ROS or direct disruption of the spindle apparatus during chromatid segregation.
29 Fibers do not induce ROS in the Ames system; however, and the *Salmonella typhimurium* strains
30 do not endocytose the fibers. Only one study was found in the published literature that used the
31 Ames assay to measure mutagenicity of tremolite. Metsovo tremolite asbestos has been shown
32 to be the causative agent of endemic pleural calcification and an increased level of malignant
33 pleural mesothelioma (see Section 4.1). To measure the mutagenicity of Metsovo tremolite,
34 *S. typhimurium* strains (TA98, TA100, and TA102) were exposed to $0\text{--}500 \mu\text{g}/\text{plate}$ of asbestos
35 (Athanasiou et al., 1992). This assay demonstrated that, like most asbestos fiber types tested in

1 earlier studies, Metsovo tremolite did not yield a significant increase in revertants in the Ames
 2 assay, including in the TA102 *Salmonella* strain, which is generally sensitive to oxidative
 3 damage. Although these strains can detect ROS mutations, they would not be able to produce
 4 ROS from fibers alone or through necessary signaling pathways, and they do not endocytose
 5 fibers. Thus, negative results in the Ames assay do not inform the cytotoxicity of Metsovo
 6 tremolite.

7 Furthermore, this study demonstrated the clastogenic effects of tremolite, including
 8 chromosomal aberrations and micronuclei induction. Tremolite exposure (0–3.0 µg/cm²) in
 9 Syrian hamster embryo (SHE) cells resulted in a statistically significant increase in chromosomal
 10 aberrations ($p < 0.02$) when all treatment groups were combined and then compared to controls;
 11 however, no clear dose-response relationship was evident (Athanasίου et al., 1992). Tremolite
 12 exposure in SHE cells did lead to a dose-dependent increase in chromosome aberrations that was
 13 statistically significant at the highest doses tested (1.0–3.0 µg/cm²) ($p < 0.01$) (see Table D-15).
 14

15 **Table D-15. Micronuclei induction (BPNi cells) and chromosomal**
 16 **aberrations (SHE cells) following exposure to tremolite for 24 hours**
 17

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

18 ^aSignificantly different from control ($p < 0.05$).

19 ^bSignificantly different from control ($p < 0.01$).

20 ^cSignificantly different from control ($p < 0.02$).

21 Source: Athanasίου et al. (1992).
 22
 23
 24
 25

26 Micronuclei induction was measured in BPNi cells after 24-hour exposure to
 27 0-2.0-µg/cm² tremolite. A statistically significant dose-dependent increase in levels of
 28 micronuclei was demonstrated following tremolite exposure at concentrations as low as
 29 0.5 µg/cm² ($p < 0.01$). Literatures searches did not find tremolite tested for clastogenicity in
 30 other cell types, but the results of this study suggest interference with the spindle apparatus by

1 these fibers. No analysis was performed to determine if fiber interference of the spindle
2 apparatus could be observed, which would have supported these results.

3 To determine if tremolite has some tumor promoter characteristics, Athanasiou et al.
4 (1992) further examined intercellular communication following exposure to 0–4.0- $\mu\text{g}/\text{cm}^2$
5 tremolite in both Chinese hamster lung fibroblasts (V79) and SHE BPNi cells, which are
6 sensitive to transformation. Inhibition of gap-junctional intercellular communication has been
7 proposed to detect tumor-promoting activity of carcinogens (Trosko et al., 1982). No effect on
8 gap-junction intercellular communication following tremolite exposure was observed.

9 Okayasu et al. (1999) analyzed the mutagenicity of Metsovo tremolite, erionite, and the
10 man-made ceramic (RCF-1) fiber. Whether this tremolite is the same as that used in previous
11 studies from this group is unclear. Tremolite from Metsovo, Greece, used in this study was
12 characterized as 2.4 ± 3.1 - μm long and 0.175 ± 0.13 - μm diameter (arithmetic mean) with the
13 number of fibers per microgram of sample equal to 1.05×10^5 . Human-hamster hybrid A(L)
14 cells contain a full set of hamster chromosomes and a single copy of human chromosome 11.
15 Mutagenesis of the CD59 locus on this chromosome is quantifiable by antibody
16 complement-mediated cytotoxicity assay. The authors state that this is a highly sensitive
17 mutagenicity assay, and previous studies have demonstrated mutagenicity of both crocidolite and
18 chrysotile (Hei et al., 1992). The cytotoxicity analysis for mutagenicity was performed by
19 exposing 1×10^5 A(L) cells to a range of concentrations of fibers as measured by weight
20 (0–400 $\mu\text{g}/\text{mL}$ or 0–80 $\mu\text{g}/\text{cm}^2$) for 24 hours at 37°C. CD59 mutant induction showed a
21 dose-dependent increase in mutation induction for erionite and tremolite, but RCF-1 did not.
22

23 **D.3. SUMMARY**

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

31 Studies that examined cellular response to tremolite also found that fiber characteristics
32 (length and width) play a role in determining ROS production, toxicity, and mutagenicity
33 (Wagner et al., 1982; Okayasu et al, 1999). As with the in vivo studies, the definition of fibers
34 and the methods of fiber measurement vary among studies.
35

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32

1 **APPENDIX E. EVALUATION OF EXPOSURE-RESPONSE DATA FOR**
2 **LOCALIZED PLEURAL THICKENING IN WORKERS FROM THE**
3 **MARYSVILLE, OH COHORT**

4 **E.1. STATISTICAL ANALYSIS OF THE 2004 POST-1972 DATA SET**

5 All analyses were performed using SAS® statistical software v. 9.1. Benchmark dose
6 lower bound 95% confidence intervals (BMCLs) were obtained by the profile likelihood method
7 as recommended by Crump and Howe (1985) using the NLMIXED procedure in SAS (Wheeler,
8 2005). As described in Section 5.2.1.4, the critical endpoint for RfC derivation is radiographic
9 evidence of localized pleural thickening (LPT; $n = 12$ cases), compared with the referent group
10 with no radiographic evidence of pleural abnormality ($n = 106$).

11
12 **E.1.1. Investigation of Explanatory Variables**

13 Dichotomous statistical models describing the probability of individual response as a
14 function of cumulative exposure as measured by cumulative human equivalent exposure for
15 continuous exposure (CHEEC) in units of fiber/cc-year were used for this analysis. In order to
16 investigate the key explanatory variables for analysis, a forward-selection process was used to
17 evaluate the association of each of the potential covariates with odds of localized pleural
18 thickening, controlling for CHEEC. Covariates considered for inclusion in the model were time
19 from first exposure, age at X-ray, gender, smoking history, and body mass index (BMI). This
20 initial modeling was done using a standard logistic regression model as commonly applied in the
21 analysis of epidemiological data. The base model was a logistic regression model with
22 cumulative exposure (natural log transformed) as the independent variable. This model provided
23 an adequate fit to the data (Hosmer-Lemeshow p -value of 0.6357), and the exposure variable was
24 statistically significantly associated with the outcome (beta standard error [SE] = 0.5676
25 [0.2420], p -value = 0.0190). Covariates were evaluated according to whether inclusion of the
26 covariate improved model fit as assessed by the Akaike Information Criterion (AIC), and
27 statistical significance of the covariate. When controlling for cumulative exposure, inclusion of
28 each of the covariates with the exception of smoking increased the AIC for the model, and none
29 were associated with odds of discrete pleural thickening: time from first exposure—
30 p -value = 0.8879; age at X-ray— p -value = 0.7735; gender— p -value = 0.7660; smoking—
31 p -value = 0.1669; BMI— p -value = 0.4095. Therefore, only exposure (i.e., CHEEC) was
32 included in further analyses (see Table E-1).

1 **Table E-1. Evaluation of covariates for the 2004 post-1972 set**

2

Covariate	Wald <i>p</i> -value for beta coefficient corresponding to covariate	Wald <i>p</i> -value for beta coefficient corresponding to exposure	AIC
Base model (only ln[CHEEC])	—	0.0190	75.5
Time from first exposure	0.8879	0.0310	77.5
Age at X-ray	0.7735	0.0186	77.4
Gender	0.7660	0.0195	77.4
Smoking history	0.1669	0.0231	75.4
BMI ^a	0.4095	0.0102	56.7

3
4 ^aNote that only 97 observations were used, due to missing values (AIC not comparable).

5
6

7 **E.1.2. Investigation of Candidate Models**

8 The candidate models were logistic (with CHEEC considered as continuous and
9 continuous with a natural logarithm transformation), probit (with CHEEC considered as
10 continuous and continuous with a natural logarithm transformation), 3-parameter log-logistic,
11 dichotomous Hill, and dichotomous Michaelis-Menten models. These are statistical models used
12 to evaluate dichotomous data and were considered appropriate given the supralinear nature of the
13 observed relationship between Libby Amphibole asbestos¹ exposure and the prevalence of
14 localized pleural thickening; model forms are provided in Table E-2. For each of the candidate
15 models, exposure lags of 0, 5, 10, 15, and 20 years were investigated. Although zero lag
16 exposures are not likely to be biologically relevant (i.e., some lag is expected for development of
17 LPT), these models were included for completeness and for comparison of relative model fits.
18 Similarly, although we explored models with exposure lagged by 20 years, there were cases of
19 localized pleural thickening in the full cohort with fewer than 20 years since first exposure;

20

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.

1
2

Table E-2. Evaluation of different model forms for the 2004 post-1972 set

Model	Exposure Metric	Form*	AIC	Hosmer-Lemeshow GOF <i>p</i> -value	BMC	BMCL
Logistic	CHEEC	$P(LPT) = 1 \div [1 + \exp(-a - b \times CHEEC)]$	77.7	0.7423	—	—
CHEEC, lag 5			77.5	0.6914	1.5245	0.8836
CHEEC, lag 10			77.4	0.6751	1.4734	0.8540
CHEEC, lag 15			77.6	0.6474	1.4510	0.8242
CHEEC, lag 20			77.8	0.8800	—	—
Logistic	ln(CHEEC)	$P(LPT) = 1 \div [1 + \exp(-a - b \times \ln(CHEEC))]$	75.5	0.6537	—	—
CHEEC, lag 5			75.2	0.5454	0.2281	0.0601
CHEEC, lag 10			74.6	0.5708	0.2028	0.0591
CHEEC, lag 15			74.7	0.6620	0.1686	0.0463
CHEEC, lag 20			75.4	0.8152	—	—
Probit model	CHEEC	$P(LPT) = \Phi(a + b \times CHEEC)$	77.2	0.7698	—	—
CHEEC, lag 5			77.0	0.7146	1.3773	0.8481
CHEEC, lag 10			77.0	0.6864	1.3336	0.8048
CHEEC, lag 15			77.2	0.6645	1.3148	0.7776
CHEEC, lag 20			77.4	0.8884	—	—
Probit model	ln(CHEEC)	$P(LPT) = \Phi(a + b \times \ln(CHEEC))$	76.0	0.6041	—	—
CHEEC, lag 5			75.7	0.4967	0.2066	0.0502
CHEEC, lag 10			75.2	0.5385	0.1843	0.0496
CHEEC, lag 15			75.0	0.6166	0.1544	0.0441
CHEEC, lag 20			75.7	0.7945	—	—
3-parameter log-logistic	ln(CHEEC)	$P(LPT) = bkg + (1 - bkg) \div [1 + \exp(-a - b \times \ln(CHEEC))]$	74.9	0.7030	—	—
CHEEC, lag 5			74.6	0.4894	0.3096	0.0979
CHEEC, lag 10			74.1	0.5853	0.2696	0.0888
CHEEC, lag 15			74.3	0.7238	0.2193	0.0693
CHEEC, lag 20			75.2	0.8277	—	—
Dichotomous Hill†	ln(CHEEC)	$P(LPT) = bkg + (Plateau - bkg) \times CHEEC^b \div [\exp(-a) + CHEEC^b]$	76.9	0.6040	—	—
CHEEC, lag 5			76.5	0.3598	0.3083	0.1015
CHEEC, lag 10			76.0	0.4244	0.2640	0.0923
CHEEC, lag 15			76.2	0.6659	0.2112	0.0724
CHEEC, lag 20			77.2	0.8277	—	—
Michaelis-Menten±	ln(CHEEC)	$P(LPT) = bkg + (Plateau - bkg) \times CHEEC \div [\exp(-a) + CHEEC]$	74.9	0.5243	—	—
CHEEC, lag 5			74.5	0.3351	0.3096	0.1352

3

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Table E-2. Evaluation of different model forms for the 2004 post-1972 set (continued)

Model	Exposure Metric	Form*	AIC	Hosmer-Lemeshow GOF <i>p</i> -value	BMC	BMCL
CHEEC, lag 10§			74.0	0.4163	0.2642	0.1177
CHEEC, lag 15			74.3	0.5664	0.2097	0.0898
CHEEC, lag 20			76.0	0.5610	—	—

*bkg indicates background rate, fixed at 1%.

†For statistical modeling, the equivalent model form was used: $P(PT) = \text{bkg} + (\text{Plateau} - \text{bkg}) \div [1 + \exp(-a - \beta \times \ln(\text{CHEEC}))]$.

± For statistical modeling, the equivalent model form was used: $P(PT) = \text{bkg} + (\text{Plateau} - \text{bkg}) \div [1 + \exp(-a - \ln(\text{CHEEC}))]$.

§Parameter estimates for the best-fitting models are as follows:

intercept = -0.1801 (SE = 1.0178), plateau = 0.5577 (SE = 0.3568, *p*-value = 0.1207).

— = no data

therefore, using such a long lag (which necessitates the assumption that these are background cases) was not judged to be appropriate, and the results are not further considered.

The various model forms were compared using AIC, and general model fit was evaluated with the Hosmer-Lemeshow (2000) test (a form of the Pearson χ^2 goodness-of-fit {GOF} statistic). This is a goodness-of-fit test that compares observed and expected events. Observations are sorted in increasing order of estimated probability of the event occurring and then divided into ~10 groups; the test statistic is calculated as the Pearson χ^2 statistic of observed and expected frequencies in these groups. The BMC was estimated for each candidate model using a Benchmark Response (BMR) of 10% and assuming a background rate of 1% (see Section 5.2.3.3). BMCs and corresponding BMCLs were estimated for each of the candidate models.

All of the candidate models had adequate fit as assessed by the Hosmer-Lemeshow test. Models were compared using the AIC values, ranging from 74.0 to 77.8. The model with the lowest AIC was the Michaelis-Menten model with 10-year lagged exposure (AIC = 74.0). See Table E-2. Note that models with exposure lagged by 0 or by 20 years, which are considered not to be biologically relevant, are shaded grey and not included as candidate models.

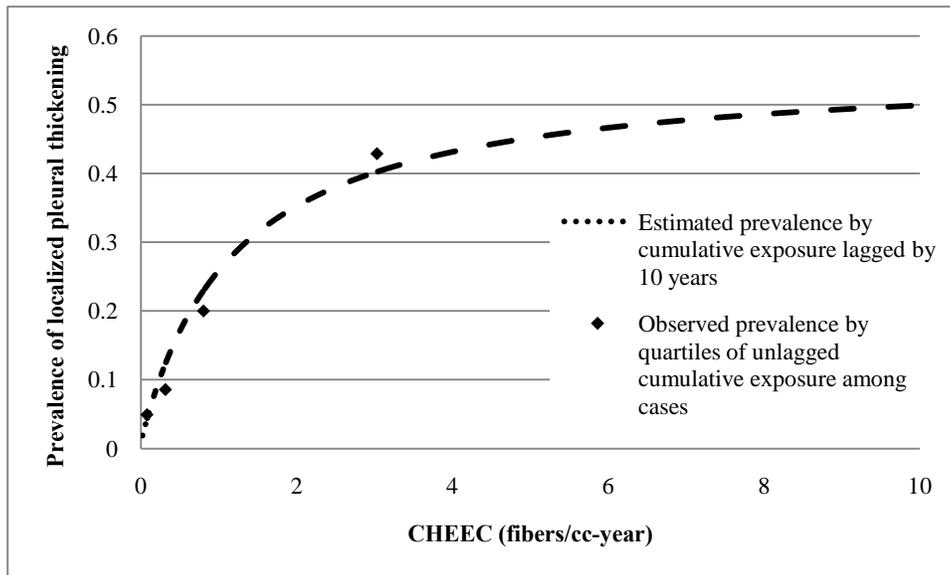
There were several models that had similar model fits (within 2 AIC units) as the best-fitting model, including the logistic and probit models with the natural log of CHEEC as the exposure metric (lags of 5, 10, and 15 years), the 3-parameter log-logistic model (lags of 5, 10, and 15 years), the Dichotomous Hill model (lag of 10 years), and the Michaelis-Menten model with exposure lagged by 5 or 15 years. All but one of these models would yield a BMCL lower than that for the best-fitting model. However, the range was relatively narrow among these

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1 similarly fitting models (BMCLs ranging from 0.0441 to 0.1352), with the lowest BMCL
2 ~2.7 times lower than the BMCL for the Michaelis-Menten model with exposure lagged by
3 10 years.

4 The Michaelis-Menten model using the 10-year lagged exposure had a p -value for fit
5 of 0.42, an AIC value of 74.0, and an estimated plateau of 0.5577 (SE = 0.3568). This model
6 yielded a BMC of 0.2642 fiber/cc-year, and corresponding BMCL of 0.1177 fiber/cc-year for a
7 10% increase in prevalence of localized pleural thickening. See Table E-2 and Figure E-1.

8
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10

11 **Figure E-1. Observed prevalence of localized pleural thickening and**
12 **estimated probability of localized pleural thickening.**

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The potential confounding effect of covariates was reexamined in the best-fitting model (see Table E-3). As in the initial assessment, after controlling for the effect of exposure (i.e., CHEEC, lagged by 10 years) there was no association between risk of LPT and time from first exposure (p -value = 0.9973), age at X-ray (p -value = 0.8734), gender (p -value = 0.5544), or BMI (p -value = 0.3806), and inclusion of each of these covariates increased the AIC (with the exception of BMI, due to missing information for some individuals). The variable representing smoking history did not meet the $\alpha = 0.05$ criteria for statistical significance (p -value = 0.0841), although inclusion of this variable decreased the AIC from 74.0 in the base model, to 72.3. Smoking was not considered further in the derivation of the RfC due to the lack of statistical significance at the $\alpha = 0.05$ level. However, because inclusion of the smoking

1 **Table E-3. Evaluation of covariates for the 2004 post-1972 set in the**
 2 **best-fitting model**
 3

Covariate	Wald <i>p</i> -value for beta coefficient corresponding to covariate	Plateau (SE)	AIC
Base model (only CHEEC)	—	0.5577 (0.3568)	74.0
Time from first exposure	0.9973	0.5580 (0.3634)	76.0
Age at X-ray	0.8734	0.5707 (0.3793)	76.0
Gender	0.5544	0.6167 (0.4138)	75.7
Smoking history	0.0841	0.5927 (0.3779)	72.3
BMI*	0.3806	0.4622 (0.2810)	55.8

4
 5 *Note that only 97 observations used due to missing values (AIC not comparable).
 6
 7

8 variable did improve model fit, it is investigated further as a sensitivity analysis in Section 2 of
 9 this appendix.

10 To evaluate the assumption of a 1% background rate of LPT, the best-fitting model (i.e.,
 11 Michaelis-Menten with 10-year lagged exposure) was rerun, allowing the background rate to be
 12 estimated as a parameter rather than fixed at 1%. The resulting estimated background rate was
 13 quite close to the assumed rate of 1%, at 3.12% (SE = 2.84%). Both the fixed and estimated
 14 values are in the range of estimates from previous studies (see Section 5.2.3.3.), and the
 15 difference in the BMCL when the background rate is fixed at 1% versus when it is estimated is
 16 ~15% (0.1177 compared to 0.1349 fiber/cc-year).
 17

18 **E.1.3. Derivation of the Candidate Point of Departure (POD) and Reference Concentration**
 19 **(RfC) for Localized Pleural Thickening Using the Michaelis-Menten Model**

20 The candidate point of departure (POD) is 0.1177 fiber/cc-year, the BMCL₁₀ for this data
 21 set. The reference concentration (RfC) is derived from the POD using the duration of exposure
 22 of 70 years, lagged by 10 years, and a total uncertainty factor of 100. See Section 5.2.4.

23
$$\text{RfC} = [0.1177 \text{ (fiber/cc)} \times (\text{year})] \times 1 \div (70 - 10) \text{ years} \times 1/100 = 1.96 \times 10^{-5} = 2 \times 10^{-5}$$

 24 fibers/cc (rounded to 1 significant digit).
 25

E.2. SENSITIVITY ANALYSIS FOR EFFECT OF SMOKING IN THE 2004 POST-1972 DATA SET

Due to the lack of statistical significance, smoking was not included in further analyses for derivation of the RfC. However, based on the literature suggesting that smoking may play a role in determining risk of LPT (see Section 5.3.6), the role of smoking was investigated further for these sensitivity analyses.

The prevalence of any smoking history was 75.0% ($n = 9$) among cases, and 51.9% ($n = 55$) among noncases. As noted above, the smoking variable was not significant at the $\alpha = 0.05$ level in the best-fitting (i.e., Michaelis-Menten) regression model controlling for CHEEC lagged by 10 years ($p = 0.08$), but inclusion of the smoking variable did decrease the AIC (AIC of 72.3 compared to 74.0 for the base model; see Table E-4). These results (borderline statistical significance of the term but nontrivial improvement in model fit) may indicate that smoking is associated with another variable that is associated with the outcome, or that the variable is too poorly measured to accurately reflect the effect of smoking.

Table E-4. Evaluation of smoking in the best-fitting model

Model*	AIC	Variable	Beta	p-value
1	74.0	(None)	—	—
2	72.3	Smoke	1.8232	0.0841
3	74.1	Smoke Ln(CHEEC, lag 10)*Smoke	2.5401 0.2182	0.2278 0.6598

*The following model forms were used for statistical analysis:

(1) $P(LPT) = bkg + (Plateau - bkg) / [1 + \exp(-a - \ln(CHEEC, lag 10))]$

(2) $P(LPT) = bkg + (Plateau - bkg) / [1 + \exp(-a - \ln(CHEEC, lag 10) + \beta * Smoke)]$

(3) $P(LPT) = bkg + (Plateau - bkg) / [1 + \exp(-a - \ln(CHEEC, lag 10) + \beta * Smoke + \beta_2 * \ln(CHEEC, lag 10) * Smoke)]$

To evaluate whether smoking may modify the effect measure for the association between Libby Amphibole asbestos exposure and risk of LPT, a third model was fit, which added an interaction term between the exposure metric and smoking; in this model, neither the smoking variable by itself nor the interaction term were significant ($p = 0.2278$ and $p = 0.6598$, respectively), and the AIC increased from the base model (i.e., AIC of 74.1). Therefore, only smoking (no interaction term) was retained for further sensitivity analyses.

1 The preferred model for RfC derivation (i.e., Model 1) yielded a BMC and a BMCL of
 2 0.26 and 0.12 fiber/cc-year, respectively (see Table E-5). Model 2, which includes the smoking
 3 variable, was used to derive estimates for smokers and nonsmokers separately. The BMC and
 4 BMCL were derived by setting the beta coefficient for smoking to zero for nonsmokers, and to
 5 the MLE-estimated value (1.82) for smokers. The BMCL for nonsmokers was about twice as
 6 high (0.25 fiber/cc-year) as that for the full cohort, while the POD for smokers was about 1/3 that
 7 of the full cohort (0.04 fiber/cc-year).

8
 9
 10 **Table E-5. Evaluation of smoking on estimated BMCs and BMCLs**

Model	Group	BMC (fiber/cc-year)	BMCL (fiber/cc-year)
1	All	0.2642	0.1177
2	Nonsmokers	0.9344	0.2463
2	Smokers	0.1509	0.0398

12
 13
 14 The lower BMCL among smokers compared to nonsmokers may indicate that smoking
 15 increases risk for development of LPT among individuals exposed to Libby Amphibole asbestos;
 16 another possibility is that smoking may affect the timing and progression of LPT development.
 17 If LPT develops sooner among smokers compared to nonsmokers, this could lead to a higher
 18 prevalence of LPT among smokers at a given observation time, and subsequently higher
 19 estimated risk. The lack of detailed smoking information in this cohort (such as pack-years)
 20 limits the ability to explore the effect of smoking on LPT risk among individuals exposed to
 21 Libby Amphibole asbestos, but these sensitivity analyses indicate that smoking should be
 22 considered when evaluating risk of respiratory health outcomes in this group.

23
 24 **E.3. STATISTICAL ANALYSIS OF THE FULL DATA SET**

25 **E.3.1. Identification of Key Explanatory Variables**

26 In order to begin modeling the data, key explanatory variables were identified using
 27 logistic regression to analyze the data of Rohs et al. (2008). Logistic regression was performed
 28 using the R statistical software, version 2.11.1. All fitting was performed using individual data,
 29 without any grouping. The dependent variable was localized pleural thickening ($n = 59$) noted
 30 on chest X-rays of former workers in the Marysville, OH facility ($n = 252$) and no reported

1 history of exposure to commercial asbestos at other locations. The available potential
2 explanatory variables included cumulative exposure at the time of X-ray, fiber/cc-year
3 (equivalent to CHEEC used in the University of Cincinnati report); time from first exposure (T ;
4 defined as time between first exposure and date of X-ray in years); age at time of X-ray; gender;
5 smoking status (i.e., ever, never); and BMI. The BMI variable was missing for 34 individuals.

6 Initial analysis showed that CHEEC was a significant explanatory variable using both
7 CHEEC and $\log(\text{CHEEC})$. The strategy used to determine what other explanatory variables
8 were influential consisted of including CHEEC and then adding one additional explanatory
9 variable at a time. Explanatory variables having $p > 0.2$ were dropped from further
10 consideration. Explanatory variables having $p < 0.2$ were given further consideration.

11 BMI was investigated as a potential explanatory variable because fat pads can sometimes
12 be misdiagnosed as pleural thickening. Thus, there might be a positive relation between BMI
13 and pleural thickening. Analysis of a model with CHEEC or $\log(\text{CHEEC})$ plus BMI ($n = 218$)
14 showed that BMI was not a significant explanatory variable. Two subsequent models using BMI
15 cutoffs of 25 and 30 also showed that BMI was not a significant explanatory variable. Analysis
16 of a model with CHEEC or $\log(\text{CHEEC})$ plus smoking indicated smoking was not a significant
17 explanatory variable.

18 Analysis of a model of CHEEC plus gender indicated gender was a potential contributing
19 explanatory variable ($p = 0.18$). However, it should be noted that the worker cohort was highly
20 imbalanced with 236 males and 16 females. Only three females have a cumulative human
21 equivalent exposure greater than 0.15 fiber/cc-year. These considerations indicated that the
22 potential relevance of gender as an explanatory variable should be viewed with caution.
23 Analysis of $\log(\text{CHEEC})$ plus gender showed that gender was not a significant explanatory
24 variable. Accordingly, gender was eliminated as an explanatory variable.

25 The importance of T (time from first exposure) is clearly illustrated by comparing the
26 results of Lockey et al. (1984) with the results of Rohs et al. (2008). These two studies were
27 conducted in the same occupational cohort 24 years apart. In the initial study (Lockey et al.,
28 1984), only 2% of the individuals showed pleural changes; in the follow-up study (Rohs et al.,
29 2008), 28% of the individuals showed pleural changes. Logistic fitting of a model including
30 CHEEC or $\log(\text{CHEEC})$ plus T showed that T was a highly significant explanatory variable with
31 $p < 0.0005$. This result is consistent with findings in other occupational cohorts exposed to
32 various forms of asbestos fibers that the time from first exposure is a significant explanatory
33 variable, even in the absence of continued exposure (Ehrlich et al., 1992; Järveholm, 1992).
34 T was retained as an explanatory variable. However, an important point of clarification is that
35 the T variable is not the same as time of event. The localized pleural thickening could have

1 formed at any time before the X-ray was taken (e.g., localized pleural thickening detected in
2 2004 could have been present in 1990).

3 Analysis of a model of CHEEC plus age at X-ray indicated that age was a significant
4 explanatory variable with $p = 0.032$. Analysis of a model of log (CHEEC) plus age at X-ray
5 showed that age at X-ray was a potentially significant explanatory variable with $p = 0.14$. It
6 should be noted that this result does not mean that age is an independent risk factor for the
7 development of localized pleural thickening. In fact, there is no biological evidence that age is
8 an independent predictor of the development of localized pleural thickening without a history of
9 previous exposure to durable mineral fibers such as amphibole fibers. With a history of exposure
10 to amphibole fibers, age has been shown to be related to pleural thickening (Amandus et al.,
11 1987b). However, it is quite possible that the association between age and prevalence is because
12 age at X-ray is related to T from first exposure, which is clearly one of the key explanatory
13 variables. Therefore, age at X-ray was not included as an explanatory variable.
14

15 **E.3.2. Selection of Model Form**

16 Figure E-2 (see Panel A) presents a plot of prevalence of localized pleural thickening as a
17 function of T , stratified by cumulative exposure (CHEEC). As seen, the prevalence appears to be
18 low (i.e., close to zero) until about 15–20 years after first exposure and then appears to rise in a
19 nonlinear fashion. Figure E-2 (see Panel B) presents a plot of prevalence as a function of
20 cumulative exposure, stratified according to time from first exposure. As seen, prevalence
21 appears to rise rapidly with increasing cumulative exposure but then tends to flatten out
22 (plateau). Based on these attributes of the base data set, the objective was to select a model that
23 included a plateau term whose value depended on T . Several alternative model forms were
24 investigated, using the Dichotomous Hill model as the starting point:
25
26

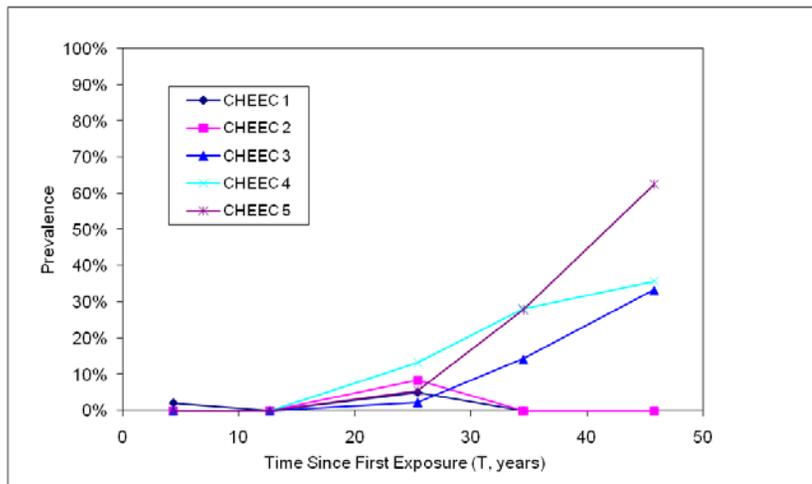
$$27 \quad p(\text{CHEEC}) = \text{bkg} + (\text{Plateau} - \text{bkg}) \div [1 + \exp\{-a - b \times \ln(\text{CHEEC})\}]$$

28
29

30 In the Dichotomous Hill model, the plateau term is a constant, with a value bounded
31 between background and 1.0. In order to be consistent with the data, this model was modified so
32 that the plateau term was a function of T . Several different nonlinear equations for the plateau
33 function were tested, including the following:

Figure E-2. Raw data plots.

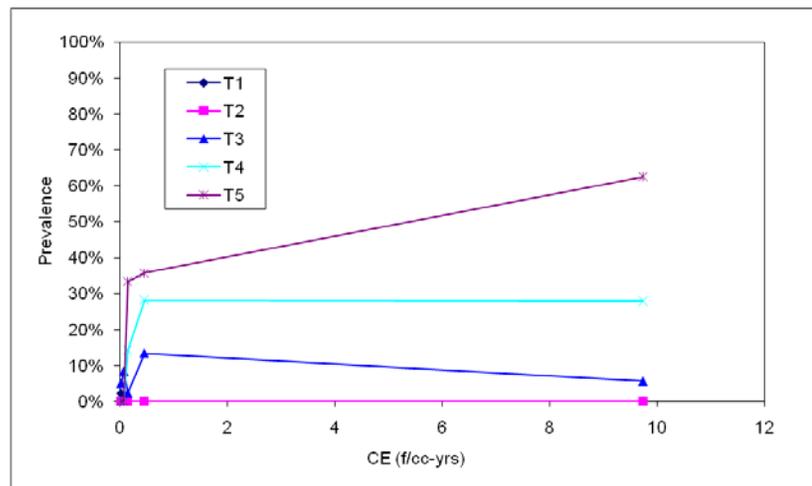
Panel A. Prevalence vs. Time From First Exposure (Grouped by CHEEC)



CHEEC Bins (f/cc-yrs)

Bin No.	Min	Max	Mean	N	Cases	Prev
CHEEC 1	0	0.05	0.021	67	2	3.0%
CHEEC 2	0.05	0.1	0.071	44	1	2.3%
CHEEC 3	0.1	0.2	0.145	108	10	9.3%
CHEEC 4	0.2	1	0.452	101	20	19.8%
CHEEC 5	1	35	9.728	114	28	24.6%

Panel B. Prevalence vs. CHEEC (Grouped by Time From First Exposure)



T Bins (years)

Index	Min	Max	Mean	N	Cases	Prev
T1	0	10	4.39	87	1	1.1%
T2	10	20	12.69	53	0	0.0%
T3	20	30	25.41	123	8	6.5%
T4	30	40	34.50	118	27	22.9%
T5	40	50	45.76	53	25	47.2%

1 Plateau = MIN[1, bkg + (1-bkg) × k1 × T]
 2 Plateau = MIN[1, bkg + (1-bkg) × k1 × T²]
 3 Plateau = MIN[1, bkg + (1-bkg) × k1 × T³]
 4 Plateau = bkg + (1-bkg) × Φ(T|m,s), where Φ(T|m,s) = cumulative normal probability
 5 function

6 Plateau = bkg + (1-bkg) × G(T|α,β), where G(T|α,β) = cumulative gamma probability
 7 function

8 Plateau = bkg + (1-bkg) × W(T|α,β), where W(T|α,β) = cumulative Weibull probability
 9 function

10
 11

12 AIC values when the plateau term is T, T², T³, cumulative normal, cumulative gamma, or
 13 cumulative Weibull are 293.97, 279.21, 276.12, 277.30, 277.07, and 276.98, respectively. The
 14 plateau term based on T³ was not chosen because the curve reaches a plateau of 1 when T is
 15 about 50 years. Of those that have a plateau less than 1 at high T, the plateau term based on the
 16 cumulative normal function was chosen because of its ease of use and familiarity.

17 Combining this equation for the plateau term with the basic probability model yields:

18
 19

$$p(\text{CHEEC}, T) = \text{bkg} + (1 - \text{bkg}) \times \Phi(T|m,s) \div [1 + \exp\{-a - b \times \ln(\text{CHEEC})\}]$$

20
 21
 22

23 Further testing indicated that the lowest AIC was achieved when the b term was set to
 24 1.0, resulting in a modified version of the discrete Michaelis-Menten equation:

25
 26

$$p(\text{CHEEC}, T) = \text{bkg} + (1 - \text{bkg}) \times \Phi(T|m,s) \div [1 + \exp\{-a - \ln(\text{CHEEC})\}]$$

27
 28
 29

30 This equation can also be written as:

31
 32

$$p(\text{CHEEC}, T) = \text{bkg} + (1 - \text{bkg}) \times \Phi(T|m,s) \times \{ \text{CHEEC} / [\text{CHEEC} + \exp(-a)] \}$$

33
 34
 35

1 This equation was selected as the preferred model for fitting to the data. In this model, T
2 (years) and CHEEC (fiber/cc-year) are explanatory variables. Fitting parameters of the
3 cumulative normal function are m (mid-point) and s (steepness). The a term is the intercept of
4 the exponential term when CHEEC equals 1 (LnCHEEC equals zero). Background is assumed
5 to be a constant (0.01) (see Section 5.2.3).

6 7 **E.3.3. Parameterization**

8 Fitting of the model to selected data sets was performed using the method of maximum
9 likelihood (MLE), using individual data without binning. The BMC for any specified value of T
10 is calculated from the MLE parameters and the specified value of T as follows:

$$11$$
$$12$$
$$13 \text{ BMC}_T = \exp [-a - \ln\{Q \times \Phi(T|m,s) - 1\}]$$
$$14$$

15 Where:

$$16 Q = (1 - \text{bkg}) \div (\text{BMR} - \text{bkg})$$
$$17$$
$$18$$

19 For a BMR of 10% extra risk, the value Q is 0.10.

20 21 **E.3.4. Model-Fitting Results**

22 Table E-6 provides the model-fitting results for each of the three data sets evaluated for
23 each of 5 lags of CHEEC and for each of 5 values of T . In all cases, the BMR is 10% extra risk.
24 Based on a background rate of 0.01, this BMR corresponds to a probability of localized pleural
25 thickening of 0.109.

26 Inspection of this table reveals that, for each of the three data sets evaluated, there is
27 relatively little effect of CHEEC lag over the interval 0–15 years. For the full data set and the
28 post-1972 data set, the lowest AIC is achieved for a lag of 10 years. It should be noted that the
29 time from first exposure in the full cohort ranged up to 47.4 years; therefore, estimates for values
30 of T greater than 47.4 years represent extrapolation outside the range of observed data, and
31 should be interpreted with caution.

32 Figure E-3 presents a graph comparing the observed data to the predicted values from the
33 model (no lag) for the full data set. As above, this requires grouping the observed data into bins,
34

Table E-6. Model-fitting results for the full data set

Study	Year of Hire	N	Cases	CHEEC Lag	MLE Parameters				T = 30		T = 35		T = 40		T = 50		T = 70	
					m	s	a	AIC	BMC	BMCL								
1980+ 2004	All	434	61	0	42.38	13.30	1.977	278.02	0.1822	0.0709	0.0731	0.0260	0.0421	0.0138	0.0224	0.0067	0.0157	0.0042
				5	42.44	13.54	2.000	277.87	0.1711	0.0666	0.0707	0.0253	0.0412	0.0136	0.0221	0.0066	0.0154	0.0042
				10	42.58	14.10	2.061	277.61	0.1477	0.0580	0.0651	0.0235	0.0389	0.0129	0.0212	0.0064	0.0146	0.0040
				15	42.86	15.16	2.167	277.67	0.1166	0.0486	0.0567	0.0219	0.0352	0.0124	0.0197	0.0062	0.0133	0.0038
				20	43.28	16.06	2.395	279.11	0.0876	0.0349	0.0449	0.0159	0.0286	0.0091	0.0162	0.0045	0.0107	0.0028
1980+ 2004	≥ 1972	198	13	0	31.41	10.47	-0.015	88.85	0.2930	0.1023	0.1900	0.0399	0.1462	0.0227	0.1177	0.0136	0.1128	0.0109
				5	31.58	11.81	0.095	88.43	0.2623	0.0956	0.1770	0.0399	0.1374	0.0232	0.1082	0.0142	0.1011	0.0112
				10	3.5E+05	3.0E+06	0.162	87.81	0.2402	0.0905	0.2402	0.0432	0.2402	0.0262	0.2402	0.0162	0.2402	0.0123
				15	1.4E+06	5.4E+06	6.5E-01	88.29	0.1766	0.0643	0.1766	0.0315	0.1766	0.0185	0.1766	0.0107	0.1766	0.0075
				20	2.1E+06	4.2E+06	1.5E+00	91.23	0.1036	0.0220	0.1036	0.0059	0.1036	0.0029	0.1036	0.0013	0.1036	0.0007
1980+ 2004	< 1972	236	48	0	43.15	13.33	2.259	192.77	0.1689	0.0227	0.0613	0.0071	0.0341	0.0037	0.0175	0.0017	0.0119	0.0010
				5	43.22	13.46	2.331	192.86	0.1540	0.0190	0.0569	0.0059	0.0318	0.0031	0.0164	0.0014	0.0111	0.0008
				10	43.44	13.88	2.472	193.04	0.1270	0.0092	0.0492	0.0028	0.0279	0.0015	0.0145	0.0007	0.0097	0.0004
				15	43.71	14.83	2.625	193.34	0.0934	--	0.0406	--	0.0241	--	0.0128	--	0.0084	--
				20	44.18	15.84	2.903	194.27	0.0642	--	0.0303	--	0.0185	--	0.0101	--	0.0065	--

The BMC for any specified value of T is calculated from the model parameter estimates and the specified value of T as follows:

$$BMC = \exp[-a - \ln\{(1 - bkg) \div (BMR - bkg) \times \Phi(T|m,s) - 1\}]$$

The BMCL is estimated by rewriting the model so that BMC appears as an explicit term in the model, for a specified T of interest:

$$BMR = bkg + (1 - bkg) \times \Phi(T|m,s) \div (1 + \exp(-a - \ln(BMC)))$$

Solving for a yields: $-a = \ln[Q \times \Phi(T|m,s) - 1] + \ln(BMC)$

Substituting yields: $p(CHEEC, T) = bkg + (1 - bkg) \times \Phi(T|m,s) \div [1 + \exp(z')]$

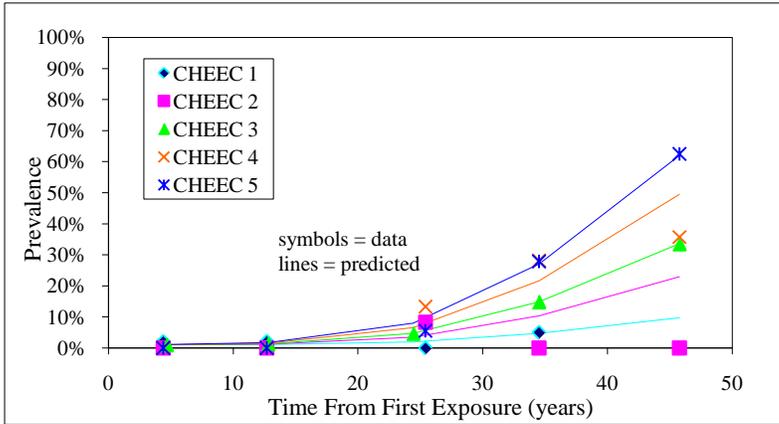
Where: $z' = \ln(Q \times \Phi(T|m,s) - 1) + \ln(BMC) - \ln(CHEEC)$

Simplifying yields: $p(CHEEC, T) = bkg + (1 - bkg) \times \Phi(T|m,s) \div [1 + Q \times \Phi(T|m,s) - 1] \times BMC \div CHEEC$

Using this equation, a trial value of the BMC is selected and treated as a constant, and the equation is refit to the data to find the MLE values of the remaining parameters (m, s). After optimization, the value of the log-likelihood is recorded for the specified trial value of the BMC, and the process is repeated for other trial values of the BMC. The BMCL is the trial value of the BMC where the log-likelihood decreases from the MLE log-likelihood value by an amount equal to $CHIDIST(2\alpha, 1) \div 2$. For $\alpha = 0.05$, the decrease is 1.3528.

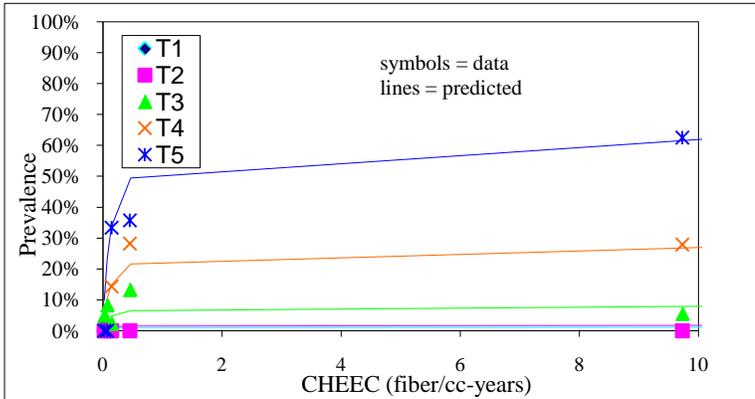
1 **Figure E-3. Observed versus predicted for base-case data set.**

2
3 **Panel A. Observed vs Predicted Prevalence as a Function of Time Since First Exposure (Grouped by CHEEC)**



CHEEC Bins (fiber/cc-years)						
Index	Min	Max	Mean	N	Cases	Prev
CHEEC 1	0	0.05	0.021	67	2	3.0%
CHEEC 2	0.05	0.1	0.071	44	1	2.3%
CHEEC 3	0.1	0.2	0.145	108	10	9.3%
CHEEC 4	0.2	1	0.452	101	20	19.8%
CHEEC 5	1	35	9.728	114	28	24.6%

4
5 **Panel B. Observed vs Predicted Prevalence as Function of CHEEC (Grouped by Time From First Exposure)**



T Bins						
Index	Min (year)	Max (year)	Mean (year)	N	Cases	Prev
T1	0	10	4.39	87	1	1.1%
T2	10	20	12.69	53	0	0.0%
T3	20	30	25.41	123	8	6.5%
T4	30	40	34.50	118	27	22.9%
T5	40	50	45.76	53	25	47.2%

6
7
8
9 even though fitting was performed using the individual data. Because the choice of bins is
10 arbitrary, the appearance of the graphs would likely be changed somewhat if different bins were
11 chosen. Nevertheless, it seems apparent that the model predictions are in good accord with the
12 data.

13
14 **E.3.5. Derivation of the POD and RfC for Localized Pleural Thickening Using the**
15 **Cumulative Normal Michaelis-Menten Model**

16 For comparison with the primary analysis, a POD and RfC are derived for localized
17 pleural thickening from the combined 1980 + 2004 data set as it provides the widest distribution
18 of T-values (see Section 5.2.3.2). A lag period of 5 years is used because Larson et al. (2010b)
19 showed that discrete pleural thickening could be observed much earlier than previously thought.

1 Because the RfC is intended to provide protection for a lifetime of exposure (exposure
2 begins at birth and continues to age 70), the POD is the BMCL₁₀ with $T = 70$ years of
3 0.0042 fiber/cc-year calculated with the cumulative normal Michaelis-Menten model (from
4 Table E-6). The POD is divided by duration of exposure of 70 years, lagged by 5 years, and then
5 divided by an uncertainty factor (see Section 5.2.4). In this case, as the model accounts for the
6 full lifetime of exposure of 70 years, the uncertainty factor of 100 is reduced to 30.

7
$$\text{RfC} = [0.0042 \text{ (fiber/cc)} \times \text{(year)}] \times 1 \div (70-5 \text{ years}) \times 1/30 = 2 \times 10^{-6} \text{ fibers/cc (rounded}$$

8 to one significant digit).

9 To provide a frame of reference, the calculation above was repeated with the data set
10 restricted to those hired in 1972 or later, when industrial hygiene data were collected in the
11 facility (from Table E-6).

12
$$\text{RfC} = [0.0112 \text{ (fiber/cc)} \times \text{(year)}] \times 1 \div (70 - 5) \text{ years} \times 1/30 = 7 \times 10^{-6} \text{ fibers/cc}$$

13 (rounded to one significant digit).

14 The reasonably good correlation in the calculated RfCs with the two different data sets
15 (2×10^{-6} versus 7×10^{-6} fiber/cc) provides some confidence in the exposure reconstruction
16 pre-1972.

17 An alternative candidate POD is the BMCL₁₀ with $T = 40$ years of 0.0136 fiber/cc-year
18 calculated with the Cumulative Normal Michaelis-Menten model (from Table E-6). The
19 BMCL₁₀ with $T = 40$ years is used because it is near the upper end of the range of T -values
20 available in the data set ($T_{\text{max}} = 47.375$ years). A lag time of 5 years and a total uncertainty
21 factor of 100 are used. See Section 5.2.5.

22
$$\text{RfC} = [0.0136 \text{ (fiber/cc)} \times \text{(year)}] \times 1 \div (40 - 5) \text{ years} \times 1 \div 100 = 4 \times 10^{-6} \text{ fibers/cc}$$

23 (rounded to one significant digit).

24 25 **E.3.6. Sensitivity Analysis**

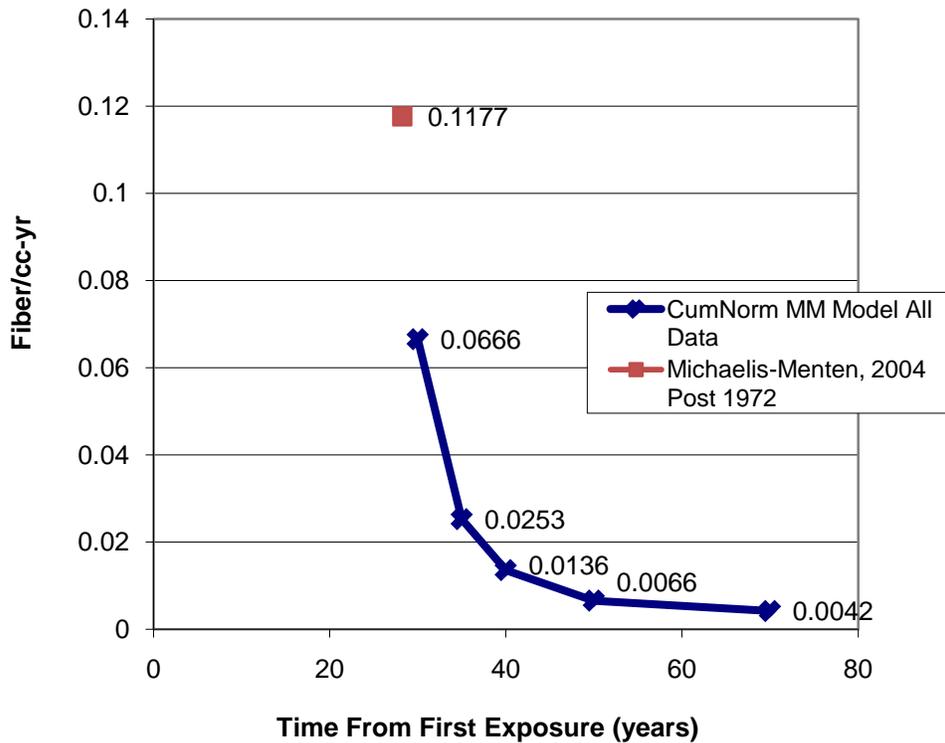
26 The University of Cincinnati increased the exposure metric by a factor of 2 between 1972
27 and 1967 to account for conditions in the facility before engineering controls were added. For
28 the purposes of comparison, the cumulative exposure was also calculated without this doubling.
29 Plots of prevalence of localized pleural thickening with these two different exposure metrics are
30 virtually identical (not shown).

31 One worker in the 1980 study was exposed only 5 months before X-ray and showed
32 localized pleural thickening. Excluding this worker from the analysis did not change the
33 calculated RfC.

34 Figure E-4 shows a plot of the PODs (fiber/cc-year) versus time from first exposure
35 (years) calculated from the Michaelis-Menten model using the 2004, post-1972 data (see
36 Section E.1), and from the Cumulative Normal Michaelis-Menten model using the full data set

1 (see Table E-6). Because the Michaelis-Menten model is independent of time from first
2 exposure, the mean value of T for the data set is used. As there are few individuals with long T
3 (maximum of 47 years) and low cumulative exposure, it is not clear whether the apparent plateau
4 with the Cumulative Normal Michaelis-Menten model is a reflection of the limitation of the data
5 or an expression of the underlying biology.

6
7



8
9

Figure E-4. PODs (fiber/cc-year) versus time from first exposure (years).

1 **APPENDIX F. MARYSVILLE, OH WORKER OCCUPATIONAL EXPOSURE**
2 **RECONSTRUCTION**

3 **The Development of a Cumulative Human Equivalent Exposure Concentration**
4
5
6
7

8 BY:

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1 **F.1. INTRODUCTION**

2 This project builds on the previous work of Dr. James Lockey et al. investigating possible
3 effects of exposures to dust containing Libby Amphiboles at a plant in Marysville, OH (Lockey
4 et al., 1984; Rohs et al., 2008). The data used in the original exposure reconstruction and as
5 reported in the published manuscripts, was based on the exposures measurements available at
6 that time (Lockey et al., 1984). This exposure reconstruction is based on approximately five
7 times additional occupational fiber exposure data than was previously utilized in 1980. These
8 exposure measurements were recently obtained by the US Environmental Protection Agency
9 (EPA) from the company and through trial transcripts from the United States of America vs. WR
10 Grace, et al., as well as the archived data used in the 1980 exposure reconstruction. Four steps
11 were undertaken to construct an exposure matrix describing exposure over each year from 1957
12 to 2000. In a final fifth step, this matrix was used to calculate an exposure metric for workers.

- 13
14
15 1. Data searches, requests, and document selection
16 2. Document evaluation, data entry, cleaning, editing and standardization
17 3. Completeness and trends in measurements
18 4. Decisions relevant to the exposure matrix
19 5. Development of a cumulative human equivalent exposure concentration

20
21
22 **F.2. DATA SEARCHES, REQUESTS, AND DOCUMENT SELECTION**

23 Three sources of paper records were identified. First, sampling reports from OM Scott
24 that included measurements at the facility pre- and post-1980 were received via the EPA. These
25 reports contained both measurement results and information about the plant. OM Scott was also
26 contacted with a request for available maps of the plant layout prior to 1980. Secondly, archived
27 files from the Lockey et al. (1984) study were identified. Lastly, as a result of the recent WR
28 Grace trial, there was additional discovery of material relevant to the OM Scott plant. The
29 Department of Justice (DOJ) was contacted for the release of these data. There were seven
30 4” binders available for review and every page (approximately 3,150 pages) was scanned
31 visually to identify pages relevant to the current project. Aspects of particular interest included
32 the manufacturing process, usage and source of raw materials, engineering and design changes in
33 the plant, work practices and exposure assessment methodology. Approval was received from
34 the DOJ to utilize the relevant data for this project.

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1 **F.3. DOCUMENT EVALUATION, DATA ENTRY (QUALITATIVE AND**
2 **QUANTITATIVE), CLEANING, EDITING AND STANDARDIZATION**

3 All of the records--both the qualitative and quantitative--were reviewed in this second
4 phase.

5
6 **F.3.1. Qualitative Information**

7 Written reports, letters, memos and notes contained background information on plant
8 operations. A total of 1,489 pages were read for potentially useful and pertinent information
9 regarding OM Scott and abstracted into a data file. From these records, we obtained:

- 10
11
- 12 • Plant layout, including changes over time. This allowed us to associate the
13 descriptions used on air sampling data forms/reports with jobs or departments
14 within the plant. A limited number of aerial images were available to identify
15 major structures.
 - 16 • Process descriptions were derived including workers per shift, workers per
17 department, sources of raw materials, and raw material volume in number of
18 railroad cars received, tonnage of railroad cars from Libby and South Carolina,
19 and tonnage of unexpanded vermiculite received.
 - 20 • For each department a list of job titles and tasks

21
22
23 Gaps in understanding were filled-in with information gathered from the focus groups,
24 specifically regarding:

- 25
26
- 27 • Plant lay-out and changes over time, including engineering controls
 - 28 • Historical pattern of job rotations within department from 1957 to 1980
 - 29 • Time spent in work locations at the plant site
 - 30 • Overtime associated with departments and season
 - 31 • Use/nonuse of respirators
- 32
33

34 **F.3.2. Quantitative Data**

35 Air sampling reports include quantitative measurement of airborne dust and fiber
36 concentration associated with a department job. These records were computerized following the

1 data entry scheme provided on June 1, 2009 and approved. Records were double entered and
2 verified.

3 Two identical Microsoft Access databases were created for initial and duplicate entry of
4 the quantitative data. Each individual performing data entry had a unique and separate database
5 to avoid possible data entry confusion. Variables to be entered have been previously provided.
6 A random 10% check of entered data was conducted throughout the data entry process to
7 maintain quality of data, to address data entry questions and to resolve potential database issues.
8 Data entry differences were below 5% throughout the entry process.

9 Each record was assigned a document and record identification (ID) number. The
10 document ID variable was based on data source. For example, if the data were provided by the
11 EPA from OM Scott then the EPA document ID was used. Data hardcopies from the EPA,
12 Department of Justice and 1980 UC data were each numbered starting from 1. The document ID
13 variable states EPA, DOJ or UC followed by the document number. Record IDs were generated
14 by using a unique identifier like a sample number for each document. If a unique identifier was
15 unable to be discerned then the entry personnel was instructed to consecutively number each
16 sample per document starting from one.

17 A final verification of data entry used SAS version 9.2 PROC COMPARE to import the
18 initial and duplicate Access tables. Discrepancies were below 5% as a result of the 10% random
19 checks throughout the entry process. All discrepancies were addressed by reviewing the original
20 document. The initial and duplicate Access databases were archived. A copy of the initial
21 database was converted to Microsoft Excel format for ease of standardization and analyses.
22

23 **F.3.3. Process of Standardization**

24 The standardization process included categorizing entered data into appropriate variable
25 fields, spell checking, identifying duplicate record entry from duplicate documents, merging
26 records for the same sample or measurement, evaluating data for completeness and categorizing
27 groups of data based on type of sample or measurement.

28 Data were reviewed and edited to ensure the information was entered into the appropriate
29 data field. A frequency of the data fields using SAS 9.2 PROC FREQ identified spelling
30 differences and patterns to ensure correct labeling of the data. Additional data variables were
31 created depending on recognized need to distinguish important pieces of data.

32 A new variable called group ID was created to identify, track and consolidate partial
33 and/or complete duplicate data into one unique sample. Partial data were identified on a
34 combination of sample date, sample record ID, sample result, volume, sampling time and/or
35 document patterns. A document pattern would include instances where only a group of sample

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1 results were available in one document and another document(s) would match the exact sequence
2 of sample results.

3 Data were further categorized based on the type of sample. Categories include dust
4 samples, bulk samples, personal and area fiber samples, limit of detection (LOD) or
5 quantification (LOQ) samples, off-site locations, and time weighted average samples. Some
6 samples were collected with a direct reading fibrous aerosol monitor, but these were not used as
7 there was no calibration information included in the records. Thus, only the fiber count data
8 collected with a sampling pump were used. In addition, group IDs lacking a sample result,
9 sample year or department were excluded.

10 Personal and area samples were plotted by year and department and found to be visually
11 similar. In addition the range, means, and standard deviations were approximately equal.
12 Therefore, personal and area sample data sets were merged and both utilized for the development
13 of the Exposure Matrix. Group IDs with only LOD or LOQ values were grouped by year and
14 categorized as trionize or background. In order to assign an estimate for the LOD or LOQ the
15 median value of each group was divided by two and assigned to all samples in that group. Given
16 the small number of LOD and LOQ samples ($n = 35$), it is unlikely any detectable bias was
17 introduced using this method. Time weighted average (TWA) values were not utilized when the
18 individual measurements that comprised the TWA were already available.

19 Sample analysis did not specify the type of fibers identified in the fiber counts. Counting
20 rules used included any fiber with the proper dimensions and not specifically Libby Amphibole
21 fibers. Attempts in other studies to convert from total dust to fiber count have relied on
22 similarities in equipment or process where side-by-side samples were collected. We did not
23 identify any ‘pairs’ of dust/fiber data from this plant. Moreover, fibers are a minor component of
24 the dust exposure, limiting an ability to find a relationship over time. Therefore, total dust
25 measurements were not converted to fiber counts and were not used as part of the fiber exposure
26 estimation.

27 28 **F.3.4. Completeness and Trends in Measurements**

29 From the paper records, we concluded that additional information would be helpful from
30 workers in order to obtain descriptions of work organization and practices. Focus groups
31 discussions were conducted with long-term OM Scott workers ($n = 15$) in 2010. These focus
32 groups provided valuable qualitative data in order to fill gaps regarding work plant operations,
33 especially during the earlier years.

34 As described earlier, the data used for exposure reconstruction was obtained from three
35 sources: UC archived records (reported previously by Lockey et al.), information obtained by the

1 EPA from the company, and from the DOJ documents. Table F-1 shows that a total of 914 IH
 2 fiber measurements were available for this analysis. Of this total, only 180 (19.6%) of the IH
 3 fiber measurements were available from the UC archived records. The yearly number of
 4 samples collected was not uniform. As shown in Table F-2, the first fiber count measurements
 5 were available in 1972 and the last in 1994. About 26% of the samples were collected in 1978.
 6 Focus group participants reported working in the summer. Summer activities, however, involved
 7 fewer work hours and included clean-up and repair activities in addition to production. Since
 8 less than 6% of the fiber samples were collected during the summer months, no seasonal trend
 9 analysis was possible.

10
 11 **Table F-1. Industrial hygiene fiber measurements by document source**

Document source	Trionize	Background	Total (%)
DOJ	38	0	38 (4.16)
EPA	398	122	520 (56.89)
UC	135	45	180(19.69)
COMBINED	172	4	176(19.26)
Total (%)	743 (81.29)	171 (18.71)	914

13
 14
 15 **F.4. DECISIONS RELEVANT TO THE EXPOSURE MATRIX**

16 **F.4.1. General Issues**

17 A graphical display of fiber count results indicated that all samples in various trionizing
 18 jobs generally followed the same pattern: higher in the early years of IH sampling, and declining
 19 *gradually* over time. Further, from the focus groups, we learned that no one, single engineering
 20 change resulted in a dramatic reduction in the perception of dustiness in the plant. Thus, the
 21 workers' recollections supported the findings from the IH data demonstrating a gradual decline
 22 in levels of exposure rather than a dramatic step-wise drop due to any one engineering change.

23 Changes in work practices such as the use of compressed air and brooms for clean-up
 24 versus the use of wet vacuuming may result in marked decreases in exposure. We discussed
 25 work practices in the focus groups, and no remarkable changes were documented. Participants
 26 did note that during some years, sampling practices included leaving pumps in control rooms
 27 during high-dust activities. High-dust activities included the use of compressed air to remove
 28 particulate from surface areas. We did not find any documentation that high exposure work was
 29 excluded from the sampling effort in the IH reports. In fact, in the early years, some activities

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Table F-2. Industrial hygiene fiber measurements by department and year

Dept.	1972	1973	1975	1976	1977	1978	1979	1980	1981	1982	1983	1984	1985	1986	1987	1988	1993	1994	Total (Dept. %)
Background	3	0	2	0	10	54	2	0	12	7	3	11	5	23	13	16	0	10	171 (18.71)
Trionize	9	40	20	115	68	183	26	23	38	24	8	27	14	52	33	31	3	29	743 (81.29)
Total	12	40	22	115	78	237	28	23	50	31	11	38	19	75	46	47	3	39	914
(Year %)	(1.31)	(4.38)	(2.41)	(12.58)	(8.53)	(25.93)	(3.06)	(2.52)	(5.47)	(3.39)	(1.20)	(4.16)	(2.08)	(8.21)	(5.03)	(5.14)	(0.33)	(4.27)	(100.00)

Dept. = department.

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1 recorded in the sampling record included reference to compressed air “blow down”, one of the
2 activities associated with potentially high exposures. Consequently, no adjustment was made for
3 any potentially unsampled periods from 1972 through 1994 when IH measurements were
4 available.

5 Per the focus groups, workers reported very sporadic usage of respirators due to heat and
6 discomfort. Because of the heat, the workers preferred paper masks, and reported reusing them
7 from day to day. There was no documentation of fit-testing of the paper masks. Paper masks
8 may provide some protection against the larger particles, but likely provided little reduction in
9 respirable particles, particularly when reused. Therefore, no adjustment was made to lower the
10 exposure estimates due to respirator use.

11 12 **F.4.2. Vermiculite Raw Material Sources**

13 Libby vermiculite usage ended in 1980 per shipping records obtained from B. Benson
14 and an Agency for Toxic Substances and Disease Registry (ATSDR) report (Benson, 2009;
15 ATSDR, 2005). Post 1980 usage included African/Virginia/South Carolina vermiculite until
16 2000. In 2000, corn cobs were introduced as an inert carrier of lawn care chemicals, and
17 vermiculite usage ended. There were two primary sources of information regarding vermiculite
18 sources:

- 19
20
21 • An internal UC document from the 1980 study with estimates of railroad car loads
22 delivered to the plant per year. Documents indicate railroad cars from Libby were
23 100 ton cars and from South Carolina 70 ton cars.
- 24 • The Chamberlain memo provides information regarding vermiculite sources for
25 1964–1972 in railroad car loads per year.

26
27
28 Per the UC document, 100% South Carolina vermiculite was estimated to be used from
29 1957–1960. Per the Chamberlain memo, Libby vermiculite began arriving in 1960. Focus
30 groups placed it earlier, in 1958 or 1959. We believe there is sufficient evidence to support a
31 1959 start date for Libby vermiculite with 1957 and 1958 assumed to be 100% South Carolina
32 vermiculite.

33 Documentation was found from the original 1980 UC documents indicating an estimated
34 Libby tonnage contribution of 32% from 1959–1963. These percentages for 1959–1963 were
35 adopted for use in this project. After adjusting for the difference in rail car sizes, the
36 Chamberlain memo indicates that Libby tonnage usage increased from 57% in 1964 to 73% in

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1 1965 to 92% in 1966. Table F-3 illustrates the distribution of unexpanded vermiculite sources
 2 received at the plant between 1957 and 1971. From 1959 until 1971 fiber level adjustments were
 3 made based on the percent Libby versus South Carolina vermiculite tonnage received at the
 4 plant. The estimates were derived from 1972 when the earliest IH samples were available and
 5 93% of the vermiculite was Libby.

6
7
8 **Table F-3. Tonnage by year and vermiculite source**
9

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 says 1960
1960	32	68	Chamberlain memo and 1980 chart
1961	32	68	Chamberlain memo and 1980 chart
1962	32	68	Chamberlain memo and 1980 chart
1963	32	68	Chamberlain memo and 1980 chart
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

10
11
12 To develop the relationship of fiber levels between South Carolina and Libby
13 vermiculite, samples that recorded a 100% of either source for vermiculite were identified. Two
14 jobs with a higher number of samples from the same year from each source were used to
15 establish the relationship: track-unload for 1977 and expander for 1978. The samples used
16 included 22 Libby track-unload, 8 Libby expander, 17 South Carolina track-unload, and 7 South
17 Carolina expander. A weighted average of these samples generated a 10:1 fiber count ratio for

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1 Libby:South Carolina vermiculite. This ratio was used for estimating the proportion of Libby
2 versus South Carolina fiber exposure levels from 1959 to 1971. From 1972 and beyond, IH
3 measurements were available and no adjustment in the IH data was made based on vermiculite
4 source. Tonnage records demonstrate that Libby was the primary source of vermiculite from
5 1972 until 1979, supplemented by African vermiculite, and that Libby vermiculite usage ended
6 in 1980.

7 The 100% Libby samples were compared to samples labeled as 50% Libby. The
8 resultant measurements were accordingly lower, demonstrating internal consistency within the
9 data.

10 Assessment of exposure in 1977 during application of the final, expanded product that
11 included a mix of South African and Libby vermiculite showed no fibers. Therefore, fiber
12 exposure estimation was restricted to jobs in the plant areas where expanding was conducted.
13

14 **F.4.3. Exposure Estimates by Time Period for the Trionizing Department**

15 For this project, exposures of interest were from 1957 through 2000. Exposure
16 measurements in the plant where vermiculite was used were initiated in 1972. For prior years, it
17 was necessary to estimate exposure from the measurements collected in 1972 and later and with
18 supporting qualitative information. Important changes occurred in production due to increasing
19 use of engineering controls to reduce airborne particulate. In addition, the source of vermiculite
20 changed over the years. Therefore, the exposure estimation process was divided into two efforts:
21 1972 and later when IH measurements were available; 1957 to 1971, when no IH measurements
22 were available. The exposure estimation process is described below, first for Trionizing where
23 vermiculite was expanded and then for other departments where either no or expanded
24 vermiculite was used.
25

26 **F.4.3.1. Trionizing Department Exposure Estimation \geq 1972-2000**

27 For the years with exposure measurements, fiber exposure level was estimated from the
28 measurement data. This was done by department.
29

30 **F.4.3.1.1. Trionizing department**

31 The trionizing department included jobs from the entry of vermiculite into the plant,
32 through final product. These were: track at raw material entry and production jobs of
33 screen/mill, dryer, expander, blender, resin, and clean-up, Workers rotated through the various
34 jobs within the department. Overall rotation among jobs reported in the 1980 Lockey et al. study
35 was verified by the focus groups.

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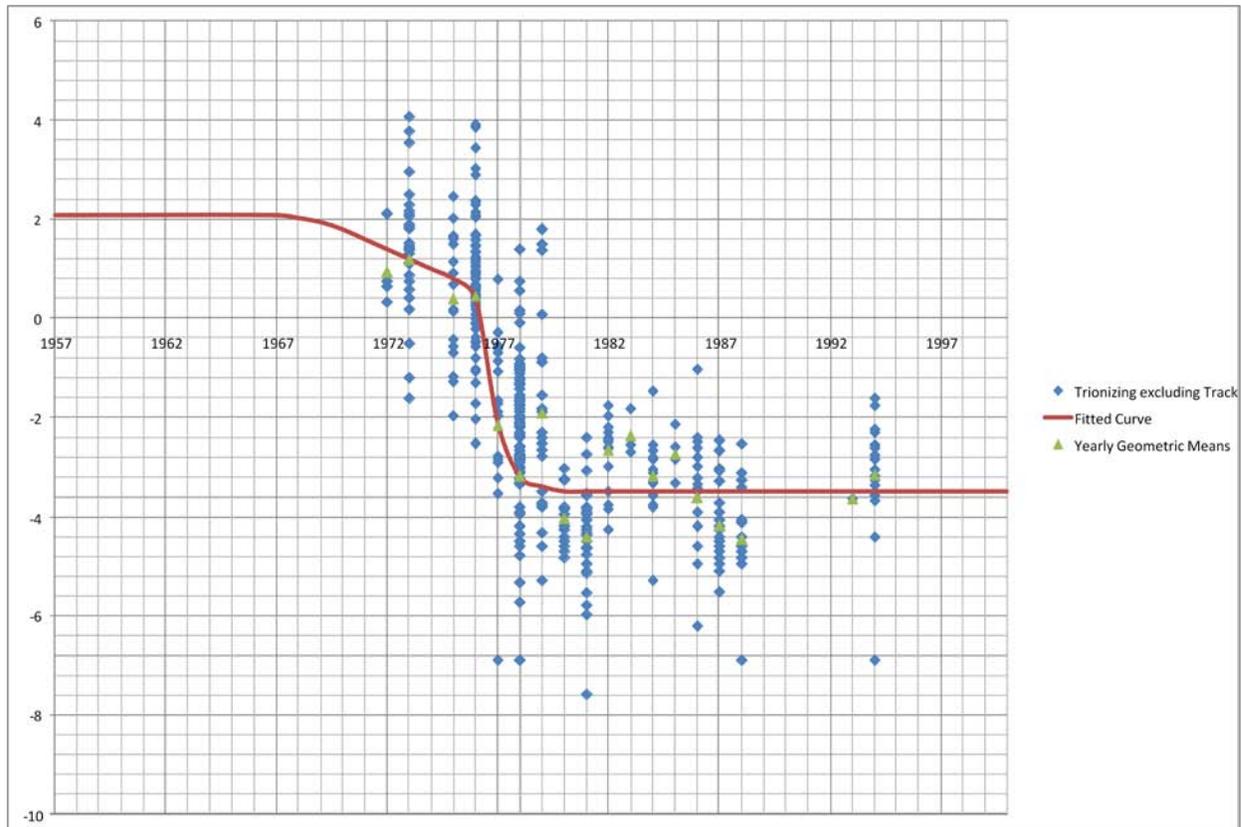
1 Plots of the measurements over time were made for individual trionizing jobs. Based on
2 these plots, it was determined that all IH sample results from the various trionizing production
3 jobs (screen/mill through clean-up) followed the same general distribution and should be
4 combined. The track job included two very different work activities: unloading rail cars
5 containing vermiculite (*track unload*) and general track work such as bringing in the rail cars,
6 and monitoring discharge (*track other*). The two track job activities (*unload* and *other*) had a
7 substantially larger range of sampling results and were treated separately.

8 The following steps were followed:

- 9
10
11 1. The data were log-transformed.
- 12 2. For all exposure values for the combined trionizing jobs from 1972–1979, a curve
13 was drawn connecting the mean values of years having at least 40 exposure
14 measurements (1973, 1976, and 1978). This criteria was chosen to assure that
15 stable means were used to define the curve over this time period. For each year,
16 the annual exposure estimate was determined by exponentiation of the value from
17 the curve. The sharp decline seen in exposures throughout this time period
18 parallels the addition of engineering controls including dust collection, enclosing
19 vibrating conveyors, adding ventilators, erecting a wall between track and
20 trionizing, and sealing leaks in the system. As values for 1980–1994 were similar
21 and near the level of detection, the mean value for all the samples was used and
22 then extended until 2000.
- 23 3. The measurement results for track unload and track other were plotted and a
24 straight line produced to best fit the data points. An estimate of exposure at each
25 year was determined by exponentiation of the value on the line for that year.
- 26 4. For the trionizing department, it was estimated that 11% of work time was spent
27 in track and 89% in all other jobs. This is consistent with the previous weights
28 used in the 1980 Lockey study and confirmed by the focus group.
- 29 5. The Focus groups reported that when working track, track unload required about
30 25% of the time and track other comprised about 75% of the track job time.
31 Therefore, a weighted average for exposure at track within the trionizing
32 department was derived. This 25% time estimate for track unload is higher than
33 that previously published (Lockey et al., 1984).

34
35
36 Figure F-1 illustrates on a log scale a fitted line of all usable IH measurements across all
37 jobs (except track) within the trionizing department.

38
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Log of fiber count (fibers/cc)

1
2
3 **Figure F-1. Illustrates on a log scale a fitted line of all usable IH**
4 **measurements across all jobs (except track) within the trionizing**
5 **department.**
6

7
8 **F.4.3.2. Trionizing Department Exposure Estimation 1957–1971**

9 There are no IH measurements available prior to 1972. Engineering changes did not
10 result in “step-function” decreases in exposures based on focus group reports. Rather a more
11 gradual decline in exposure occurred beginning with improvements in 1968, when two dust
12 collectors were added. Focus group workers report that dust exposures in trionizing were at least
13 two times higher in the 1960’s. Track jobs, however, were outdoors and likely unaffected by
14 plant engineering controls. Hence, estimates for fiber exposure levels for track duties were
15 adjusted by type of vermiculite only.

16 For trionizing employees, excluding outdoor track duties, the estimate from the focus
17 group of ‘twice as high’ was generated beginning from 1972 and increasing until 1967. The year
18 1972 was used as the start of the “gradual” retrospective increase in exposure back to 1967 as

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1 1972 was the first year when IH measurements were available, and the percent Libby vermiculite
2 utilized was 93%. The year 1967 was selected as this was the year preceding engineering
3 controls. A line was drawn to connect these two points and then the adjustment was made for
4 the percent yearly Libby and South Carolina vermiculite utilized from 1967 through 1971. Prior
5 to 1967, exposure was extended backward in time, assuming no change from the 1967 value
6 except for a yearly adjustment for percent Libby and South Carolina usage. As described above
7 and shown in figure 1, after 1980 when Libby vermiculite was no longer used and major
8 environmental controls had been implemented, fiber exposure levels remained near the level of
9 detection (0.01) through the last available IH information in 1994. The levels were estimated to
10 be the same from 1994 forward until 2000 when vermiculite was no longer used.

11 12 **F.4.4. Exposure Estimates for Nontrionizing Departments**

13 Departments using only expanded vermiculite or no vermiculite were defined as having
14 “plant background” exposure. These included the departments of polyform, plant maintenance,
15 office, research, pilot plant, warehouse, central maintenance, and packaging. This decision was
16 based on plots of available sampling data showing similar levels, and qualitative reports
17 documenting that there were not fibers in the finished product. Plant background prior to 1972
18 was calculated using similar methodology as for trionizing. Although the background level was
19 not affected by engineering control as in trionizing, exposures would be affected by the percent
20 of Libby vermiculite used. Therefore, for the years prior to 1972, the measured plant
21 background rate in 1972 of 0.02 was adjusted by the yearly percent Libby vermiculite utilized.
22 The two years prior to Libby vermiculite usage, 1956 and 1957, were assigned level of
23 detection (0.01). This is in line with IH measurements post Libby vermiculite usage through
24 1994.

25 Polyform began in 1969, and no unexpanded vermiculite was used there. The
26 background exposure level was used for any time in Polyform.

27 Plant Maintenance—Although there were some differences of opinion in the focus group
28 regarding where plant maintenance spent their time, the consensus reached was to assign
29 approximately 50% of time in trionizing and 50% in areas defined as plant background for their
30 work in shop and other departments.

- 31
32
33
 - Office—Assigned plant background.
 - Research—Assigned plant background.

34

- 1 • Pilot plant—Per the focus group participants, the pilot plant did not have its own
2 expander, and used only expanded vermiculite in test and run simulations. Plant
3 background levels were thus assigned to the pilot plant.
- 4 • Warehouse—Only expanded vermiculite was in this area. Although bags did
5 break, the exposure was to final product, not unexpanded vermiculite.
- 6 • Central Maintenance—According to the focus group, these employees worked
7 outside of trionizing for about 90% time (background) and 10% (trionizing) for
8 installation of new equipment/parts. Around 1982 central maintenance
9 department was discontinued, and the work was contracted to outside personnel.
- 10 • Packaging—Assigned plant background.

11
12
13 Table F-4 illustrates the fiber exposure matrix from 1957 to 2000 using this methodology.
14

15 **F.4.5. Decisions Related to Break Periods and Hours Worked**

16 Cumulative exposure is the product over time of the level of exposure and duration.
17 Level of exposure is derived from the exposure matrix and duration from the work history.
18 However, in this workforce, work time is complicated by breaks where exposure is at a lower
19 level and seasonal changes resulting in extra hours worked beyond the usual 40 hour week. Each
20 of these factors is described below:

21 According to the focus group data there was approximately a 30 minute break for lunch
22 and two fifteen minute breaks during the day. Therefore, every worker was considered to have at
23 least one hour of background exposure daily. There was no documentation that a 3rd fifteen
24 minute break was provided when working longer than eight hours in a day.

25 Employees in some departments frequently worked extra hours each day, and weekends
26 as well, depending on the production needs and season. Decisions regarding this work
27 organization are summarized below:

- 28
29
30 1. Extra hours—Were defined as hours worked in excess of 8 hours per day.
- 31 2. Four departments worked no extra hours—office, pilot plant, research, central
32 maintenanceAccording to focus group data, the only departments that worked
33 extra hours outside of their own department were trionizing and polyform. Thus,
34 a decision was needed as to how to appropriate the amount of overtime spent
35 outside trionizing and polyform.

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Table F-4. Exposure matrix assuming doubling of fiber levels from 1972 to 1967 but with adjustment for vermiculite source from 1957–1971

Department	1957	1958	1959	1960	1961	1962	1963	1964	1965	1966	1967	1968	1969	1970	1971
Trionizing	0.729	0.729	2.825	2.825	2.825	2.825	2.825	4.462	5.510	6.755	6.427	5.542	5.279	4.923	4.316
Plant maint (50/50)	0.369	0.369	1.416	1.416	1.416	1.416	1.416	2.237	2.763	3.387	3.222	2.779	2.648	2.470	2.168
Central maint (90/10)	0.082	0.082	0.289	0.289	0.289	0.289	0.289	0.457	0.565	0.692	0.659	0.569	0.543	0.509	0.449
Background ^a	0.010	0.010	0.008	0.008	0.008	0.008	0.008	0.012	0.015	0.019	0.018	0.016	0.017	0.018	0.019
	1972	1973	1974	1975	1976	1977	1978	1979	1980	1981	1982	1983	1984	1985	1986–2000
Trionizing	3.674	3.007	2.464	2.019	1.391	0.150	0.086	0.077	0.063	0.063	0.060	0.060	0.055	0.055	0.052
Plant maint (50/50)	1.847	1.513	1.242	1.020	0.705	0.090	0.053	0.044	0.036	0.036	0.035	0.035	0.032	0.032	0.031
Central maint (90/10)	0.385	0.319	0.264	0.220	0.157	0.030	0.027	0.017	0.015	0.015	0.015	0.015			
Background ^a	0.020	0.020	0.020	0.020	0.020	0.020	0.020	0.010	0.010	0.010	0.010	0.010	0.010	0.010	0.010

^a Background applies to Pilot Plant, Research, Polyform, Office, Packaging, Warehouse.

- 1 3. Extra hours for polyform workers—According to the focus groups, polyform
2 workers first worked in their own department, and went to trionizing to work
3 extra hours. According to workers, about 75% of the daily overtime was in their
4 own department. Therefore, for each four hours worked beyond the normal eight
5 hour day, it is estimated that they spent three hours in polyform and one in
6 trionizing. This rule was not applied to 8-hour weekend days worked.
- 7 4. Extra hours for trionizing workers—As for polyform workers, above, it is
8 estimated that trionizing workers spent three hours in trionizing and one hour in
9 polyform as a daily average.

10
11
12 Schedules by season differed due to production rate:

- 13
14
- 15 • For trionizing, plant maintenance, polyform, warehouse, and packaging the spring
16 schedule was from January through May—7 days @ 12 hours.
 - 17 • For trionizing, plant maintenance, polyform, warehouse, and packaging the
18 summer schedule was from June through August—5 days @ 8 hours. Due to the
19 difficulty that heat and humidity brought to the process, polyform was shut down
20 during summer. During the summer, polyform workers did outside jobs. As
21 these jobs have the same exposure level as polyform (background rate), no
22 adjustment was made for the summer polyform shutdowns. The trionizing
23 department more typically slowed down production in the summer, and this is
24 reflected in the number of hours worked from June through August.
 - 25 • For trionizing, plant maintenance, polyform, warehouse, and packaging the fall
26 schedule was from September through December—5 days @ 12 hours and
27 2 weekend days @ 8 hours.

28
29
30 In light of these extra hours, exposure values by department and season were modified
31 for use in the cumulative equivalent human equivalent exposure concentration estimations.
32

33 **F.5. DEVELOPMENT OF A CUMULATIVE HUMAN EQUIVALENT EXPOSURE** 34 **CONCENTRATION**

35 An EPA adjustment of cumulative occupational exposure to fibers to continuous human
36 exposure to fibers (24 hours/day; 7 days/week) was provided by B. Benson. This adjustment
37 was accepted as provided for the development of a cumulative human equivalent exposure
38 concentration (CHEEC) for the Marysville, OH occupational cohort.

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1 **F.5.1. Seasonal Schedule Correction Factor**

2 For this project the Correction Factor was adjusted for the specific information on work
3 schedules related to the seasonal changes to meet production demands as described above in
4 Section 4.4. UC applied these correction factors supplied by the EPA (B. Benson) to the work
5 history data obtained by UC during 1980 and updated in 2004.

6
7 **F.5.2. Decision Rules to address Department Changes Occurring Within Seasons**

8 Decision rules were implemented to systematically standardize each worker's
9 occupational history to a format that corresponded directly with the seasonal changes that
10 occurred at the plant. Previous decisions related to department exposure levels and seasonal
11 work resulted in six unique exposure categories: trionizing, plant maintenance, central
12 maintenance, polyform, background (office, research, pilot plant), and background with extra
13 time (warehouse, packaging). The date of any job change by a worker between these six
14 categories was adjusted so the change occurred at the starting month for the nearest season.

15
16 **F.5.3. Development of CHEEC**

17 In preparation for creating the CHEEC, the exposure matrix was converted to a seasonal
18 (spring, summer, fall) exposure value. This value is the estimate of the amount of exposure
19 occurring by department for each season of each year. With the worker's occupational histories
20 standardized to the same seasons, the CHEEC for each worker was then calculated as the sum of
21 exposure values for all seasons worked between 1957–2000. The correction factors used in
22 derivation of the CHEEC are outlined below.

23
24
25 **General Procedure**

- 26
- $(\text{Cumulative Fibers})_{\text{OCCUP}} \times \text{Correction Factor} = (\text{Cumulative Fibers})_{\text{HEC}}$

27

 - OCCUP = Occupational Exposure

28

 - HEC = Human Equivalent Concentration for exposure of 24 hours/day, 7
29 days/week

30

 - The Correction Factor usually used with an occupational study is
31 $5 \text{ days} \div 7 \text{ days} \times 10 \text{ m}^3 \div 20 \text{ m}^3$
- 32

1 **UC Procedure**

2 CHEEC= (Exposure Est_{year-dept-season 1} × Correction Factor_{season 1}
3 × Seasonal Duration Factor) + (Exposure Est_{year-dept-season 2}
4 × Correction Factor_{season 2} × Seasonal Duration Factor)
5 + ... (Exposure Est_{year-dept-season x} × Correction Factor_{season}
6 × Seasonal Duration Factor)
7
8

9 Where the Seasonal Duration Factor for the Spring is 5/12 year; the Summer is 3/12 year;
10 the Fall is 4/12 year.
11

12 **F.5.3.1. Detailed Calculations Follow**

13 **F.5.3.1.1. Work schedule for trionizing, plant maintenance, polyform, warehouse, and**
14 **packaging**

15 **F.5.3.1.1.1. Spring**

16 January 1 to May 31: 7 days/week, 12 hours/day, with New Years' Day off, and
17 accounting for leap years:
18
19

- 20
- 21 • 151.25-1 = 150.25 days
 - 22 • Breathing rate, working = 1.25 m³/hour × 12 hours = 15 m³
 - 23 • Breathing rate, not working = 0.625 m³/hour × 12 hours = 7.5 m³
 - 24 • Total breathing rate = 15 + 7.5 = 22.5 m³/day
 - 25 • Correction Factor Spring = 150.25 ÷ 151.25 × 15 ÷ 22.5 = 0.662259
- 26

27 **F.5.3.1.1.2. Summer**

28 June 1 to August 31: 5 days/week, 8 hours/day, 2 week summer vacation:
29
30

- 31
- 32 • (92 – 14) × 5 ÷ 7 = 55.714286 days
 - 33 • Breathing rate, working = 1.25 m³/hour × 8 hours = 10 m³
 - 34 • Breathing rate, not working = 0.625 m³/hour × 16 hours = 10 m³
 - 35 • Total breathing rate = 10 + 10 = 20 m³/day
 - 36 • Correction Factor Summer = 55.714286 ÷ 92 × 10 ÷ 20 = 0.302795

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1 **F.5.3.1.1.3. Fall**

2 September 1 to December 31: 5 days/week, 12 hours/day and 2 days/week, 8 hours/day,
3 with Christmas Day off:

4
5
6
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15

- $122 - 1 = 121$ days
- Breathing rate, working, 12 hour day = $1.25 \text{ m}^3/\text{hour} \times 12 \text{ hours} = 15 \text{ m}^3$
- Breathing rate, working, 8 hour day = $1.25 \text{ m}^3/\text{hour} \times 8 \text{ hours} = 10 \text{ m}^3$
- Breathing rate, not working = $0.625 \text{ m}^3/\text{hour} \times 16 \text{ hours} = 10 \text{ m}^3$
- Total breathing rate, 12 hour work day = $15 + 7.5 = 22.5 \text{ m}^3/\text{day}$
- Total breathing rate, 8 hour work day = $10 + 10 = 20 \text{ m}^3/\text{day}$
- Correction Factor Fall = $121 \div 122 \times (86.42857 \times 15 \div 22.5 + 34.57143 \times 10 \div 20) \div 121 = 0.613973$

16 **F.5.3.1.2. Work schedule for office, pilot plant, research, and central maintenance**

17 No extra days or extra hours.

18

19 **F.5.3.1.2.1. Spring**

20 January 1 to May 31: 5 days/week, 8 hours/day, with New Years' Day off, and
21 accounting for leap years.

22
23
24
25
26
27
28
29

- $(151.25 - 1) \times 5 \text{ days} \div 7 \text{ days} = 107.321429$
- Breathing rate, working = $1.25 \text{ m}^3/\text{hour} \times 8 \text{ hours} = 10 \text{ m}^3$
- Breathing rate, not working = $0.625 \text{ m}^3/\text{hour} \times 16 \text{ hours} = 10 \text{ m}^3$
- Total breathing rate = $10 + 10 = 20 \text{ m}^3/\text{day}$
- Correction Factor Spring = $107.321429 \div 151.25 \times 10 \div 20 = 0.354782$

30 **F.5.3.1.2.2. Summer**

31 June 1 to August 31: 5 days/week, 8 hours/day, 2 week summer vacation.

32
33
34
35
36

- $(92 - 14) \times 5 \div 7 = 55.714286$ days
- Breathing rate, working = $1.25 \text{ m}^3/\text{hour} \times 8 \text{ hours} = 10 \text{ m}^3$
- Breathing rate, not working = $0.625 \text{ m}^3/\text{hour} \times 16 \text{ hours} = 10 \text{ m}^3$

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- Total breathing rate = $10 + 10 = 20 \text{ m}^3/\text{day}$
- Correction Factor Summer = $55.714286 \div 92 \times 10 \div 20 = 0.302795$

F.5.3.1.2.3. *Fall*

September 1 to December 31: 5 days/week, 8 hours/day, with Christmas Day off.

- $(122 - 1) \times 5 \div 7 = 86.428571$ days
- Breathing rate, working, 8 hour day = $1.25 \text{ m}^3/\text{hour} \times 8 \text{ hours} = 10 \text{ m}^3$
- Breathing rate, not working = $0.625 \text{ m}^3/\text{hour} \times 16 \text{ hours} = 10 \text{ m}^3$
- Total breathing rate = $10 + 10 = 20 \text{ m}^3/\text{day}$
- Correction Factor Fall = $86.428571 \div 122 \times 10 \div 20 = 0.354215$

F.5.4. Results of the Cumulative Human Equivalent Exposure Concentration (CHEEC)

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 hand-calculated to ensure all programming was correct. Tables 5-7 provide a list of all 280 subjects participating in the 2004 Marysville health update (Rohs et al., 2008). These tables describe each subject's identification number, job start and stop date, date of radiograph, age, gender, body mass index, smoking history, asbestos exposures, health outcomes, and the cumulative human equivalent exposure concentration (CHEEC) for all departmental exposures they reported while employed at the OM Scott Marysville, Ohio plant.

F.6. STRENGTHS AND LIMITATIONS

There are major strengths in this exposure reconstruction project:

1. Data were gathered from court records, federal sources and archived files, totaling over 3,000 pages. These data were reviewed and both qualitative and quantitative data were abstracted to aid in this reconstruction.
2. Approximately five times more fiber measurements became available than had been used in the original studies.

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- 1 3. Two focus groups were conducted in 2010 with long term workers who provided
2 input regarding exposure and production process changes.
- 3 4. There were sufficient data available to examine exposure intensity over time for
4 jobs within the trionizing department as well as for other departments. These data
5 enhanced exposure estimates for all departments from 1972 to 1994.
- 6 5. IH data were available allowing for comparisons of fiber counts when 100%
7 Libby or 100% South Carolina vermiculite was used in order to calculate a ratio
8 of fibers in each.
- 9 6. There were data available from archived records, Scott memos, and worker
10 information that allowed for exposure estimates to be adjusted for type of
11 vermiculite used from 1957 until 1971 when no IH data were available.
- 12 7. Worker report data were available that provided documentation for increased
13 dustiness before IH data were available, compared with years when measurements
14 were available.
- 15 8. Based on past and current data gathered in the focus group, exposures were
16 adjusted to account for seasonal work schedules by departments.
- 17 9. All decisions based on level of exposure by year were data driven.

18
19

20 The limitations for this project are also recognized:

21
22
23
24
25
26
27
28

- 29 1. The exposure metric used (fibers/cc) results from an analytical method that is a
30 count of fibers (defined as any viewed elongated particle in excess of 5 μm in
length and with a length to width ratio of 3:1) collected on a filter and viewed at
400 \times with light microscopy. The composition of the fiber is not known. Also, a
fiber with diameter less than a limit of resolution of 0.2 μm cannot be viewed
with this method.
- 31 2. It is unknown if other sampling results exist. If any are found in the future, these
32 can be incorporated into a future exposure assessment.
- 33 3. Some dusty activities may not have been sampled or rarely sampled e.g., summer
cleanup. We have no way of estimating the effect of these activities on overall
exposure estimates.
- 34 4. We did not reduce exposure estimates due to possible use of respiratory
35 protection. Substantially more documentation regarding enforced usage, fit

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1 testing and cleaning/storage protocols would be needed for meaningful reduction
2 in exposure estimates.

3 5. By combining all individual trionizing job duties into one department exposure,
4 the nonexpander trionizing exposure estimates may have been overestimated as
5 there were more expander measurements, and these were somewhat higher than
6 for other job duties.

7 6. From 1980 forward, Libby vermiculite was not used. Thus for any individual
8 year during this period, exposure from a qualitative and quantitative perspective
9 does not reflect Libby Amphibole exposure.

10 7. Seasonal work schedule adjustments were based on recall of focus group
11 participants and may over or under estimate true durations and location of
12 additional work hours.

13
14 **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 asbestos¹-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.² 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

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.

²This program is an adaptation of the approach previously used by the Committee on the Biological Effects of Ionizing Radiation (BEIR, 1988). Compared to life-table methods based on full life exposures from birth, the method used here yielded unit risk differences between full life exposure to scaled adult-only exposure between -3% to -2% for the mesothelioma mortality unit risks for the two mesothelioma models (see Tables G-1 and G-2). A spreadsheet containing the extra risk calculation for the derivation of the LEC₀₁ for mesothelioma mortality is presented in Tables G-1 and G-2.

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1 are shown in Section 5.4.5.3. This current assessment does not directly apply life-table
2 calculations to estimate partial lifetime risk scenarios; the use of the IUR for partial lifetime
3 extrapolations is discussed in Section 5.4.5.4.

4 U.S. age-specific all-cause mortality rates from the 2010 *National Vital Statistics Report*
5 (*NVSR*) for deaths in 2007 among all race and gender groups combined (NCHS, 2010) were used
6 to specify the all-cause background mortality rates (R_o) in the life-table analysis. The risk with
7 exposure (R_x) was computed up to age 85 years,³ assuming continuous environmental exposure
8 to Libby Amphibole asbestos. Conversions between occupational Libby Amphibole asbestos
9 exposures and continuous environmental asbestos exposures were made to account only for
10 differences in the amount of air inhaled per day during a higher effort occupational shift
11 (8 hours; 10 m³) compared to a standard 24-hour (20 m³) day (U.S. EPA, 1994) because results
12 were already based on a 365-day calendar year. The computation of the unit risk involved three
13 steps. The first step was to compute the unit risk for adults. This was achieved by initiating
14 exposure at age 16 years and maintaining continuous exposure throughout the remainder of life
15 while allowing for the incremental mathematical decay of previously accumulated exposure.⁴
16 An age of 16 years was used because it roughly matched the youngest age of a worker in the
17 subcohort and was consistent with the application of a similar life-table methodology when the
18 age-dependent adjustment factors (ADAFs) are applied; however, the application of ADAF was
19 not recommended in this case (see Section 4.6.2.2). An adjustment was also made in the
20 life-table for the lag period, so that the age-specific risk calculations began at 16+ (the length of
21 the lag period) years of age. The standard assumption used by the U.S. Environmental
22 Protection Agency (EPA) is that the average lifetime spans 70 years. Because the adult-only-
23 exposure unit risk excluded the first 16 years, the adult-only-exposure unit risk based on 54 years
24 was then rescaled for an entire lifetime of continuous exposure by multiplying the interim value
25 for adult-only-exposure by 70/54 to cover the childhood years (<16 years) to compute the
26 “adult-based” unit risk. After rescaling, the resulting “adult-based” lifetime unit risk estimate (in
27 contrast to the unscaled “adult-only-exposure” unit risk estimate obtained from the life-table
28 calculations) may be prorated for less-than-lifetime exposure scenarios in the same manner as
29 would be used for an “adult-based” unit risk estimate derived from a rodent bioassay (see
30 Section 5.4.5.4).

31 Consistent with the *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a), the
32 same data and methodology were also used to estimate the exposure level effective concentration
33 (EC_x) and the associated 95% lower confidence limit of that exposure level effective

³Note 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.

⁴Exposures in the life-tables were computed at the mid-point of each age interval and appropriately lagged.
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1 concentration (LEC_x) corresponding to an absolute risk of 1% ($x = 0.01$). A 1%-risk level is
2 commonly used for the determination of the point of departure (POD) for low-dose extrapolation
3 from epidemiological data, and the LEC value corresponding to that risk level was used as the
4 actual POD.

5 The following tables illustrate the computational details of the unit risks for
6 mesothelioma mortality (see Tables G-1 and G-2). The results of Tables G-1 and G-2 are shown
7 in Table 5-16 and are not adjusted for the underascertainment of mesothelioma described in
8 Section 5.4.5.1.1. The unit risks adjusted for underascertainment are shown in Table 5-17.

9
10

11 Column Definitions for Tables G-1 and G-2:

12 Column A: Age interval up to age 85.

13 Column B: All-cause mortality rate for interval i ($\times 10^5/\text{year}$) (U.S. DHHS, 2010: 2007 data
14 NVSR 58[19] 2010).

15 Column C: All-cause hazard rate for interval i (h^*_i) (= all-cause mortality rate \times number of
16 years in age interval).

17 Column D: Probability of surviving interval i (q_i) [= $\exp(-h^*_i)$].

18 Column E: Probability of surviving up to interval i (S_i) ($S_1 = 1$; $S_i = S_{i-1} \times q_{i-1}$, for $i > 1$).

19 Column F: Lagged exposure at mid-interval (x dose) assuming constant exposure was initiated
20 at age 16.

21 Column G: Mesothelioma mortality hazard rate in exposed people for interval. To estimate the
22 LEC_{01} , i.e., the 95% lower bound on the continuous exposure giving an extra risk of
23 1%, the 95% upper bound on the regression coefficient is used.

24 Column H: All-cause hazard rate in exposed people for interval i ($h^*_{x_i}$) [= $h^*_i + (hx_i - h_i)$].

25 Column I: Probability of surviving interval i without dying from mesothelioma for exposed
26 people (qx_i) [= $\exp(-h^*_{x_i})$].

27 Column J: Probability of surviving up to interval i without dying from mesothelioma for
28 exposed people (Sx_i) ($Sx_1 = 1$; $Sx_i = Sx_{i-1} \times qx_{i-1}$, for $i > 1$).

29 Column K: Conditional probability of dying from mesothelioma in interval i for exposed people
30 [= $(hx_i \div h^*_{x_i}) \times Sx_i \times (1 - qx_i)$] (R_x , the lifetime probability of dying from
31 mesothelioma for exposed people = the sum of the conditional probabilities across
32 the intervals).

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1 Note that the life-tables for mesothelioma mortality estimate the extra risk as the absolute
2 risk as there is no assumption of a background risk in the absence of exposure. In each of the
3 life-tables, inhalation exposure commences at age 16 years and continues at the same exposure
4 concentration for the duration of the life-table. This allows for the computation of an
5 “adult-only-exposure” occupational lifetime unit risk, which is then scaled by a ratio of 70:54 to
6 account for risk over the standard 70-year lifetime. While exposure is initiated in the life-table at
7 age 16 years, this exposure is lagged to match the corresponding exposure-response models,
8 which provide the hazard rates per unit of exposure. For example, in Table G-1, Column F
9 shows exposure lagged by 10 years so that no lagged exposure appears in the table prior to age
10 26 years (16 + 10). In Table G-2, Column F shows exposure lagged by 15 years so that no
11 lagged exposure appears in the table prior to age 31 years (16 + 15). Note that risks are initially
12 shown in 1-year intervals because children’s risk intervals can be smaller, and there was a need
13 to be able to begin exposures at 16 years.

Table G-1. Mesothelioma extra risk calculation for environmental exposure to 0.1479 fibers/cc Libby Amphibole asbestos using the metric of cumulative exposure with a 10-year exposure lag and a 5-year half-life of exposure, as described in Section 5.4.5.3 as the reasonable upper bound

A	B	C	D	E	F	G	H	I	J	K
Age int.	All-cause mortality ($\times 10^5$/year)	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	29.9	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

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Table G-1. Mesothelioma extra risk calculation for environmental exposure to 0.1479 fibers/cc Libby Amphibole asbestos using the metric of cumulative exposure with a 10-year exposure lag and a 5-year half-life of exposure, as described in Section 5.4.5.3 as the reasonable upper bound (continued)

A	B	C	D	E	F	G	H	I	J	K
Age int.	All-cause mortality ($\times 10^5$/year)	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)
17	61.9	0.0006	0.9994	0.9892	0.000	0.0000	0.0006	0.9994	0.9892	0.0000
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

Table G-1. Mesothelioma extra risk calculation for environmental exposure to 0.1479 fibers/cc Libby Amphibole asbestos using the metric of cumulative exposure with a 10-year exposure lag and a 5-year half-life of exposure, as described in Section 5.4.5.3 as the reasonable upper bound (continued)

A	B	C	D	E	F	G	H	I	J	K
Age int.	All-cause mortality ($\times 10^5$/year)	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)
55–59	726.3	0.0363	0.9643	0.9149	2.107	0.0011	0.0374	0.9633	0.9098	0.0010
60–64	1,068.3	0.0534	0.9480	0.8823	2.121	0.0011	0.0545	0.9470	0.8764	0.0009
65–69	1,627.5	0.0814	0.9218	0.8364	2.127	0.0011	0.0825	0.9209	0.8299	0.0009
70–74	2,491.3	0.1246	0.8829	0.7710	2.131	0.0011	0.1256	0.8819	0.7642	0.0008
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 years); scaled occupational lifetime unit risk = 0.0876 (scaled by ratio of 70:54 to account for risk over 70-year lifetime).

Table G-2. Mesothelioma extra risk calculation for environmental exposure to 0.2446 fibers/cc Libby Amphibole asbestos using the metric of cumulative exposure with a 15-year exposure lag and a 5-year half-life of exposure, as described in Section 5.4.5.3 as the lowest information criterion

A	B	C	D	E	F	G	H	I	J	K
Age int.	All-cause mortality ($\times 10^5$/ year)	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	29.9	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

Table G-2. Mesothelioma extra risk calculation for environmental exposure to 0.2446 fibers/cc Libby Amphibole asbestos using the metric of cumulative exposure with a 15-year exposure lag and a 5-year half-life of exposure, as described in Section 5.4.5.3 as the lowest information criterion (continued)

A	B	C	D	E	F	G	H	I	J	K
Age int.	All-cause mortality ($\times 10^5$/year)	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)
17	61.9	0.0006	0.9994	0.9892	0.000	0.0000	0.0006	0.9994	0.9892	0.0000
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	0.000	0.0000	0.0010	0.9990	0.9815	0.0000
27	99.4	0.0010	0.9990	0.9806	0.000	0.0000	0.0010	0.9990	0.9806	0.0000
28	99.4	0.0010	0.9990	0.9796	0.000	0.0000	0.0010	0.9990	0.9796	0.0000
29	99.4	0.0010	0.9990	0.9786	0.000	0.0000	0.0010	0.9990	0.9786	0.0000
30	110.8	0.0055	0.9945	0.9777	0.000	0.0000	0.0011	0.9989	0.9777	0.0000
31	110.8	0.0055	0.9945	0.9777	0.238	0.0001	0.0012	0.9988	0.9766	0.0001
32	110.8	0.0055	0.9945	0.9777	0.664	0.0002	0.0013	0.9987	0.9754	0.0002
33	110.8	0.0055	0.9945	0.9777	1.035	0.0004	0.0015	0.9985	0.9741	0.0003
34	110.8	0.0055	0.9945	0.9777	1.357	0.0005	0.0016	0.9984	0.9727	0.0005

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Table G-2. Mesothelioma extra risk calculation for environmental exposure to 0.2446 fibers/cc Libby Amphibole asbestos using the metric of cumulative exposure with a 15-year exposure lag and a 5-year half-life of exposure, as described in Section 5.4.5.3 as the lowest information criterion (continued)

A	B	C	D	E	F	G	H	I	J	K
Age int.	All-cause mortality ($\times 10^5/\text{year}$)	All-cause hazard rate (h^*)	Prob. of surviving interval (q)	Prob. of surviving up to interval (S)	Lagged exp. mid. int. ($X\text{dose}$)	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)
35–39	145.8	0.0073	0.9927	0.9723	2.097	0.0007	0.0080	0.9920	0.9712	0.0007
40–44	221.6	0.0111	0.9890	0.9652	2.813	0.0010	0.0120	0.9880	0.9634	0.0009
45–49	340.0	0.0170	0.9831	0.9546	3.171	0.0011	0.0181	0.9821	0.9519	0.0010
50–54	509.0	0.0255	0.9749	0.9385	3.350	0.0011	0.0266	0.9738	0.9348	0.0011
55–59	726.3	0.0363	0.9643	0.9149	3.440	0.0012	0.0375	0.9632	0.9103	0.0011
60–64	1,068.3	0.0534	0.9480	0.8823	3.485	0.0012	0.0546	0.9469	0.8768	0.0010
65–69	1,627.5	0.0814	0.9218	0.8364	3.507	0.0012	0.0826	0.9207	0.8302	0.0010
70–74	2,491.3	0.1246	0.8829	0.7710	3.518	0.0012	0.1258	0.8818	0.7644	0.0009
75–79	3,945.9	0.1973	0.8209	0.6807	3.524	0.0012	0.1985	0.8200	0.6740	0.0007
80–84	6,381.4	0.3191	0.7268	0.5588	3.527	0.0012	0.3203	0.7259	0.5527	0.0006
Absolute $R_x = 0.0100$										

exp. = exposure, haz. = hazard, int. = interval, meso. = mesothelioma, mid. = mid-interval, Prob. = probability
 Absolute risk = 0.01000; exp. level = 0.2446; Occupational lifetime unit risk = 0.01/0.2446 = 0.0409 (Based on occupational exposures beginning at age 16 years); Scaled occupational lifetime unit risk = 0.0530 (Scaled by ratio of 70:54 to account for risk over 70-year lifetime).

1 **G.2. LUNG CANCER MORTALITY**

2 Lung cancer mortality risk computations are very similar to mesothelioma mortality
3 computations above (see G.1), with one important difference that extra risk is used for lung
4 cancer. Extra risk is defined as equaling $(R_x - R_o) \div (1 - R_o)$, where R_x is the lifetime lung
5 cancer mortality risk in the exposed population and R_o is the lifetime lung cancer mortality risk
6 in an unexposed population (i.e., the background risk). U.S. age-specific all-cause mortality
7 rates from the 2010 *National Vital Statistics Report* NVSR 58(19) 2010 for deaths in 2007
8 among all race and gender groups combined (NCHS, 2010) were used to specify the all-cause
9 background mortality rates (R_o) in the life-table analysis. Cause-specific background mortality
10 rates for cancers of the lung, trachea, and bronchus were obtained from a Surveillance,
11 Epidemiology, and End Results (SEER) report on mortality during 2003–2007 (SEER Table
12 15.10, age-specific U.S. death rates).

13 The following tables show details of the computations of the unit risks for lung-cancer
14 mortality (see Tables G-3 and G-4). The results of Tables G-3 and G-4 are shown in Table 5-19.

15
16
17 Column Definitions for Tables G-3 and G-4:

18 Column A: Age interval up to age 85.

19 Column B: All-cause mortality rate for interval i ($\times 10^5/\text{year}$) (U.S. DHHS, 2010: 2007 data
20 NVSR 58[19] 2010).

21 Column C: Lung-cancer mortality rate for interval i ($\times 10^5/\text{year}$) (2003—2007 Surveillance,
22 Epidemiology and End Results Table 15.10, age-specific U.S. death rates).

23 Column D: All-cause hazard rate for interval i (h^*_i) (= all-cause mortality rate \times number of
24 years in age interval).

25 Column E: Probability of surviving interval i (q_i) [= $\exp(-h^*_i)$].

26 Column F: Probability of surviving up to interval i (S_i) ($S_1 = 1$; $S_i = S_{i-1} \times q_{i-1}$, for $i > 1$).

27 Column G: Lung-cancer mortality hazard rate for interval i (h_i)
28 (= lung-cancer mortality rate \times number of years in interval).

29 Column H: Conditional probability of dying from lung cancer in interval i
30 [= $(h_i \div h^*_i) \times S_i \times (1 - q_i)$], i.e., conditional upon surviving up to interval i (R_o , the
31 background lifetime probability of dying from lung cancer = the sum of the
32 conditional probabilities across the intervals).

- 1 Column I: Lagged exposure at mid-interval (x dose) assuming constant exposure was initiated
2 at age 16.
- 3 Column J: Lung-cancer mortality hazard rate in exposed people for interval. To estimate the
4 LEC_{01} , i.e., the 95% lower bound on the continuous exposure giving an extra risk of
5 1%, the 95% upper bound on the regression coefficient is used, i.e.,
6 Maximum Likelihood Estimate + $1.645 \times$ standard error.
- 7 Column K: All-cause hazard rate in exposed people for interval i (h^*x_i) [$= h^*_i + (hx_i - h_i)$].
- 8 Column L: Probability of surviving interval i without dying from lung cancer for exposed
9 people (qx_i) [$= \exp(-h^*x_i)$].
- 10 Column M: Probability of surviving up to interval i without dying from lung cancer for exposed
11 people (Sx_i) ($Sx_1 = 1$; $Sx_i = Sx_{i-1} \times qx_{i-1}$, for $i > 1$).
- 12 Column N: Conditional probability of dying from lung cancer in interval i for exposed people
13 [$= (hx_i \div h^*x_i) \times Sx_i \times (1 - qx_i)$] (R_x , the lifetime probability of dying from lung
14 cancer for exposed people = the sum of the conditional probabilities across the
15 intervals).
16
17

18 In each of the life-tables, inhalation exposure commences at age 16 years and continues
19 at the same exposure concentration for the duration of the life-table. This allows for the
20 computation of an “adult-only-exposure” occupational lifetime unit risk, which is then scaled by
21 a ratio of 70:54 to account for risk over the standard 70-year lifetime. While exposure is initiated
22 at age 16 years, this exposure is lagged to match the corresponding exposure-response models,
23 which provide the hazard rates per unit of exposure. For example, in Tables G-3 and G-4,
24 Column I shows exposure lagged by 10 years so that no lagged exposure appears prior to age
25 26 years.

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Table G-3. Lung cancer extra risk calculation for environmental exposure to 0.191 fibers/cc Libby Amphibole asbestos using a linear exposure-response model based on the metric of cumulative exposure with a 10-year exposure lag, as described in Section 5.4.5.3 as the reasonable upper bound

A	B	C	D	E	F	G	H	I	J	K	L	M	N
Age Int.	All-cause mortality ($\times 10^5$ /year)	Lung CA mortality ($\times 10^5$ /year)	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)
<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	29.9	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

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Table G-3. Lung cancer extra risk calculation for environmental exposure to 0.191 fibers/cc Libby Amphibole asbestos using a linear exposure-response model based on the metric of cumulative exposure with a 10-year exposure lag, as described in Section 5.4.5.3 as the reasonable upper bound (continued)

A	B	C	D	E	F	G	H	I	J	K	L	M	N
Age Int.	All-cause mortality ($\times 10^5/\text{year}$)	Lung CA mortality ($\times 10^5/\text{year}$)	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_0)	Lagged exp. mid. int. ($X\text{dose}$)	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)
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
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

Table G-3. Lung cancer extra risk calculation for environmental exposure to 0.191 fibers/cc Libby Amphibole asbestos using a linear exposure-response model based on the metric of cumulative exposure with a 10-year exposure lag, as described in Section 5.4.5.3 as the reasonable upper bound (continued)

A	B	C	D	E	F	G	H	I	J	K	L	M	N
Age Int.	All-cause mortality ($\times 10^5/\text{year}$)	Lung CA mortality ($\times 10^5/\text{year}$)	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. ($X\text{dose}$)	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)
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
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 years); scaled occupational lifetime unit = 0.0679 (scaled by ratio of 70:54 to account for risk over 70-year lifetime).

1
2
3

Table G-4. Lung cancer extra risk calculation for environmental exposure to 0.333 fibers/cc Libby Amphibole asbestos using the metric of cumulative exposure with a 10-year exposure lag and a 10-year half-life of exposure, as described in Section 5.4.5.3 as the lowest information criterion

A	B	C	D	E	F	G	H	I	J	K	L	M	N
Age int.	All-cause mortality ($\times 10^5$ /year)	Lung CA mortality ($\times 10^5$ /year)	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 hazard 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	29.9	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

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Table G-4. Lung cancer extra risk calculation for environmental exposure to 0.333 fibers/cc Libby Amphibole asbestos using the metric of cumulative exposure with a 10-year exposure lag and a 10-year half-life of exposure, as described in Section 5.4.5.3 as the lowest information criterion (continued)

A	B	C	D	E	F	G	H	I	J	K	L	M	N
Age int.	All-cause mortality ($\times 10^5/\text{year}$)	Lung CA mortality ($\times 10^5/\text{year}$)	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. ($X\text{dose}$)	Exposed lung CA hazard rate (hx)	Exposed all-cause hazard 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)
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
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	0.16	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	0.48	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	0.77	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	1.04	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	1.74	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	2.64	0.0001	0.0073	0.9927	0.9722	0.0001

Table G-4. Lung cancer extra risk calculation for environmental exposure to 0.333 fibers/cc Libby Amphibole asbestos using the metric of cumulative exposure with a 10-year exposure lag and a 10-year half-life of exposure, as described in Section 5.4.5.3 as the lowest information criterion (continued)

A	B	C	D	E	F	G	H	I	J	K	L	M	N	
Age int.	All-cause mortality ($\times 10^5/\text{year}$)	Lung CA mortality ($\times 10^5/\text{year}$)	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. ($X\text{dose}$)	Exposed lung CA hazard rate (hx)	Exposed all-cause hazard 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)	
40–44	221.6	7.9	0.0111	0.9890	0.9652	0.0004	0.0004	3.27	0.0004	0.0111	0.9889	0.9652	0.0004	
45–49	340.0	20.2	0.0170	0.9831	0.9546	0.0010	0.0010	3.72	0.0012	0.0172	0.9830	0.9545	0.0011	
50–54	509.0	39.8	0.0255	0.9749	0.9385	0.0020	0.0018	4.04	0.0023	0.0258	0.9746	0.9383	0.0021	
55–59	726.3	74.7	0.0363	0.9643	0.9149	0.0037	0.0034	4.26	0.0044	0.0370	0.9637	0.9144	0.0039	
60–64	1,068.3	139.8	0.0534	0.9480	0.8823	0.0070	0.0060	4.42	0.0083	0.0547	0.9468	0.8812	0.0071	
65–69	1,627.5	220.9	0.0814	0.9218	0.8364	0.0110	0.0089	4.53	0.0131	0.0834	0.9200	0.8343	0.0105	
70–74	2,491.3	304.3	0.1246	0.8829	0.7710	0.0152	0.0110	4.61	0.0181	0.1274	0.8803	0.7675	0.0130	
75–79	3,945.9	369.5	0.1973	0.8209	0.6807	0.0185	0.0114	4.67	0.0220	0.2008	0.8180	0.6757	0.0135	
80–84	6,381.4	379.4	0.3191	0.7268	0.5588	0.0190	0.0091	4.71	0.0226	0.3227	0.7242	0.5527	0.0107	
							$R_o = 0.0531$							$R_x = 0.0626$

CA = cancer, cond. = conditional, exp. = exposure, haz. = hazard, int. = interval, mid. = mid-interval, Prob. = probability.

Extra risk = 0.01001; exp. level = 0.333; occupational lifetime unit risk = 0.01/0.333 = 0.0300 (based on occupational exposures beginning at age 16 years); scaled occupational lifetime unit = 0.0389 (scaled by ratio of 70:54 to account for risk over 70-year lifetime).

1 **APPENDIX H. GLOSSARY OF ASBESTOS TERMINOLOGY**

2 **Acicular**: The very long and very thin, often needle-like shape that characterizes some
3 prismatic crystals. (Prismatic crystals have one elongated dimension and two
4 other dimensions that are approximately equal). Acicular crystals or fragments do
5 not have the strength, flexibility, or other properties often associated with
6 asbestiform fibers.

7
8 **Actinolite**: An amphibole mineral in the tremolite-ferroactinolite series. Actinolite can
9 occur in both asbestiform and nonasbestiform mineral habits. The asbestiform
10 variety is often referred to as actinolite asbestos.

11
12 **Amosite**: An amphibole mineral in the cummingtonite-grunerite series that occurs in the
13 asbestiform habit. The name amosite is a commercial term derived from the
14 acronym for “Asbestos Mines of South Africa.” Amosite is sometimes referred to
15 as “brown asbestos.”

16
17 **Amphibole**: A group of minerals composed of double-chain SiO₄ tetrahedra linked at the
18 vertices and generally containing ions of iron and/or magnesium in their
19 structures. Amphibole minerals are of either igneous or metamorphic origin.
20 Amphiboles can occur in a variety of mineral habits including asbestiform and
21 nonasbestiform.

22
23 **Anthophyllite**: An amphibole mineral that can occur in both the asbestiform and
24 nonasbestiform mineral habits. The asbestiform variety is referred to as
25 anthophyllite asbestos.

26
27 **Asbestiform**: A specific type of mineral fibrosity in which crystal growth is primarily in
28 one dimension, and the crystals form as long, flexible fibers. In minerals
29 occurring in asbestiform habit, fibers form in bundles that can be separated into
30 smaller bundles and ultimately into fibrils.

31
32 **Asbestos**: A generic term for silicate minerals occurring in the asbestiform habit, usually
33 used to refer to those minerals that have been commercially exploited as asbestos,
34 including chrysotile in the serpentine mineral group and tremolite asbestos,

1 actinolite asbestos, anthophyllite asbestos, cummingtonite-grunerite asbestos
2 (amosite), and riebeckite asbestos (crocidolite) in the amphibole mineral group.

3
4 **Asbestos Structure:** A term applied to any connected or overlapping grouping of asbestos
5 fibers or bundles, with or without other particles.

6
7 **Aspect Ratio:** The ratio of the length of a particle to its diameter.

8
9 **Biopersistence:** The ability to remain in the lung or other tissue. Biopersistence of
10 mineral fibers is a function of their fragility, solubility, and clearance.

11
12 **Chrysotile:** A mineral in the serpentine mineral group that occurs in the asbestiform
13 habit. Chrysotile generally occurs segregated as parallel fibers in veins or veinlets
14 and can be easily separated into individual fibers or bundles. Often referred to as
15 “white asbestos,” chrysotile is used commercially in cement or friction products
16 and for its good spinnability in the making of textile products.

17
18 **Cleavage Fragment:** A particle, formed by comminution (i.e., crushing, grinding, or
19 breaking) of minerals, often characterized by parallel sides. In contrast to fibers
20 from an asbestos mineral; elongate mineral particles in a population of cleavage
21 fragments are generally wider and shorter, generally have a lower aspect ratio,
22 and do not exhibit fibrillar bundling at any level of examination.

23
24 **Countable Particle:** A particle that meets specified dimensional criteria and is (to be)
25 counted according to an established protocol. A countable particle under the
26 National Institute for Occupational Safety and Health asbestos fiber definition is
27 any acicular crystal, asbestiform fiber, prismatic crystal, or cleavage fragment of a
28 *covered mineral* that is longer than 5 μm and has a minimum aspect ratio of 3:1
29 based on a microscopic analysis of an airborne sample using NIOSH Method
30 7400 or an equivalent method.

31
32 **Crocidolite:** An asbestiform amphibole mineral in the glaucophane-riebeckite series.
33 Crocidolite, commonly referred to as “blue asbestos,” is a varietal name for the
34 asbestiform habit of the mineral riebeckite.

35
36 **Durability:** The tendency of particles to resist degradation in body fluids.

1 **Elongated mineral particle (EMP)**: Any particle or fragment of a mineral (e.g., fibril or
2 bundle of fibrils: acicular, prismatic, or cleavage fragment) with a minimum
3 aspect ratio of 3:1, based on a microscopic analysis of an airborne sample using
4 NIOSH Method 7400 or an equivalent method.

5
6 **Elongated Particle (EP)**: A particle with a minimum aspect ratio of 3:1, based on a
7 microscopic analysis of an airborne sample using NIOSH Method 7400 or an
8 equivalent method.

9
10 **Fiber**: “Fiber” can be used in a regulatory context or in a mineralogical context.

11
12 In the regulatory context, a fiber is an elongated particle equal to or longer than
13 5 µm with a minimum aspect ratio of 3:1. The dimensional determination is made
14 based on a microscopic analysis of an air sample using NIOSH Method 7400 or
15 an equivalent method.

16
17 In the mineralogical context, a fiber is an elongated crystalline unit that resembles
18 an organic fiber and that can be separated from a bundle or appears to have grown
19 individually in that shape.

20
21 **Fibril**: A single fiber of asbestos that cannot be further separated longitudinally
22 into thinner components without losing its fibrous properties or appearances.

23
24 **Fibrous**: A descriptive characteristic of a mineral composed of parallel, radiating, or
25 interlaced aggregates of fibers, from which the fibers are sometimes separable.

26
27 **Fragility**: The tendency of particles to break into smaller particles.

28
29 **Libby Amphibole Asbestos**: The term used in this document to identify the mixture of
30 amphibole mineral fibers of varying elemental composition (e.g., winchite,
31 richterite, tremolite, etc.) that have been identified in the Rainy Creek complex
32 near Libby, MT as described in Section 2.2.

33
34 **Nonasbestiform**: The term used to describe fibers not having an asbestiform habit. The
35 massive nonfibrous forms of the asbestos minerals have the same chemical
36 formula and internal crystal structure as the asbestiform variety but have crystal

1 habits where growth is more equivalent in two or three dimensions instead of
2 primarily one dimension. When milled or crushed, nonasbestiform minerals
3 generally do not break into fibers/fibrils but rather into fragments resulting from
4 cleavage along the two or three growth planes. Often, cleavage fragments can
5 appear fibrous.

6
7 **Primary Structure:** A fibrous structure that is a separate entity in the transmission
8 electron microscope image.

9
10 **Refractory Ceramic Fiber (RCF):** An amorphous, synthetic fiber produced by melting
11 and blowing or spinning calcined kaolin clay or a combination of alumina (Al_2O_3)
12 and silicon dioxide (SiO_2). Oxides (such as zirconia, ferric oxide, titanium oxide,
13 magnesium oxide, and calcium oxide) and alkalis may be added.

14
15 **Solid Solution Series:** A grouping of minerals that includes two or more minerals in
16 which the cations in secondary structural position are similar in chemical
17 properties and size and can be present in variable but frequently limited ratios.

18
19 **Structure:** A single fiber, fiber bundle, cluster, or matrix.

20
21 **Synthetic Vitreous Fiber (SVF):** Any of a number of manufactured fibers produced by
22 the melting and subsequent fiberization of kaolin clay, sand, rock, slag, etc.
23 Fibrous glass, mineral wool, ceramic fibers, and alkaline earth silicate wools are
24 the major types of SVF, also called man-made mineral fiber (MMMF) or man-
25 made vitreous fiber (MMVF).

26
27 **Thoracic-size Particle:** A particle with an aerodynamic equivalent diameter that enables
28 it to be deposited in the airways of the lung or the gas exchange region of the lung
29 when inhaled.

30
31 **Tremolite:** An amphibole mineral in the series tremolite-ferroactinolite. Tremolite can
32 occur in both fibrous and nonfibrous mineral habits. The asbestiform variety is
33 often referred to as tremolite asbestos. Due only to changes in the International
34 Mineralogical Association's amphibole nomenclature, subsets of what was
35 formerly referred to as tremolite asbestos are now mineralogically specified as
36 asbestiform winchite and asbestiform richterite.