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TOXICOLOGICAL REVIEW

OF

LIBBY AMPHIBOLE ASBESTOS

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

August 2014

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

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

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LIST OF ABBREVIATIONS AND ACRONYMS

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

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

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

FOREWORD

The purpose of this Toxicological Review is to provide scientific support and rationale for the hazard and dose-response assessment in the Integrated Risk Information System (IRIS) pertaining to chronic inhalation exposure to Libby Amphibole asbestos, a 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 U.S. Environmental Protection Agency's (EPA's) IRIS Hotline at (202) 566-1676 (phone), (202) 566-1749 (fax), or hotline.iris@epa.gov (email address).

AUTHORS, CONTRIBUTORS, AND REVIEWERS

CHEMICAL MANAGERS/AUTHORS

Thomas F. Bateson, ScD, MPH
National Center for Environmental Assessment
U.S. Environmental Protection Agency
Washington, DC

Robert Benson, PhD
Region 8
Office of Partnerships and Regulatory Assistance
U.S. Environmental Protection Agency
Denver, CO

AUTHORS

Krista Yorita Christensen, PhD
National Center for Environmental Assessment
U.S. Environmental Protection Agency
Washington, DC

Glinda Cooper, PhD
National Center for Environmental Assessment
U.S. Environmental Protection Agency
Washington, DC

Danielle DeVoney, PhD, DABT, PE
Captain in the U.S. Public Health Service
OSRTI Science Policy Branch
US EPA Office of Solid Waste and Emergency Response
U.S. Environmental Protection Agency
Washington, DC

Maureen R. Gwinn, PhD, DABT
National Center for Environmental Assessment
U.S. Environmental Protection Agency
Washington, DC

Leonid Kopylev, PhD
National Center for Environmental Assessment
U.S. Environmental Protection Agency
Washington, DC

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

CONTRIBUTING AUTHORS

Rebecca Dzubow, MPH, MEM
Office of Children's Health Protection
U.S. Environmental Protection Agency
Washington, DC

David Berry, PhD
Region 8
U.S. Environmental Protection Agency
Denver, CO

Malcolm Field, PhD
National Center for Environmental Assessment
U.S. Environmental Protection Agency
Washington, DC

Annie M. Jarabek
National Center for Environmental Assessment
U.S. Environmental Protection Agency
Research Triangle Park, NC

Keith Salazar, PhD
National Center for Environmental Assessment
U.S. Environmental Protection Agency
Washington, DC

Patricia Sullivan, ScD
Division of Respiratory Disease Studies
National Institute for Occupational Safety and Health
Morgantown, WV

CONTRIBUTORS

David Bussard
National Center for Environmental Assessment
U.S. Environmental Protection Agency
Washington, DC

Samantha J. Jones, PhD
National Center for Environmental Assessment
U.S. Environmental Protection Agency
Washington, DC

CONTRIBUTORS (continued)

Babasaheb Sonawane, PhD
National Center for Environmental Assessment
U.S. Environmental Protection Agency
Washington, DC

Paul White
National Center for Environmental Assessment
U.S. Environmental Protection Agency
Washington, DC

CONTRACTOR SUPPORT

William Brattin, PhD
Syracuse Research Corporation
Denver, CO

Highlight Technologies, LLC, Fairfax, VA
      Dan Heing
      Debbie Kleiser
      Sandra Moore
      Ashley Price
      Kathleen Secor

CACI International, Inc, Arlington, VA
      Thomas Schaffner
      Linda Tackett

ECFlex, Inc., Fairborn, OH
      Heidi Glick
      Crystal Lewis
      Carman Parker-Lawler
      Lana Wood

IntelliTech Systems, Inc., Fairborn, OH
      Cris Broyles

REVIEWERS

     This document was provided for review to EPA scientists, interagency reviewers from other federal agencies and the Executive Office of the President, and the public, and peer reviewed by independent scientists external to EPA. A summary and EPA's disposition of the comments received from the independent external peer reviewers and the public is included in Appendix A.

Science Advisory Board (SAB) Panel for Review of EPA's Draft Toxicological Review of Libby Amphibole Asbestos

CHAIR
Dr. Agnes Kane
Professor and Chair
Department of Pathology and Laboratory Medicine
Brown University
Providence, RI

MEMBERS
Dr. John R. Balmes
Professor
Department of Medicine, Division of Occupational and Environmental Medicine
University of California
San Francisco, CA

Dr. James Bonner
Associate Professor
Toxicology
North Carolina State University
Raleigh, NC

Dr. Jeffrey Everitt
Director
Department of Laboratory Animal Science
GlaxoSmithKline Pharmaceuticals
Research Triangle Park, NC

Dr. Scott Ferson
Senior Scientist
Applied Biomathematics
Setauket, NY

MEMBERS (continued)
Dr. George Guthrie
Focus Area Leader
Geological and Environmental Sciences
National Energy Technology Laboratory, U.S. Department of Energy
Pittsburgh, PA

Mr. John Harris
Principal
LabCor Portland, Inc.
Portland, OR

Dr. Tom Hei
Professor and Vice-Chairman
Radiation Oncology, College of Physicians and Surgeons
Columbia University Medical Center
New York, NY

Dr. David Kriebel
Professor and Chair
Department of Work Environment
School of Health & Environment, University of Massachusetts
Lowell, MA

Dr. Morton Lippmann
Professor
Nelson Institute of Environmental Medicine
New York University School of Medicine
Tuxedo, NY

Dr. John Neuberger
Professor
Preventive Medicine and Public Health, School of Medicine
University of Kansas
Kansas City, KS

Dr. Lee Newman
Professor of Medicine
Division of Environmental and Occupational Health Sciences
School of Public Health, University of Colorado
Aurora, CO

MEMBERS (continued)
Dr. Michael Pennell
Assistant Professor
Division of Biostatistics
College of Public Health, Ohio State University
Columbus, OH

Dr. Julian Peto
Professor
Department of Epidemiology and Population Health
London School of Hygiene and Tropical Medicine
London, UK

Dr. Carrie Redlich
Professor of Medicine
Internal Medicine
School of Medicine, Yale University
New Haven, CT

Dr. Andrew G. Salmon
Senior Toxicologist
Office of Environmental Health Hazard Assessment
California Environmental Protection Agency
Oakland, CA

Dr. Elizabeth A. (Lianne) Sheppard
Professor
Biostatistics and Environmental & Occupational Health Sciences
School of Public Health, University of Washington
Seattle, WA

Dr. Randal Southard
Professor of Soils
AES Dean's Office
University of California at Davis
Davis, CA

Dr. Katherine Walker
Senior Staff Scientist
Health Effects Institute
Boston, MA

MEMBERS (continued)
Dr. James Webber
Research Scientist
Wadsworth Center
New York State Department of Health
Albany, NY

Dr. Susan Woskie
Professor
Work Environment, Health and Environment
University of Massachusetts Lowell
Lowell, MA

SCIENCE ADVISORY BOARD STAFF

Dr. Diana Wong
Designated Federal Officer
U.S. Environmental Protection Agency
Washington, DC

1. INTRODUCTION

This document presents background information and justification for the Integrated Risk

Information System (IRIS) summary of the hazard and exposure-response assessment of Libby

Amphibole asbestos (LAA),[1] a mixture of amphibole fibers identified in the Rainy Creek

complex and present in ore from the vermiculite mine near Libby, MT. IRIS summaries may

include oral reference dose (RfD) and inhalation reference concentration (RfC) values for

chronic exposure durations, and a carcinogenicity assessment. This assessment reviews the

potential hazards, both cancer and noncancer health effects, from exposure to LAA and provides

quantitative information for use in risk assessments: an RfC for noncancer and an inhalation unit

risk (IUR) addressing cancer risk. LAA-specific data are not available to support RfD or cancer

slope factor derivations for oral exposures.

A RfC is defined as "an estimate of an exposure (including sensitive subgroups) that is

likely to be without an appreciable risk of adverse health effects over a lifetime." (U.S. EPA,

2002). In the case of LAA, the RfC is expressed in terms of the lifetime exposure in units of

fibers per cubic centimeter of air (fibers/cc) in units of the fibers as measured by phase contrast

microscopy (PCM). The inhalation RfC for LAA considers toxic effects for both the respiratory

system (portal of entry) and for effects peripheral to the respiratory system (extrarespiratory or

systemic effects) that may arise after inhalation of LAA.

The carcinogenicity assessment provides information on the carcinogenic hazard

potential of the substance in question, and quantitative estimates of risk from inhalation

exposures are derived. The information includes a weight-of-evidence judgment of the

likelihood that the agent is a human carcinogen and the conditions under which the carcinogenic

effects may be expressed. Quantitative risk estimates are derived from the application of a

low-dose extrapolation procedure from human data. An IUR is typically defined as a plausible

upper bound on the estimate of cancer risk per $\mu g/m^3$ air breathed for 70 years. For LAA, the

RfC is expressed as a lifetime daily exposure in fibers/cc (in units of the fibers as measured by

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

PCM).

Development of these hazard identification and exposure-response assessments for LAA

has followed the general guidelines for risk assessment as set forth by the National Research

Council (NRC, 1983). U.S. Environmental Protection Agency (EPA) Guidelines and Risk

Assessment Forum technical panel reports that may have been used in the development of this

assessment include the following: *Guidelines for the Health Risk Assessment of Chemical*

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[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   *Mixtures* (U.S. EPA, 1986c), *Guidelines for Mutagenicity Risk Assessment* (U.S. EPA, 1986b),
2   *Recommendations for and Documentation of Biological Values for Use in Risk Assessment* (U.S.
3   EPA, 1988b), *Guidelines for Developmental Toxicity Risk Assessment* (U.S. EPA, 1991a),
4   *Interim Policy for Particle Size and Limit Concentration Issues in Inhalation Toxicity* (U.S. EPA,
5   1994a), *Methods for Derivation of Inhalation Reference Concentrations and Application of*
6   *Inhalation Dosimetry* (U.S. EPA, 1994b), *Use of the Benchmark Dose Approach in Health Risk*
7   *Assessment* (U.S. EPA, 1995), *Guidelines for Reproductive Toxicity Risk Assessment* (U.S. EPA,
8   1996), *Guidelines for Neurotoxicity Risk Assessment* (U.S. EPA, 1998), *Science Policy Council*
9   *Handbook*: *Risk Characterization* (U.S. EPA, 2000b), *Benchmark Dose Technical Guidance*
10   *Document* (U.S. EPA, 2012), *Supplementary Guidance for Conducting Health Risk Assessment*
11   *of Chemical Mixtures* (U.S. EPA, 2000c), *A Review of the Reference Dose and Reference*
12   *Concentration Processes* (U.S. EPA, 2002), *Guidelines for Carcinogen Risk Assessment* (U.S.
13   EPA, 2005a), *Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to*
14   *Carcinogens* (U.S. EPA, 2005b), *Science Policy Council Handbook: Peer Review* (U.S. EPA,
15   2006c), and *A Framework for Assessing Health Risks of Environmental Exposures to Children*
16   (U.S. EPA, 2006b).
17   The literature search strategy employed for this assessment is based on EPA's National
18   Center for Environmental Assessment's Health and Environmental Research Online database
19   tool (which includes PubMed, MEDLINE, Web of Science, JSTOR, and other literature
20   sources). The key search terms included the following: Libby Amphibole, tremolite, asbestos,
21   richterite, winchite, amphibole, and Libby, MT. The relevant literature was reviewed through
22   July 2011. Any pertinent scientific information submitted by the public to the IRIS Submission
23   Desk was also considered in the development of this document. It should be noted that
24   references have been added to the Toxicological Review after the external peer review SAB
25   (2013) in response to peer reviewers' comments and for the sake of completeness.
26
27   **1.1. RELATED ASSESSMENTS**
28   **1.1.1. Integrated Risk Information System (IRIS) Assessment for Asbestos (U.S. EPA,**
29   **1988a)**
30   The IRIS assessment for asbestos was posted online in IRIS in 1988 and includes an IUR
31   of 0.23 excess cancers per 1 fiber/cc (U.S. EPA, 1988a); this unit risk is given in units of the
32   fibers as measured by PCM. The IRIS IUR for general asbestos (CAS Number 1332-21-4) is
33   derived by estimating excess cancers for a continuous lifetime exposure and is based on the
34   central tendency—not the upper bound—of the risk estimates (U.S. EPA, 1988a) and is
35   applicable to exposures across a range of exposure environments and types of asbestos.
36   Although other cancers have been associated with asbestos (e.g., laryngeal, stomach, ovarian;
37   Straif et al., 2009), the IRIS IUR for asbestos accounts for only lung cancer and mesothelioma.
38   Additionally, pleural and pulmonary effects from asbestos exposure (e.g., pleural thickening,

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1 asbestosis, and reduced lung function) are well documented, although currently, there is no RfC

2 for these noncancer health effects.

3   The derivation of the unit risk for general asbestos is based on the *Airborne Asbestos*

4 *Health Assessment Update* (AAHAU; U.S. EPA, 1986a). The AAHAU provides various cancer

5 potency factors and mathematical models of lung cancer and mesothelioma mortality based on

6 synthesis of data from occupational studies and presents estimates of lifetime cancer risk for

7 continuous environmental exposures (0.0001 fiber/cc and 0.01 fiber/cc; U.S. EPA, 1986a; see

8 Table 6-3). For both lung cancer and mesothelioma, life table analysis was used to generate risk

9 estimates based on the number of years of exposure and the age at onset of exposure. Although

10 various exposure scenarios were presented, the unit risk is based on a lifetime continuous

11 exposure from birth. The final asbestos IUR is 0.23 excess cancer per 1 fiber/cc continuous

12 exposure[2] and was posted on the IRIS database in 1988 (U.S. EPA, 1988a; see Table 1-1).

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

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

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

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

13   The IRIS database has an IUR[3] for asbestos based on 14 epidemiologic studies that

14 included occupational exposure to chrysotile, amosite, or mixed-mineral exposures (chrysotile,

15 amosite, crocidolite; U.S. EPA, 1988a, 1986a). Some uncertainty remains in applying the

16 resulting IUR for asbestos to exposure environments and minerals different from those analyzed

17 in the AAHAU (U.S. EPA, 1986a). No RfC, RfD, or oral slope factor are currently derived for

18 asbestos on the IRIS database.

19

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

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1 **1.1.2. EPA Health Assessment for Vermiculite (U.S. EPA, 1991b)**

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 mines with similar exposure to vermiculite but much lower

6 exposures to asbestos fibers. Therefore, it was concluded that the health effects observed from

7 the materials mined from Zonolite Mountain near Libby, MT, were most likely due to amphibole

8 fibers not the vermiculite itself (U.S. EPA, 1991b). At the time, EPA recommended the

9 application of the IRIS IUR for asbestos fibers (0.23 per fiber/cc) in addressing potential risk of

10 the amphibole fibers entrained in vermiculite mined in Libby, MT.

11

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

13   LAA is a complex mixture of amphibole fibers―both mineralogically and

14 morphologically (see Section 2.3). The mixture primarily includes tremolite, winchite, and

15 richterite fibers with trace amounts of magnesioriebeckite, edenite, and magnesio-arfvedsonite.

16 These fibers exhibit a complete range of morphologies from prismatic crystals to asbestiform

17 fibers (Meeker et al., 2003). Epidemiologic studies of workers exposed to LAA fibers indicate

18 increased lung cancer and mesothelioma, as well as asbestosis and other nonmalignant

19 respiratory diseases (Larson et al., 2010b; Larson et al., 2010a; Moolgavkar et al., 2010; Rohs et

20 al., 2008; Sullivan, 2007; McDonald et al., 2004, 2002; Amandus et al., 1988; Amandus et al.,

21 1987b; Amandus and Wheeler, 1987; Amandus et al., 1987a; McDonald et al., 1986a; McDonald

22 et al., 1986b; Lockey et al., 1984).

1   **2. LIBBY AMPHIBOLE ASBESTOS: GEOLOGY AND EXPOSURE POTENTIAL**

2   **2.1. INTRODUCTION**

3   Libby is a community in northwestern Montana that is located near a large open-pit
4   vermiculite mine that operated from the mid 1920s to 1990 (see Figure 2-1). Vermiculite is a
5   silicate mineral that exhibits a sheet-like structure similar to mica (see Figure 2-2, Panel A).
6   When heated to approximately 870°C, water molecules between the sheets change to vapor and
7   cause the vermiculite to expand like popcorn into a light, porous material (see Figure 2-2,
8   Panel B). This process of expanding vermiculite is termed "exfoliation" or "popping." Both
9   unexpanded and expanded vermiculite have found a range of commercial applications, the most
10   common of which include packing material, attic and wall insulation, various garden and
11   agricultural products, and various cement and building products.
12

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

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

Source: USGS Field Collection, Meeker (2007)

Panel B: Expanded vermiculite

Figure 2-2. Unexpanded and expanded vermiculite.

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

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

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

9

10 **2.2. GEOLOGY AND MINERALOGY OF AMPHIBOLES**

11 **2.2.1. Overview**

12   Asbestos is the generic name for a group of naturally-occurring silicate minerals that
13 crystallize in long thin fibers. The basic chemical unit of asbestos and other silicate minerals is
14 $[SiO_4]^{4-}$. This basic unit consists of four oxygen atoms at the apices of a regular tetrahedron
15 surrounding and coordinated with one silicon ion (Si^{4+}) at the center (see Figure 2-3, Panel A).
16 The silicate tetrahedra can bond to one another through the oxygen atoms, leading to a variety of
17 crystal structures (see Figure 2-3, Panels B, C, and D).

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

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

30

31 **2.2.2. Mineralogy of Amphibole Asbestos and Related Amphibole Minerals**

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

(A) Nesosilicates or single tetrahedron.
The single tetrahedron comprises four oxygen molecules covalently bound to the silicon, at the center of the $[SiO_4]^{4-}$-tetrahedron.
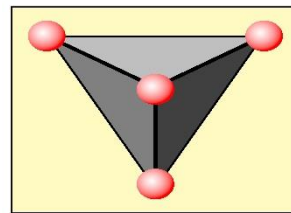
(B) Inosilicates [*ino* (*gr.*) = thread]—Single-chain silicates.
Chain silicates are realized by linking $[SiO_4]^{4-}$-tetrahedrons in a way to form continuous chains. They can be represented by a composition of $[SiO_3]^{2-}$. A typical example is diopside $CaMg[Si_2O_6]$, in which the "endless" chains are also held together by Ca^{2+} and Mg^{2+} ions.
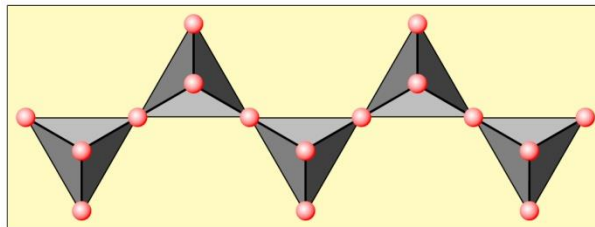
(C) Inosilicates—Double-chain silicates.
Two silicate chains of the inosilicates are linked at the corners, forming double-chains and yielding $[Si_4O_{11}]_{6-}$ ions, as realized in the tremolite-ferro-actinolite series $Ca_2(Mg,Fe)_5Si_8O_{22}(OH,F,Cl)_2$. Double-chain silicates are commonly grouped with the single-chain inosilicates.
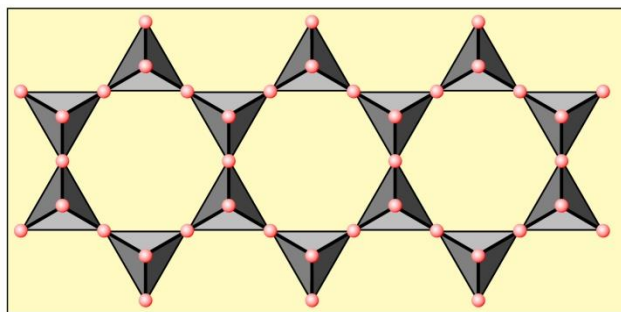
(D) Phyllosilicates [*phyllo* (*gr.*) = sheet] or sheet silicates. These are formed if the double-chain inosilicate $[Si_4O_{11}]^{6-}$ chains are linked to form continuous sheets with the chemical formula $[Si_2O_5]^{2-}$. Examples of sheet silicates include chrysotile $Mg_3Si_2O_5(OH)_4$ and vermiculite $[(Mg, Fe,Al)_3(Al,Si)_4O_{10}(OH)_2 \bullet 4H_2O]$.
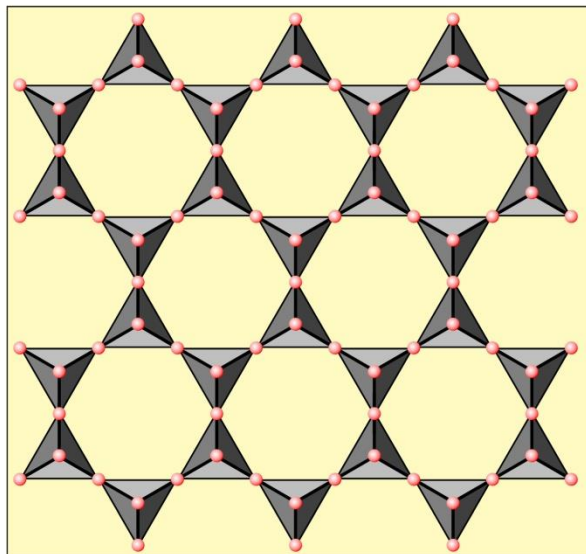
Figure 2-3. Structure of the silicate minerals, illustrating silicate subclasses by the linking of the basic silicon tetrahedron (A) into more complex structures (B, C, or D).
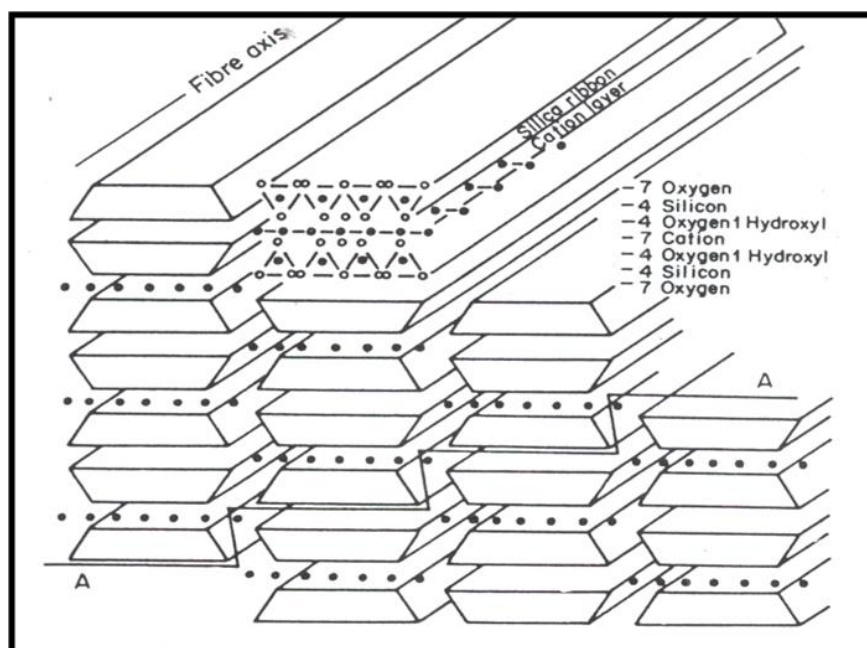
Figure 2-4. Cross section of amphibole fibers showing the silicon tetrahedrons (triangles with open circles at apex) that make up each double-chain plate (shown along the fiber axis). Cations (shown as the darkened dots) occur between the plates forming the basic fiber.

Source: Kroschwitz et al. (2007).

1 $$A_{0-1}B_2C_5T_8O_{22}(OH, F, Cl)_2 \qquad\qquad (2\text{-}1)$$
2
3 where:
4 A = Na, K
5 B = Na, Li, Ca, Mn, Fe^{2+}, Mg
6 C = Mg, Fe^{2+}, Mn, Al, Fe^{3+}, Ti
7 T = Si, Al.
8
9 The mineral subgroup within amphiboles is determined by the elemental composition.
10
11 • Calcic amphiboles (tremolite)

12 • Sodic-calcic amphiboles (richterite, winchite)

13 • Sodic amphiboles (riebeckite, arfvedsonite)

14 • Iron-magnesium-manganese-lithium amphiboles (anthophyllite,
15 cummingtonite-grunerite)
16
17 Because the stoichiometry of the cations is not fixed, a continuum of compositions may
18 occur. These are referred to as "solid solution series." The series are defined by their end

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1   members. For example, a solid solution series for the cation Site A will have one end member

2   with 100% sodium ions and one end member with 100% potassium ions. This series would

3   include all intervening ratios.

4   Because each cation site has multiple possibilities, the elemental composition of the

5   amphibole silicates can be quite complex. It is the complexity of the amphiboles that has

6   historically given rise to a proliferation of mineral names with little systematic basis (Hawthorne,

7   1981). Currently, amphiboles are identified by a clear classification scheme based on crystal

8   chemistry that uses well-established names based on the basic mineralogy, with prefixes and

9   adjective modifiers indicating the presence of substantial substitutions that are not essential

10   constituents of the end members (Leake et al., 1997). As implemented, this mineral

11   classification system does not designate certain amphibole minerals as asbestos. However, some

12   mineral designations have traditionally been considered asbestos (in the asbestiform habit; e.g.,

13   tremolite, actinolite). Other commercial forms of asbestos were known by trade names (e.g.,

14   Amosite) rather than mineralogical terminology (cummingtonite-grunerite).

15

16   **2.2.3. Morphology of Amphibole Minerals**

17   Most amphibole minerals occur in a variety of growth habits, depending on the

18   temperature, pressure, local stress field, and solution chemistry conditions during crystallization.

19   The nomenclature used to describe the crystal forms varies between disciplines;(field geologist,

20   microscopist; e.g., see Lowers and Meeker, 2002). Text Box 2-1 provides definitions for

21   common terms used to describe the morphology of asbestos and other related minerals.

Text Box 2-1: Nomenclature

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

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

Asbestiform (mineralogical): A specific type of mineral fibrosity in which the fibers and fibrils are long, thin, and possess high tensile strength and flexibility.

Asbestiform (regulatory): A specific type of fibrosity in which the fibers and fibrils possess high tensile strength and flexibility.

Asbestos: A group of highly fibrous silicate minerals that readily separate into long, thin, strong fibers that have sufficient flexibility to be woven, are heat resistant and chemically inert, are electrical insulators, and therefore are suitable for uses where incombustible, nonconducting, or chemically resistant materials are required.

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

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

Cluster: A group of overlapping fibers oriented at random.

Fiber (regulatory): A particle that has an aspect ratio (length of the particle divided by its width), and depending on the analytical methods used, a particle is considered a fiber if it has a greater than 3:1 (by PCM) or 5:1 (by transmission electron microscopy [TEM]) aspect ratio.

Fiber (mineralogical): The smallest, elongate crystalline unit that can be separated from a bundle or appears to have grown individually in that shape, and that exhibits a resemblance to organic fibers.

Fibril: An individual unit of structure, single, elementary fibers that have a small width. A substructure of a fiber.

Fibrous: The occurrence of a mineral in bundles of fibers, resembling organic fibers in texture, from which the fibers can usually be separated. Crystallized in elongated, thin, needlelike grains or fibers.

Massive: A mineral form that does not contain fibrous crystals.

Matrix: A particle of nonasbestos material that has one or more fibers associated with it.

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

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

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

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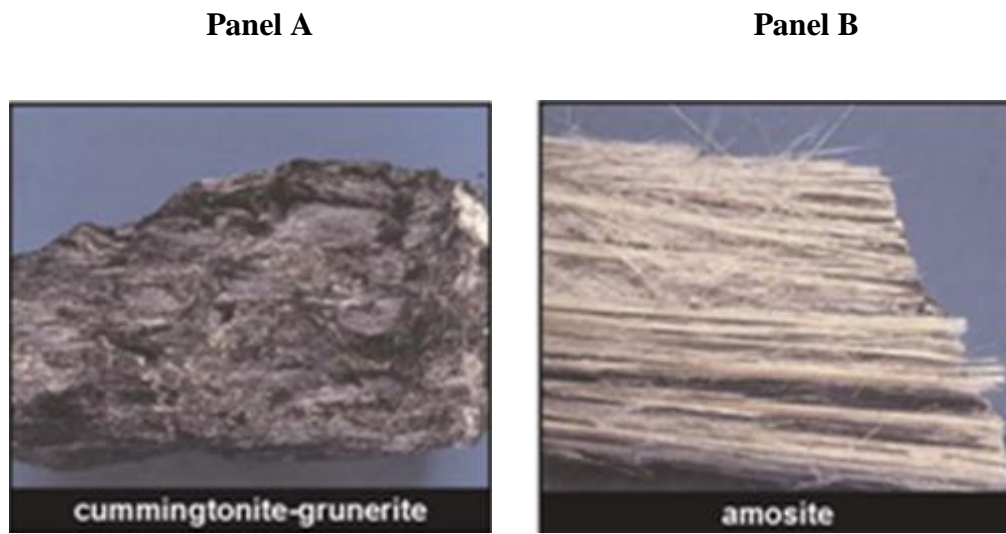
Figure 2-5. Comparison of crystalline forms of amphibole minerals. Panel A
shows a specimen identified as an amphibole mineral in the
cummingtonite-grunerite solid solution series. Although crystalline in form, the
habit of formation did not favor formation of individual particles and fibers, hence
its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

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

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

1 **2.3. METHODS FOR ANALYSIS OF ASBESTOS**

2   Because asbestos is a solid that does not dissolve in water or other solvents, methods for

3 the analysis of asbestos are somewhat different than for most other chemical substances. This

4 section provides a brief overview of the most common methods for the analysis of asbestos.

5

6 **2.3.1. Methods for Air Samples**

7   The exposure pathway of primary health concern for humans is inhalation of asbestos.

8 Air is evaluated for the presence of asbestos by drawing a known volume of air through a filter

9 that traps the solid particles in the air on the filter surface, and the number of asbestos particles

10 are then determined. The concentration is generally expressed as fibers[4] per cubic centimeter of

11 air (fiber/cc) and is computed by dividing the number of asbestos fibers on the filter by the

12 volume of air drawn through the filter.

13   In all cases, the evaluation of the particles that are collected on an air filter is performed

14 using a microscope. All methods begin with the basic shape (morphology) of a particle to

15 classify it as a possible asbestos particle or not. In general, particles that are clearly fibrous

16 (substantially longer than they are thick) are considered to be potential asbestos. However, other

17 minerals besides asbestos may occur in long thin particles, and a number of nonmineral fibers

18 may be present in a sample as well. Consequently, some techniques rely on other physical or

19 optical properties of the particles to help distinguish asbestos from nonasbestos and to classify

20 the type of asbestos. These differences in the ability to visualize and distinguish asbestos

21 particles are the most important differences between the various microscopic techniques.

22   The most common technique in the past for analyzing asbestos in air samples was PCM,

23 and this method remains the current industrial hygiene (IH) standard methodology, usually using

24 National Institute for Occupational Safety and Health (NIOSH) method 7400

25 (http://www.cdc.gov/niosh/docs/2003-154/pdfs/7400.pdf). Under this method, a fiber is defined

26 as any particle greater than 5 μm in length with an aspect ratio greater than or equal to 3:1. The

27 limit of resolution of PCM is usually about 0.25 μm, so fibers thinner than this are usually not

28 observable. A key attribute of PCM is that identification of countable fibers is based only on

29 morphology, and does not consider mineralogy or crystal structure. Because of this, it is not

30 possible to classify asbestos fibers by mineral type, or even to reliably distinguish between

31 asbestos and nonasbestos fibers. This is not usually a significant concern when applied to air

32 samples collected in a workplace where asbestos is present, but can become an issue in

33 nonworkplace settings where asbestos concentrations tend to be lower and other types of fibers

34 are more common.

---

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

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1   Transmission electron microscopy (TEM) has also been developed for analysis of air

2 samples for asbestos. TEM uses a high energy electron beam rather than a beam of light to

3 irradiate the sample, and this allows visualization of structures much smaller than can been seen

4 under light microscopy. In addition, most TEM instruments used for asbestos analysis have

5 equipment that allows a more detailed characterization of a particle than is possible by PCM:

6

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

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

15   • WDS (wavelength-dispersive x-ray spectroscopy) provides x-ray spectral data from a
16   single wavelength at a time, providing detailed atomic composition of a particle.
17   Generally, WDS is a more precise measure of the atomic composition of a particle
18   than EDS and is often used with an electron microprobe attached to a scanning
19   electron microscope.
20

21   Several different standard methods have been developed for TEM analyses of air

22 samples, the most common of which is ISO 10312 (ISO 10312:1995). Under ISO 10312

23 counting rules, a fiber is defined as any structure ≥0.5 μm in length that has substantially parallel

24 sides and an aspect ratio ≥5:1. Fibers observed under TEM that meet PCM counting rules are

25 generally referred to as PCMe (PCM-equivalent).

26

27 **2.3.2. Methods for Solid Materials**

28   Measurement of asbestos in solid samples (vermiculite, building materials, soil, etc.)

29 usually employs polarized light microscopy (PLM). There are several standard PLM methods

30 for the analysis of asbestos in bulk materials, including NIOSH 9002, EPA/600/R-93/116, and

31 CARB 435. PLM uses the optical properties of asbestos to identify and classify different types

32 of asbestos fibers. In general, these methods are most reliable for materials that contain

33 relatively high concentrations of asbestos, and results tend to become more variable as

34 concentrations decrease below about 1% by mass. At present, the use of TEM for the analysis of

35 bulk materials is not a well-developed procedure.

36

37 **2.4. CHARACTERISTICS OF LIBBY AMPHIBOLE ASBESTOS**

38   Amphibole asbestos occurs in the Libby vermiculite ore body both in high concentration

39 veins (>80%), as well as in lower concentrations (0.1 to 3%) within the layers of the vermiculite

ore itself (Lowers et al., 2012; U.S. EPA, 2000a; Boettcher, 1967; Pardee and Larsen, 1928).
Analysis of historical ore samples from the Harvard and Smithsonian Museums (circa 1920s),
the Butte Museum (circa 1960), and recent ore samples from the mine (circa 1999) indicate that
the amphibole content of vermiculite ore from the mine has remained approximately constant
over the 70-year mining history at the Rainy Creek complex (Sanchez et al., 2008; Meeker et al.,
2003).

2.4.1. Mineralogy of Libby Amphibole Asbestos

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

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

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

The relationship between the cationic compositions of the three primary minerals is
illustrated in Figure 2-7. In some fibers, the composition differed within the length of the fiber
(e.g., winchite at one end and richterite at the other end). All of these minerals are within the
solid solution series for tremolite-richterite-magnesio-riebecktite. Magneiso-riebeckite and
magnesio-arfvedsonite fall within the range of sodic amphiboles, winchite and richterite fall
within the range of sodic-calcic amphiboles, and tremolite and edenite are considered calcic
amphiboles. Structural formulae and optical and crystallographic data are presented in
Table 2-1.

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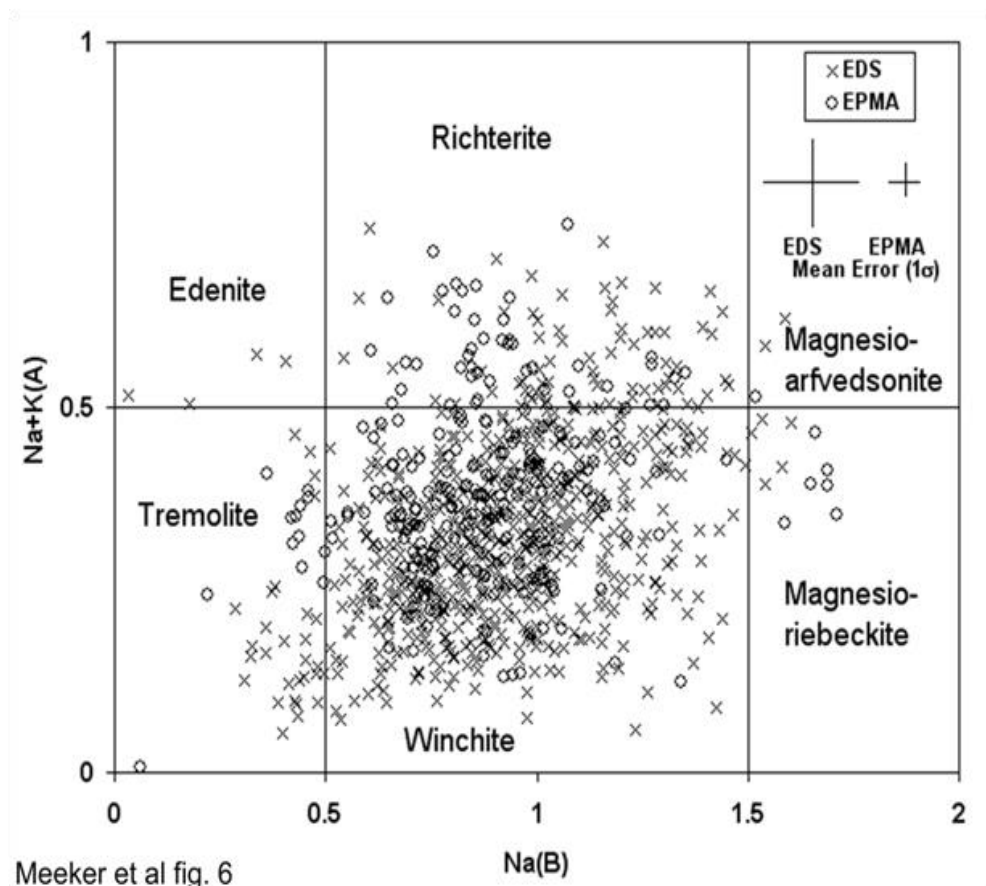
Figure 2-6. Mineralogy of LAA structures from samples taken from the Zonolite Mountain site. An evaluation of the textural characteristics shows the material to include a complete range of morphologies from prismatic crystals to fibers. Each data point represents the cation composition (number of occupied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

Source: Meeker et al. (2003)
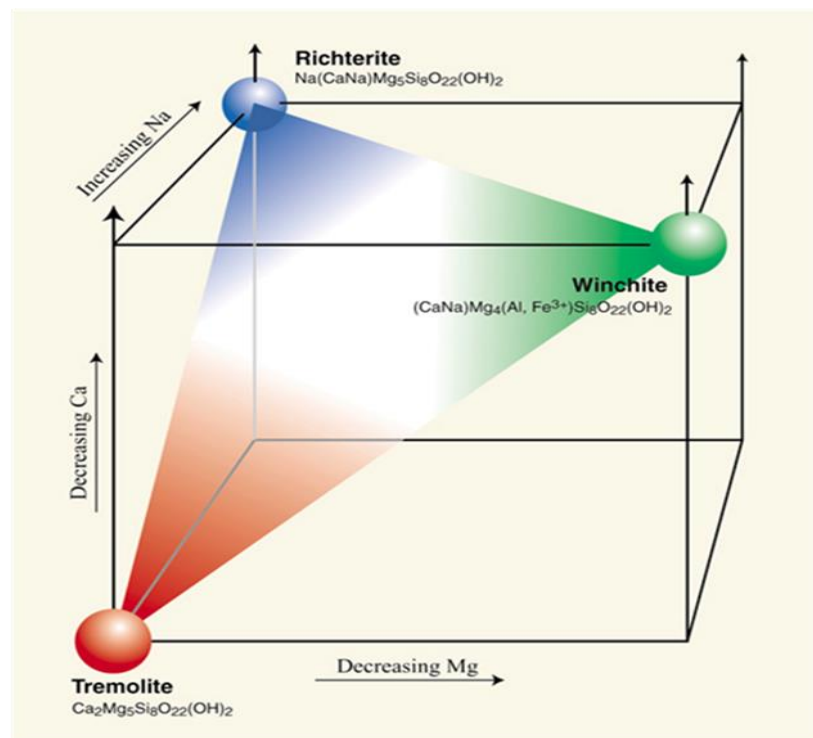
Figure 2-7. Solution series linking tremolite, winchite, and richterite amphibole fibers.

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

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

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

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

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

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2.4.2. Morphology of Libby Amphibole Asbestos

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

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

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

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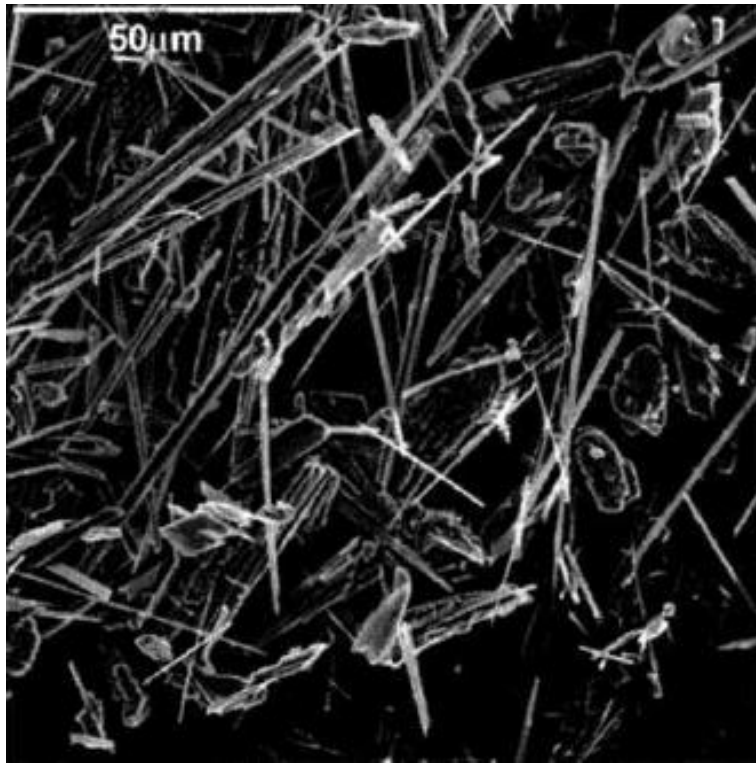
Figure 2-8. Scanning electron microscope image of amphibole mineral structures from the Libby, MT mine. An evaluation of the textural characteristics shows the material to include a range of morphologies from prismatic crystals to fibers. Acicular and prismatic crystals, fibers bundles, and curved fibers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

Source: Meeker et al. (2003).
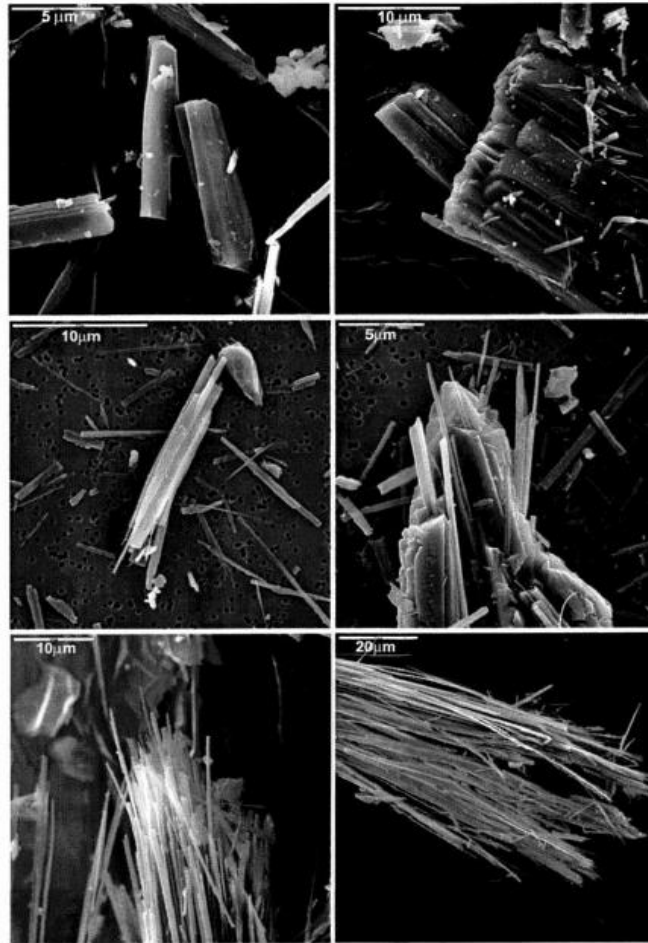
Figure 2-9. Fiber morphology of amphibole asbestos from the Libby, MT mine viewed under a scanning electron microscope.

Source: Meeker et al. (2003).

1   Sanchez et al. (2008) evaluated fiber morphology using the optical system of an electron
2   microprobe, and reported that most structures could be classified as either prismatic or fibrous.
3   There was no difference in the mineralogy between the two morphologies, and the authors
4   concluded the different habits were formed at the same time.
5   Figure 2-10 shows cumulative particle-size-distribution frequencies (CDFs) for LAA
6   fibers (aspect ratio ≥3:1) observed using TEM in Libby ore Grade 3, expanded Libby ore
7   Grade 3, and ambient air samples collected in Libby. The data used to construct this plot are
8   described in Appendices B and C. In general, most fibers identified as LAA have thicknesses
9   that range from about 0.1 μm to 1 μm, with an average of about 0.6 μm. Fiber lengths vary
10   greatly, ranging from <1 μm to ≥100 μm. Aspect ratios also range widely, from 3:1 to greater
11   than 100:1.
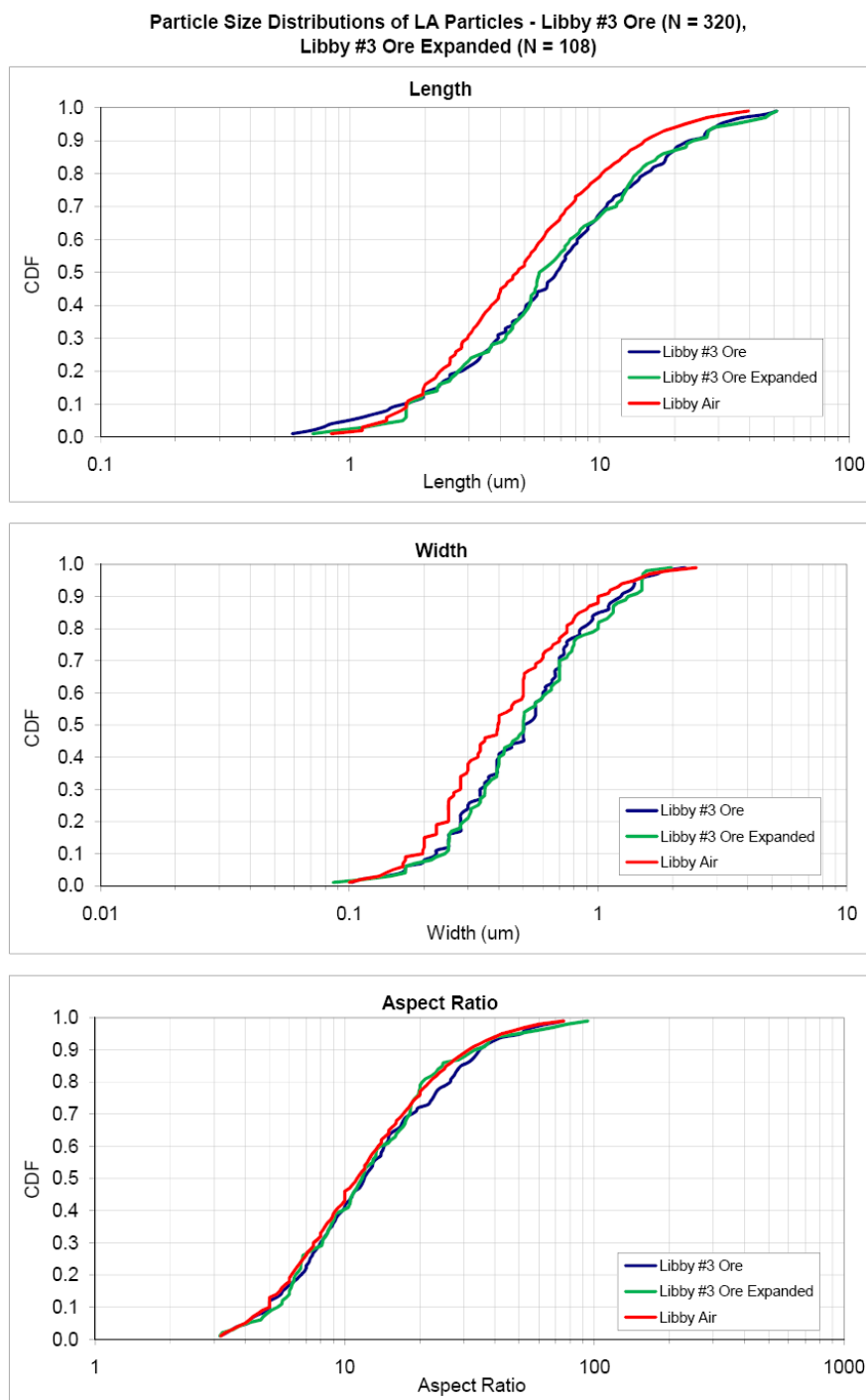
Figure 2-10. Particle size (length, width, aspect ratio) of fibers in Libby ore and Libby air.

CDF = cumulative distribution frequency; LA = Libby Amphibole.

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

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

14

2.5. HUMAN EXPOSURE POTENTIAL

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

22

2.5.1. Exposures Pathways in the Libby Community

24   When the mine in Libby, MT was active, miners, mill workers, and those working in the
25 processing plants were exposed to vermiculite, silica dust, and amphibole structures released to
26 air from the ore during the mining and processing operations (Meeker et al., 2003; Amandus et
27 al., 1987b; McDonald et al., 1986a). In some cases, workers may have inadvertently transported,
28 typically on their clothing, shoes, and hair, contaminated materials from the workplace to
29 vehicles, homes, and other establishments. This transported material may have resulted in
30 "take-home exposure" for the workers, their families, and other coresidents. The magnitude of
31 these historic take-home exposures was not measured, so the levels to which individuals in the
32 home might have been exposed are not known.
33   The Agency for Toxic Substances and Disease Registry (ATSDR) performed an exposure
34 survey in Libby to identify activities that may have led to the exposure of residents to vermiculite
35 and LAA. Based on the responses of survey participants, it was found that men were more likely
36 than women to have had both occupational and nonoccupational exposures, while women were
37 more likely to have had only household contact with exposed workers (Peipins et al., 2003;

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2-20   DRAFT—DO NOT CITE OR QUOTE

1 ATSDR, 2001b). Expanded vermiculite, as a finished product (Zonolite), was used for

2 insulation in attics and walls in homes in Libby, and was also used as a soil amendment in homes

3 and recreational areas. Community members may have been exposed, and are possibly still

4 exposed, to these consumer (Zonolite) products. In a survey of Libby residents conducted by

5 ATSDR in 2000−2001, almost 52% reported using vermiculite for gardening, 8.8% used

6 vermiculite around the home, and 51% reported handling vermiculite attic insulation (VAI,

7 Peipins et al., 2003). Because vermiculite ore, vermiculite product, and waste stoner rock (the

8 waste material from exfoliation) were present in the community, numerous other activities may

9 also have resulted in exposure. Individuals also reported exposures from the following activities:

10 participating in recreational activities along Rainy Creek Road, which is the road leading to the

11 mine (67%); playing at the ball field near the expansion plant (66%); playing in the vermiculite

12 piles (34%); heating the vermiculite to make it expand/pop (38%); or other activities in which

13 contact with vermiculite occurred (31%; Peipins et al., 2003).

14 Because a number of different activities may be associated with exposure to LAA in

15 Libby, it is important to recognize that the overall health hazard to an individual is related to the

16 sum of the exposures across all scenarios that apply to that individual.

17

18 **2.5.2. Exposure Pathways in Communities with Vermiculite Expansion and Processing**

19 **Plants**

20 While some vermiculite concentrate was exfoliated and used in Libby, MT, most of the

21 concentrate was transported to expansion plants at other locations across the country where it

22 was exfoliated and distributed. A review of company records from 1964−1990 indicates that

23 more than 6 million tons of vermiculite concentrate was shipped to over 200 facilities outside of

24 Libby (ATSDR, 2008). Figure 2-11 shows the locations of facilities that received and processed

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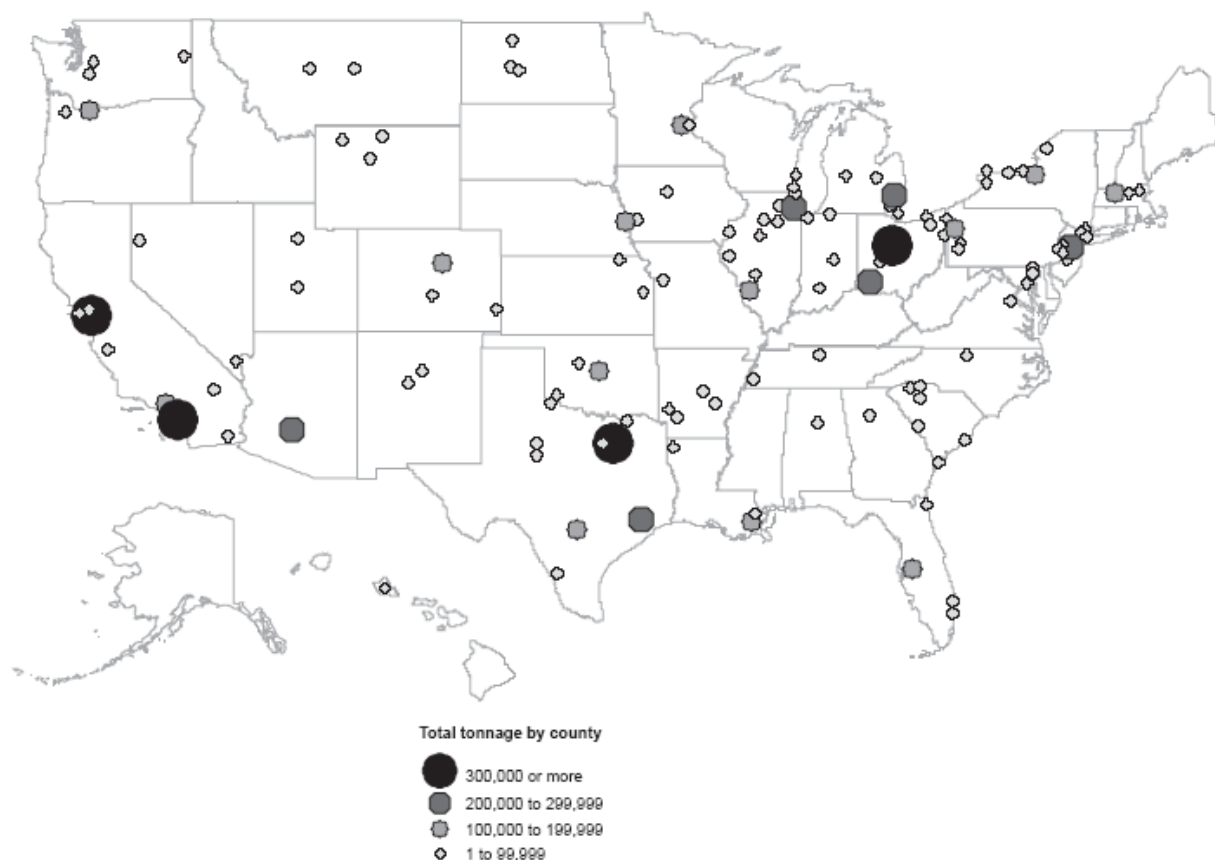
Figure 2-11. Nationwide distribution of Libby ore by county (in tons). Data on the distribution of ore are based on approximately 80,000 invoices that EPA obtained from W.R. Grace that document shipments of vermiculite ore made from the Libby mine between 1964 and 1990. EPA tabulated this shipping information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

Source: U.S. GAO (2007).

1   Workers in these expansion and processing facilities likely were exposed to LAA that
2 was released during the processing operations. The 2008 ATSDR Summary Report (ATSDR,
3 2008) on the 28 Libby vermiculite expansion and processing facilities stated that in some cases
4 household residents may also have been exposed by contact with vermiculite from the workers'
5 clothes, shoes, and hair. Workers' personal vehicles likely contained vermiculite dust from
6 facility emissions and from vermiculite that fell from their clothing and hair on the drive home
7 after work.
8   Other residents living in communities near the expansion plants may also have been
9 subjected to some of the same exposure pathways as for the Libby community. The 2008
10 ATSDR Summary Report observed that individuals in a community with a vermiculite
11 expansion and processing plant could have been exposed by breathing airborne emissions from

1   the facility or by inhalation exposure to contaminants brought into the home on workers'

2   clothing or from outdoor sources (ATSDR, 2008).

3

4   **2.5.3. Exposure Pathways in Other Communities**

5   Because expanded vermiculite from Libby was widely used in numerous consumer and

6   construction products throughout the United States, even people not associated with Libby or

7   other communities with expansion plants may also have the potential for exposure to LAA (see

8   Table 2-2). Vermiculite was most notably used as attic insulation (VAI; Versar, 2003), as a soil

9   amendment for gardening, fireproofing agent, and in the manufacturing of gypsum wallboard.

10

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

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

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

Source: Ewing et al. (2010).

3. FIBER TOXICOKINETICS

There are no published data on the toxicokinetics of Libby Amphibole asbestos (LAA).[5]
However, to help inform the reader as to the expected toxicokinetics of LAA, this section
contains a general summary description of the toxicokinetics of inhaled particles, with specific
discussion of dosimetry differences for fibers. A more detailed discussion of fiber dosimetry is
beyond the scope of this document and is reviewed elsewhere (NIOSH, 2011; ICRP, 1994).
LAA includes fibers with a range of mineral compositions, including amphibole fibers
primarily identified as richterite, winchite, and tremolite (see Section 2.2). Although the fiber
size varies somewhat from sample to sample for LAA, a large percentage (~45%) is less than
5 μm long in bulk samples examined from the Libby mine site (Meeker et al., 2003). Limited
data from air samples taken in the mill and screening plant at the Libby mine site also document
a large percentage of fibers (including both respirable[6] fibers as well as fibers >3 μm long; see
Section 4.1.1.2 and Table 4-3). Laboratory animal studies have examined the biologic response
to LAA fibers from both raw samples (Blake et al., 2007; Pfau et al., 2005) and rat respirable
samples (<2.5 μm) following water elutriation (Cyphert et al., 2012b; Cyphert et al., 2012a;
Shannahan et al., 2012a; Shannahan et al., 2012c; Shannahan et al., 2012b; Shannahan et al.,
2012d; Padilla-Carlin et al., 2011; Shannahan et al., 2011a; Shannahan et al., 2011b; Shannahan
et al., 2010; see Section 4.2, Appendix D). The mean fiber dimensions in the rat respirable
fractions are in the range of length = 4.99 μm; width = 0.26 μm; aspect ratio ≥5:1 (as measured
by TEM)[7]. The importance of the dimensions and density of fibers to their inhalation
dosimetry—how they deposit and are subsequently cleared—is described below. Due to a lack
of toxicokinetic data specific to LAA, these dosimetry mechanisms are discussed for inhaled
fibers in general, with a specific focus on amphibole asbestos.
The main route of human exposure to mineral fibers is through inhalation. Inhaled dose
of fibers to the respiratory tract tissue depends on the fiber concentration in the breathing zone,
the physical (aerodynamic) characteristics of the fibers, the breathing mode (nose only or also
oronasal), anatomical and physiological features of the respiratory tract (e.g., airway branching
pattern and ventilation rate), and clearance mechanisms (Oberdorster et al., 2002; U.S. EPA,
1994a; Oberdorster, 1991). Ingestion is another pathway of human exposure and occurs mainly
through the swallowing of material removed from the respiratory tract via mucociliary clearance
or drinking water contaminated with asbestos, or eating, drinking, or smoking in

---

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

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

[7]Detailed fiber dimension information for each study can be found in Appendix D when available.

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1   asbestos-contaminated work environments (Condie, 1983). Handling asbestos can result in
2   heavy dermal contact and exposure. Asbestos fibers can become lodged in the skin, producing a
3   callus or corn—but generally with no serious health effects (Lockey et al., 1984). Because few
4   studies have examined the deposition and clearance of fibers following ingestion or dermal
5   exposure to fibers, the focus of this section is on the main route of exposure: inhalation.
6   Studies useful for assessing the relationship between airborne fiber concentrations and
7   respiratory disease must involve meaningful measurements of environmental exposure and an
8   understanding of how to apply these measurements to the target tissue dose. Tissue dose is a
9   more specific measure associated with disease development than is external dose. Many studies
10 have examined the role of the physical and chemical characteristics of fibers in asbestos-induced
11 disease in the lung and are reviewed in more depth elsewhere (NIOSH, 2011; ATSDR, 2001a;
12 Myojo and Takaya, 2001; Witschi and Last, 1996; Lippmann, 1990; Merchant, 1990; Yu et al.,
13 1986; Griffis et al., 1983; Harris and Fraser, 1976; Harris and Timbrell, 1975). Factors
14 influencing dose to other tissues in the body (e.g., pleura, peritoneum, stomach, and ovaries) are
15 not as well known, but they are discussed below where data are available.
16   The principal components of inhaled fiber dosimetry in mammalian respiratory tract
17 systems are (1) inhalability, (2) deposition on the epithelial surface, (3) clearance from the lung
18 due to both physical (e.g., dissolution) and biological mechanisms (including mucociliary
19 transport, phagocytosis, and translocation from the lung to other tissues [including the pleura]),
20 and (4) elimination from the body (see Figure 3-1).
21
22 **3.1. DEPOSITION OF FIBERS IN THE RESPIRATORY TRACT**
23   The respiratory tract encompasses the extrathoracic region (nasal passages, pharynx, and
24 larynx), tracheobronchial region (the conducting airways [trachea bronchi, bronchioles]), and the
25 gas-exchange or pulmonary region of the lung (respiratory bronchioles, alveolar ducts, and
26 alveoli). Each region has unique anatomic and functional features, including dramatically
27 different architecture, cell types, and defense mechanisms, that determine the dosimetry of
28 inhaled agents in each region (U.S. EPA, 1994a). A full review of the anatomy and architecture
29 of the respiratory tract is beyond the scope of this document but has been reviewed by the
30 International Commission on Radiological Protection for its reference human respiratory tract
31 model (ICRP, 1994). Figure 3-2 illustrates the major anatomical features of the human
32 respiratory tract and mechanisms of fiber deposition.
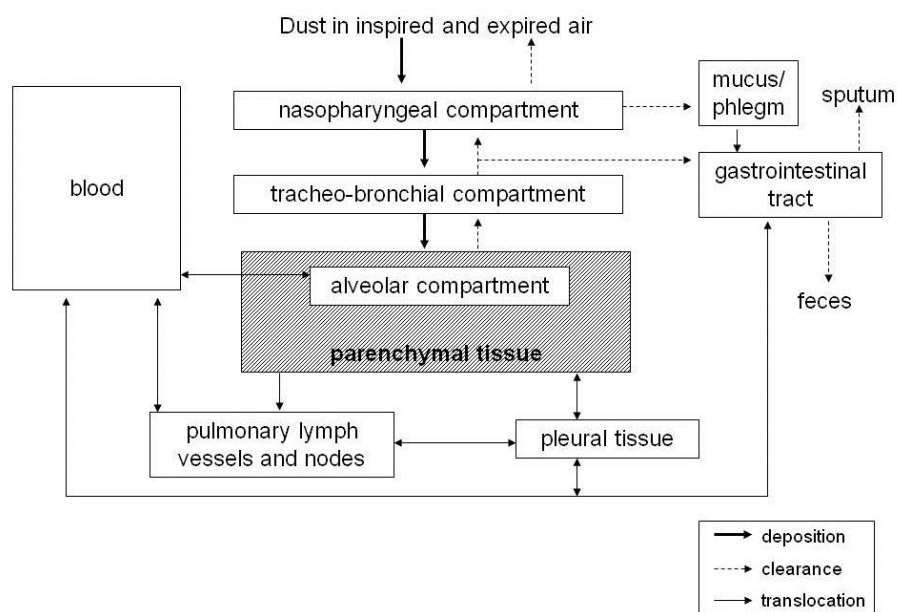
Figure 3-1. General scheme for fiber deposition, clearance, and translocation of fibers from the lung and gastrointestinal tract. General scheme for fiber inhalation and deposition (heavy arrows), clearance (light dotted arrows), and translocation (light arrows). Diagram of Bignon et al. (1978) derived from International Commission on Radiological Protection lung model by the Task Group on Lung Dynamics (Bates et al., 1966), as cited in ICRP (1994).

Source: ICRP (1994).
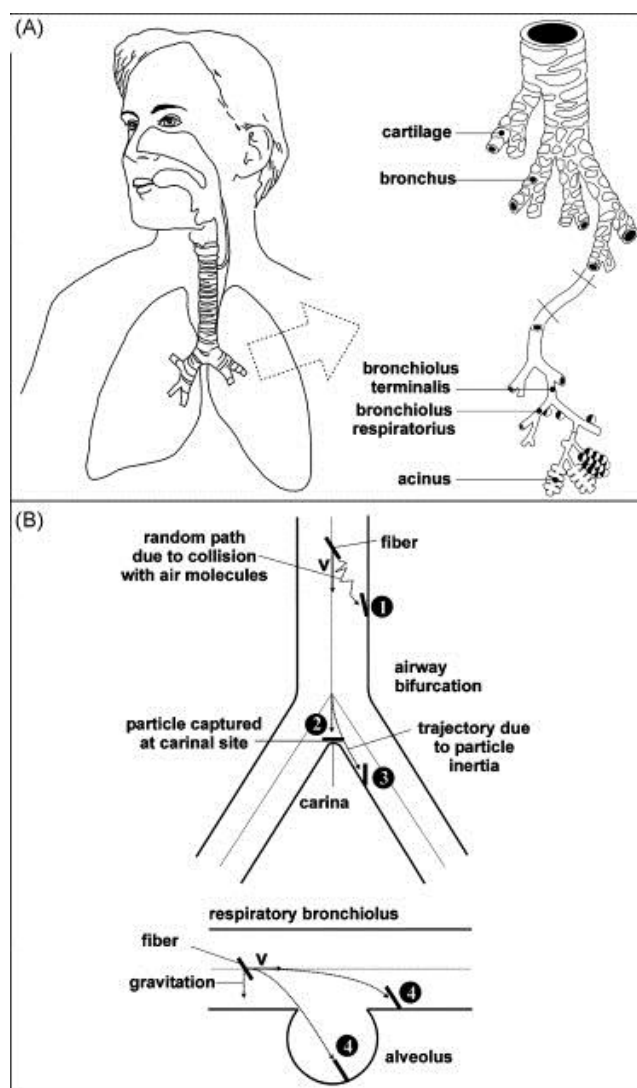
Figure 3-2. Architecture of the human respiratory tract and schematic of major mechanisms of fiber deposition. Mechanisms of fiber deposition illustrated in panel (B) are as follows: (1) diffusion, (2) interception, (3) impaction, and (4) sedimentation.

Source: Sturm and Hofmann (2009).

1   Four major mechanisms determine fiber deposition: impaction, interception,
2   sedimentation, and diffusion. Some authors also suggest electrostatic precipitation plays a role
3   in fiber deposition, but no experimental data exist to verify its presence (Sturm and Hofmann,
4   2009). The relative contribution to deposition in each region of the respiratory tract depends on
5   the fiber dimensions and density, breathing mode and ventilation rate, and the airway
6   architecture of the species in question (e.g., rat vs. human). The deposition mechanisms and
7   where these mechanisms are typically dominant in the human respiratory tract are described
8   below (see Table 3-1).

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

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

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

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

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

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

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

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

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

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

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

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

The conducting airways beyond the nasopharyngeal region serially bifurcate into airways of decreasing internal diameters that restrict the size of fibers deposited in these regions. Fiber length enhances bronchial deposition via interception, especially fibers exceeding lengths of 10 μm (Sussman et al., 1991a, b). The aerodynamic diameter of fibers that can deposit in the tracheobronchial region is in the range of 1−5 μm. Fibers with an aerodynamic diameter of <1 μm deposit in the bronchioles and the alveoli (ICRP, 1994). However, as reviewed in Aust et al. (2011), some studies have demonstrated that short fibers (<5 μm) are present in substantially greater numbers than long fibers (>5 μm) when examining the whole lung (Churg, 1982). Although information is limited on how fibers get to the pleura, fibers observed in pleural tissue from mesothelioma cases are more likely to be short (<5 μm; Suzuki et al., 2005). These observations could be partly due to the increased deposition of smaller fibers or the breakage of larger fibers over time (Bernstein et al., 1994; Davis, 1994).

Fibers with aerodynamic characteristics conducive to penetrating the peribronchiolar space and depositing in the alveoli may cause pulmonary fibrosis and other associated diseases. Regardless of shape, mineralogy, or concentration, the majority of fibers that are small enough to reach the alveoli are deposited at the alveolar duct bifurcations (Brody and Roe, 1983).

1 Deposition is controlled by air flow characteristics and is greatest at the bifurcations that are
2 closest to the terminal bronchioles (Brody et al., 1981). Furthermore, deposition in the
3 bifurcations is consistent across laboratory animal species (Warheit and Hartsky, 1990). Alveoli
4 deposition is limited when fiber length approaches 40 μm (Morgan et al., 1978). However,
5 alveolar deposition of fibers can occur with high aspect ratios and lengths ranging from <1 μm to
6 >200 μm long (Morgan et al., 1978). All fibers having an aerodynamic diameter less than
7 approximately 2 μm, which includes LAA, meet the physical criteria necessary for deposition in
8 the deeper regions of the respiratory tract at the level of the terminal bronchioles or alveoli.
9

10 **3.2. CLEARANCE MECHANISMS**

11   Once fibers deposit on the surface of the respiratory tract, they may be removed (cleared)
12 in several ways—including physical clearance, dissolution, phagocytosis, encapsulation, or
13 transcytosis. Some of these mechanisms, such as dissolution of the fibers or removal via the
14 mucociliary apparatus, can result in the fibers being cleared from the body (see Figure 3-1).
15 Other clearance mechanisms may remove fibers from the surface of the respiratory tract but
16 result in transport of the fibers to different locations or tissues by translocation. Translocation of
17 fibers from the terminal bronchioles and alveoli into the peribronchiolar space, lymph nodes, and
18 pleura has been implicated in disease causation (e.g., pleural plaques, mesothelioma; Dodson et
19 al., 2001). In human studies, the translocation of asbestos fibers following inhalation has been
20 observed to varying degrees throughout the pulmonary and extrapulmonary tissues of the
21 respiratory system (Dodson et al., 2005; Dodson et al., 2001; Kohyama and Suzuki, 1991;
22 Suzuki and Kohyama, 1991; Armstrong et al., 1988), as well as to other organs, including the
23 brain, kidney, liver (Miserocchi et al., 2008), and ovaries (Langseth et al., 2007). In many cases,
24 the type of fiber is not defined, and the individual exposure information not available. Fibers
25 that are not cleared can remain at the epithelial surface or enter the parenchymal tissue of the
26 lung. Retention of fibers in the human thoracic region generally shows two distinct phases. The
27 first, on the order of 24 hours, is considered to represent mucociliary clearance to the
28 gastrointestinal tract from the conducting airways and bronchioles; the second represents
29 clearance from the alveolar region (ICRP, 1994).
30   Berry (1999) provided a review of the animal toxicity literature specifically for fiber
31 clearance. There are limited data on clearance patterns based on autopsy studies in humans.
32 Two studies estimated clearance half-life for amphibole asbestos (~20 years) as compared with
33 chrysotile asbestos (~10 years; Finkelstein and Dufresne, 1999; Churg and Vedal, 1994); in
34 evaluating the data on lung fiber burden, Berry et al. (2009) estimated the range of the half-life
35 for crocidolite to be between 5 and 10 years. Generally, studies have focused on determining the
36 size and type of asbestos retained in specific tissues (Suzuki et al., 2005; McDonald et al., 2001;
37 Suzuki and Yuen, 2001; Dumortier et al., 1998; Gibbs et al., 1991; Dodson et al., 1990) and do

1 not discuss changes in fiber content since exposure. Sebastien et al. (1980) concluded that lung
2 fiber burden could not be used as an accurate reflection of pleural fiber burden.
3

3.2.1. Physical and Physicochemical Clearance of Fibers

5   Different mechanisms of physical and physicochemical clearance of fibers depends on
6 the fiber size, physicochemical characteristics, and site of deposition (IOM, 2006). Physical
7 clearance includes mechanical mechanisms, including transport via the mucociliary apparatus,
8 macrophage uptake, and translocation. Fibers can also translocate due to physical forces
9 associated with the mechanics of respiration (e.g., expansion, contraction of the rib cage; Davis,
10 1989). Physicochemical clearance of fibers includes dissolution and breakage of fibers.
11

3.2.1.1. *Mechanical Reflex Mechanisms*

13   Fibers deposited in the nasal passages can be removed by all clearance mechanisms.
14 When breathing occurs through the nose, many fibers are filtered by the turbulent airflow in the
15 nasal passages, impacting against the hairs and nasal turbinates, as well as becoming entrained in
16 mucus in the upper respiratory tract where they can be subsequently removed by mucociliary
17 action (described below) or reflexive mechanical actions such as coughing or sneezing.
18 Dissolution can also occur in this region, especially for soluble fibers.
19

3.2.1.2. *Mucociliary Clearance*

21   Physiological mechanisms include mucociliary escalator movement and how specific
22 cells or mechanisms in various regions of the respiratory tract respond and attempt to detoxify or
23 remove inhaled fibers.
24   The mucociliary escalator removes fibers through ciliary movement of the sticky mucus
25 lining (Wanner et al., 1996; Churg et al., 1989). Fibers removed from the conducting airways
26 through this mechanism are coughed out or swallowed and enter the digestive tract where they
27 may adversely affect the gastrointestinal tissue, enter the blood stream, or be excreted.
28 Clearance of fibers via mucociliary action is usually complete within hours or days (Albert et al.,
29 1969).
30   The mucociliary escalator extends only down to the level of the terminal bronchioles and
31 not to the alveoli. Thus, the particles deposited in the alveolar region of the lung cannot be
32 cleared through this process. Particles can reach the mucociliary escalator from the alveoli either
33 by way of surface fluids that are drawn onto the mucociliary escalator by surface tension or by
34 travelling through lymphatic channels that empty onto the escalator at bronchial bifurcations.
35   Although ingestion is a potential route of exposure due to subsequent swallowing of
36 material from the mucociliary escalator, limited research has examined clearance (e.g.,
37 translocation) of fibers following ingestion, and no clearance studies are available specific to

1   LAA. An early study to examine the tissue response to asbestos fibers is not truly representative

2   of a natural ingestion exposure, as the researchers directly injected a suspension of amosite fibers

3   into the duodenal wall (Meek and Grasso, 1983). This study, however, also examined oral

4   ingestion of amosite in healthy animals and those with gastrointestinal ulcers to determine

5   whether translocation of fibers occurs through ulcers. Following injection of amosite,

6   granulomatous lesions were observed. Ingestion of the same material resulted in no such lesions

7   or in any other histopathological changes in either healthy or rats compromised with ulcers.

8   Thus, no translocation was observed from either the healthy or the compromised rat

9   gastrointestinal tracts in this study. Truhaut and Chouroulinkov (1989) examined the effects of

10 chrysotile and crocidolite ingestion in Wistar rats. No translocation was observed. No further

11 studies have been found on clearance or translocation of fibers from the gastrointestinal tract.

12   Some fibers are not cleared from the respiratory tract, leading to an accumulation with

13 time (Case et al., 2000; Finkelstein and Dufresne, 1999; Jones et al., 1988). The fibers that

14 remain in the conducting airways and alveolar regions may undergo a number of processes

15 including translocation, dissolution, fragmentation, splitting along the longitudinal axis, or

16 encapsulation with protein and iron. Available data indicate prolonged clearance from the

17 thoracic region of long (>5 μm) or short amphibole fibers (Coin et al., 1994; Tossavainen et al.,

18 1994).

19   The prolonged clearance times for long amphibole fibers have led some investigators to

20 conclude that long fibers (>5 μm) rather than short amphibole fibers (i.e., LAA) are predominant

21 in the cause of disease due to their persistence in the lung (Mossman et al., 2011; ATSDR,

22 2003). However, others argue that fibers of all lengths induce pathological responses and urge

23 caution in excluding, based on length, any population of fibers from consideration as possibly

24 contributing to the disease process (Aust et al., 2011; Dodson et al., 2003). Respirable-sized

25 fibers of LAA have been identified in air samples from Libby, MT and in airborne fibers

26 suspended from both Libby vermiculite ore and in the exfoliated product from that ore (length

27 range from 1 μm to 20−30 μm, with average length of 7 μm; width range from 0.1−2 μm, with

28 average of 0.5 μm; see for details Appendix B and Appendix C). Based on fibers counted by the

29 TEM analytical method (ISO 10312), the majority of counted fibers are respirable (see

30 Figure 2-10).

31

32 **3.2.1.3. *Phagocytosis by Alveolar Macrophages***

33   The principal clearance pathway for short, insoluble fibers deposited in the alveoli is

34 through phagocytosis by macrophages. Durable fiber impaction in the deeper region of the

35 respiratory tract stimulates activation of alveolar macrophages. In vitro and in vivo studies

36 clearly indicate that macrophage cells play a role in the translocation of fibers (Dodson et al.,

37 2000a; Castranova et al., 1996; Brody et al., 1981; Bignon et al., 1979). These studies

38 demonstrated the presence of asbestos fibers in cell cytoplasm where the fibers can be

1   transported in association with cytoskeletal elements to the proximity of the cell nucleus.
2   Alveolar macrophages that have phagocytized insoluble fibers migrate to the bronchoalveolar
3   junctions where they are removed via the mucociliary escalator (Green, 1973). Alternatively,
4   alveolar macrophages that have phagocytized insoluble fibers can also migrate through the
5   epithelial wall into the interstitial space and enter the lymphatic system (Green, 1973).

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

15   Fibers that are too large to be easily engulfed by the alveolar macrophage can stimulate
16 the formation of "asbestos bodies." Asbestos bodies are fibers that become coated with proteins,
17 iron, and calcium oxalate as a result of prolonged residence in the lung where they can remain
18 throughout an individual's lifetime. Due to their iron content, histological stains for iron have
19 long been used to identify them in tissue; thus, they are sometimes called "ferruginous bodies."
20 The mechanisms that result in the formation of asbestos bodies are poorly understood, although
21 most appear to be formed around amosite fibers (Dodson et al., 1996). The iron in the coating is
22 derived from the asbestos fiber, cells, or medium surrounding the fiber and can remain highly
23 reactive (Lund et al., 1994; Ghio et al., 1992). Asbestos bodies comprise a minor portion of the
24 overall fiber burden of the lung. These fibers may or may not participate directly in asbestos
25 disease once the fiber is fully coated. For instance, the presence of iron in the coating could
26 provide a source for catalysis of reactive oxygen species (ROS) similar to that observed with
27 fibers.
28

29 **3.2.1.4. *Epithelial Transcytosis***

30   In addition to phagocytosis by alveolar macrophages, fibers deposited on Type I alveolar
31 epithelial cells may also be subjected to transcytosis with subsequent sequestration to the
32 alveolar interstitium (Sturm, 2011). Fiber length would play a key role in this aspect of
33 clearance, much as described above for phagocytosis by alveolar macrophages.
34

35 **3.2.1.5. *Translocation***

36   Translocation represents the movement of intact fibers along the epithelial surface
37 towards the terminal bronchiole, or into and through the epithelium. Translocation typically

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1 occurs via drainage of the alveolar macrophages to the lymphatics, but trancytosis of fibers by

2 type I alveolar epithelial cells can also result in transport to the interstitium. The relative

3 contribution of a specific mechanism and translocation route depends both on fiber

4 characteristics and the tissue of deposition. Fiber translocation depends on the fibers'

5 physicochemical characteristics, including two-dimensional size (length and width), durability,

6 solubility, and reactivity. This translocation is aided by high durability and an

7 inflammation-induced increase in permeability but could be hindered by fibrosis.

8   Translocation of fibers to extrapulmonary tissues was reported in multiple studies;

9 however, the precise mechanism is still unknown. This process was recently reviewed by

10 Miserocchi et al. (2008). Fibers were identified in all of the analyzed locations, including pleural

11 plaques and mesothelial tissue (i.e., pleural or peritoneal) in miners, brake workers, insulation

12 workers, and shipyard workers (Roggli et al., 2002; Dodson et al., 2000b; Churg, 1994;

13 Kohyama and Suzuki, 1991). However, amphibole fibers were less prevalent than chrysotile

14 fibers in the pleura and mesothelial tissues (Kohyama and Suzuki, 1991; Sebastien et al., 1989;

15 Armstrong et al., 1988; Churg, 1988; Bignon et al., 1979). Confocal microscopic observations of

16 rats inhalationally exposed to amosite fibers showed that fibers were present on the parietal

17 pleural surface 7 days postexposure and more than twofold thickening of the pleural wall was

18 noted (Bernstein et al., 2011). Bignon et al. (1979) also reported increased amphibole fibers in

19 the lymph nodes. Conflicting results from an inhalational rat study do not indicate any evidence

20 of fiber translocation from the central to peripheral compartments, although this could be due to

21 the short duration of the study (29 days postexposure; Coin et al., 1992).

22   Few studies have examined the size distribution of fibers translocated to specific tissues.

23 For example, one early study suggested that the longer amphibole fibers predominate in the lung

24 (Sebastien et al., 1980); other studies showed that the fiber-length distribution was the same by

25 fiber type regardless of location (Kohyama and Suzuki, 1991; Bignon et al., 1979). Dodson et al.

26 (1990) observed that the average-length fiber found in the lung (regardless of type) was longer

27 than those found in the lymph nodes or plaques. Most fibers at all three sites were short

28 (<5 μm). Similar results were observed in a later study by this group (i.e., Dodson et al., 2000b)

29 which examined tissue from 20 individuals with mesotheliomas, most with known

30 nonoccupational asbestos exposures.

31   Transplacental transfer of both asbestos (tremolite, actinolite, and anthophyllite) and

32 nonasbestos fibers occurs in humans, as measured in the placenta and in the lungs of stillborn

33 infants (Haque et al., 1998; Haque et al., 1996; Haque et al., 1992; Haque and Kanz, 1988). It is

34 hypothesized that maternal health might influence the translocation of fibers, as some of the

35 mothers had preexisting health conditions (e.g., hypertension, diabetes, or asthma; Haque et al.,

36 1992). This group also measured transplacental translocation in a mouse study and observed

37 early translocation of crocidolite fibers (Union for International Cancer Control [UICC]) through

38 the placenta in animals exposed via tail-vein injection (Haque et al., 1998). These studies did not

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1 evaluate the source or levels of exposure, only the presence of fibers in the body during early life

2 stages in mice and humans.

3

4 **3.2.1.6.** *Dissolution and Fiber Breakage*

5   Dissolution, or the chemical breakdown of fibers, is another method of physical removal

6 of fibers from the respiratory tract. This process varies, depending on the solubility and

7 chemical composition of the fibers, as well as the physiological environment. Dissolution can

8 occur in the lung's extracellular fluids or in the macrophage phagolysosome; the former can

9 make the breakdown products available for uptake into the blood. Studies performed in vitro to

10 determine dissolution rate of fibers attempt to mimic the extracellular lung fluids and

11 macrophage-phagolysosome system to understand the length of time that fibers remain in the

12 system (Rendall and Du Toit, 1994). Fibers can also be physically diminished through splitting

13 or breakage. These smaller fragments are then more easily removed by phagocytosis or

14 translocation.

15

16 **3.3. DETERMINANTS OF TOXICITY**

17   Multiple determinants of fiber toxicity, including dimension (length, diameter, aspect

18 ratio, and surface area), chemical characteristics (solubility, charge, and surface chemistry) and

19 durability (dissolution, breakage) have been studied relative to specific biological responses to

20 fibers and recently reviewed (Aust et al., 2011; Broaddus et al., 2011; Bunderson-Schelvan et al.,

21 2011; Case et al., 2011; Huang et al., 2011; Mossman et al., 2011).

22

23 **3.3.1. Dosimetry and Biopersistence**

24   The dosimetry factors discussed in the previous sections are major factors influencing

25 toxicity as the initial deposition sites in the respiratory tract tissues determine the subsequent

26 clearance mechanisms (Brain and Mensah, 1983); solubility and composition also influence the

27 biopersistence of fibers once deposited (Maxim et al., 2006; ILSI, 2005). Thus, fiber toxicity has

28 been associated with dose, density, dimensions, and durability, and likely involves a combination

29 of these and other factors. To the extent that a fiber and its composition are resistant to the

30 clearance mechanisms described in Section 3.1., biopersistence becomes a determinant of toxic

31 response. The degree of fiber durability determines the retained dose at the site of deposition

32 and likely plays a role in chronic inflammation, fibrosis, and lung burden following chronic

33 exposure to fibers. Biopersistence is influenced by fiber characteristics such as size (length,

34 width) and chemistry. Hesterberg et al. (1998b; 1998a) observed that, in general, increased in

35 vitro solubility decreases in vivo biopersistence. Several supporting studies reported increased

36 levels of crocidolite, tremolite, and amosite in respiratory diseases (asbestosis, mesothelioma)

37 compared to chrysotile and controls (Churg and Vedal, 1994; Churg et al., 1993) and found that

chrysotile has a lower biopersistence than amphibole fibers (Churg and Vedal, 1994; Wagner et al., 1974). The role of fiber size in biopersistence was examined by Bernstein et al. (2004) who found that the clearance half-time of longer fibers (>20 μm; 1.3 days) was less than that of shorter fibers (<5 μm; 23 days) for one form of chrysotile. Biopersistence is the basis of short-term in vitro testing required for new fibers introduced to the market (Maxim et al., 2006; ILSI, 2005).

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

3.3.2. Biological Response Mechanisms

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

Table 3-2. Determinants of fiber toxicity

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

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

1   Studies have also associated exposure to fibers to other biological activities, including
2   autoimmune effects and pulmonary function impacts. Limited studies have examined the role of
3   specific fiber determinants in autoimmune disease or pulmonary function, and therefore these
4   endpoints are not discussed in this section.
5
6   **3.3.2.1.** *Inflammation and Reactive Oxygen Species (ROS) Production*
7   Inflammation is an important biologic response to fibers and is related to multiple
8   pathways following exposure. Fiber exposure leads to ROS production, which in turn has been
9   shown to increase the activation of inflammatory and immune signaling pathways (Mossman et
10   al., 2011). Inflammation often occurs at the site of fiber deposition; therefore those fiber
11   characteristics that play a role in fiber deposition (e.g., length and width) will also play a role in
12   chronic inflammation. Further, those additional characteristics that lead to ROS production (e.g.,
13   surface chemistry) may also contribute to induction of chronic inflammation. Acute
14   inflammation in response to asbestos further contributes to chronic inflammation with the
15   activation of signaling pathways (e.g., mitogen-activated protein kinase[MAPK]) that lead to the
16   release of proinflammatory cytokines.
17   Increased ROS production is hypothesized to result from frustrated phagocytosis and
18   activation of signaling pathways in various cell types or through iron catalysis, which may
19   account for the differential induction of ROS due to variable intrinsic or acquired iron by
20   different fibers (Aust et al., 2011). Either indirect or direct ROS release following exposure to
21   fibers may in turn lead to increased damage to DNA or other biological molecules.
22
23   **3.3.2.2.** *Genotoxicity*
24   Genotoxicity (including mutagenicity) from exposure to fibers likely involves multiple
25   pathways, and the role of specific fiber determinants is not completely understood. This
26   genotoxicity is generally described as direct (e.g., fiber interference with spindle formation) or
27   indirect (e.g., reactive oxygen species production). A recent review by Huang et al. (2011)
28   examines the role of fiber determinants in genotoxicity and mutagenicity in detail. Briefly,
29   research studies designed to examine the role of fiber dimensions or surface characteristics in
30   genotoxicity are limited, and are mainly in vitro work. In general, fiber dimensions are expected
31   to play a role in genotoxicity. Long thin fibers are associated with interference with the spindle
32   apparatus during mitosis, as well as increased ROS/reactive nitrogen species (RNS) production
33   through frustrated phagocytosis, which in turn may lead to increased genotoxicity. Similarly,
34   increased iron associated with fibers may also lead to increased ROS/RNS production and
35   increased genotoxicity.

3.3.2.3. *Carcinogenicity*

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

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

Analyses of fiber dimensions in exposed humans have not led to any clear determinants of toxicity for fibers in general. Lippmann (1990) correlated fiber length with disease status in exposed humans and concluded that asbestosis was associated with short (>2 μm), thick fibers, >0.15 μm,); mesothelioma with longer (>5 μm), thinner fibers, <0.1 μm); and lung cancer with longer(>10 μm), thicker fibers, >0.15 μm). Throughout the years, some laboratory animal

1 studies have demonstrated a role for longer (>20 μm) and thinner (<0.3 μm) fibers in lung cancer

2 (Berman et al., 1995) or mesothelioma (Miller et al., 1999), while yet other laboratory animal

3 studies have suggested a role for shorter structures (<0.5−5 μm) in disease based in part on

4 increased numbers in dust clouds and in lung retention (Dodson et al., 2003). Some human

5 epidemiology studies have supported the role of longer (>20 μm), thinner (<0.3 μm) fibers in

6 lung cancer (Loomis D, 2009; Berman and Crump, 2008; Dement JM, 2008). However, these

7 results have not been confirmed in other studies and are in some cases contradicted. For

8 instance, Churg and Vedal (1994) did not find an association between fiber length and cancer.

9 However, McDonald et al. (2001) observed that shorter fibers (<6 μm) were more abundant in

10 diseased tissues than longer fibers (>10 μm), and Dodson et al. (1997) concluded that all sized

11 fibers are associated with increased mesothelioma risk. More recently, Berman (2011)

12 performed a quantitative analysis of previous studies and demonstrated that differences in

13 biological potency among various amphibole fiber types may be due to differences in their

14 dimensions, particularly fiber length. In all cases, the analytical methods used need to be

15 carefully described in order to draw any conclusions across studies.

16

17 **3.4. FIBER DOSIMETRY MODELS**

18   Modeling of fiber deposition has been examined for various fiber types (e.g., refractory

19 ceramic fibers, chrysotile asbestos; Sturm, 2009; Zhou et al., 2007; Lentz et al., 2003; Dai and

20 Yu, 1998; Yu et al., 1997; Coin et al., 1992), but not for LAA. In general, the pattern of

21 deposition for fibers is expected to have some similarities to the well-studied deposition pattern

22 for particles that are essentially spherical (reviewed in ICRP, 1994). For example, the multipath

23 particle dosimetry model (Brown et al., 2005; Jarabek et al., 2005) uses information on the

24 physical properties of the particles (length, width [also called bivariate distribution] and density),

25 the anatomy and architectural features of the airways, airflow patterns that influence the amount

26 and the location of the deposition of the particles, and the dissolution and clearance mechanisms

27 that are operative to estimate the retained dose in the target tissue. The site of fiber deposition

28 within the respiratory tract has implications related to lung retention and surface dose of fibers.

29 It should be noted that differences in airway structure and breathing patterns across life stages

30 (i.e., children, adults) change the depositional pattern of differently sized fibers, possibly altering

31 the site of action and causing differential clearance and health effects (see Section 4.7).

32

33 **3.5. SUMMARY**

34   Although oral and dermal exposure to fibers does occur, inhalation is considered the main

35 route of human exposure to mineral fibers, and therefore, it has been the focus of more fiber

36 toxicokinetic analyses in the literature. Similar to other forms of asbestos, exposure to LAA is

37 presumed to be through all three routes of exposure; however, this assessment specifically

1   focuses on the inhalation pathway of exposure. Generally, fiber deposition in the respiratory
2   tract is fairly well defined based on fiber dimensions and density, although the same cannot be
3   said for fiber translocation to extrapulmonary sites (e.g., pleura). The deposition location within
4   the pulmonary and extrapulmonary tissues plays a role in the clearance of the fibers from the
5   organism.
6   Fiber clearance from the respiratory tract can occur through physical and biological
7   mechanisms. Limited mechanistic information is available on fiber clearance mechanisms in
8   general, and no information specific to clearance of LAA fibers is available. Fibers have been
9   observed in various pulmonary and extrapulmonary tissues following exposure, suggesting
10   translocation occurs to a variety of tissues. Studies have also demonstrated fibers may be cleared
11   through physical mechanisms (coughing, sneezing) or through dissolution of fibers.
12   Multiple fiber characteristics (e.g., dimensions, density, and durability) play a role in the
13   toxicokinetics and toxicity of fibers. There is extensive literature examining a variety of fiber
14   determinants and their role in disease, with a focus on fiber length, width, and durability;
15   however, these studies are often contradictory, making conclusions difficult for fibers in general.
16   This is in part due to the variety of fibers analyzed, inadequate study design, and/or lack of
17   information on fiber dimensions in earlier studies. However, due to the importance in
18   understanding the role of these fiber determinants in the biological response, careful attention has
19   been paid to these fiber characteristics when analyzing research studies on LAA and asbestiform
20   tremolite, an amphibole fiber that comprises part of LAA (see Appendix D). No toxicokinetic
21   data are currently available specific to LAA, tremolite, richterite, or winchite. When available,
22   fiber characteristic data are presented in the discussion of each study in relation to the toxic
23   endpoints described.

1   **4. HAZARD IDENTIFICATION OF LIBBY AMPHIBOLE ASBESTOS**

2   This section discusses the available data derived from studies of people exposed to Libby

3   Amphibole asbestos (LAA),[8] either at work or in the community, and from various laboratory

4   studies. The effects in humans (e.g., parenchymal damage and pleural thickening, lung cancer,

5   and mesothelioma) are supported by the available LAA experimental animal in vivo and

6   laboratory in vitro studies. The health effects from tremolite exposure, one of the constituent

7   minerals of LAA, reported in both human communities and laboratory animals, are consistent

8   with the human health effects reported for LAA. Studies examining the health effects of

9   exposure to winchite or richterite alone were not available in the published literature. The

10   review presents noncancer and cancer health effects observed from exposures to LAA.

11

12   **4.1. STUDIES IN HUMANS—EPIDEMIOLOGY**

13   The LAA epidemiologic database includes studies based in occupational settings and

14   community-based studies of workers, family members of workers, and others in the general

15   population. Occupational epidemiology studies have been conducted at two worksites where

16   workers were exposed to LAA: the vermiculite mine and mill at the Zonolite Mountain

17   operations near Libby, MT, and a manufacturing plant using the vermiculite ore in Marysville,

18   OH. Community-based studies have also been conducted among residents around Libby, MT,

19   (ATSDR, 2001b, 2000) and in an area around a manufacturing plant producing vermiculite

20   insulation in Minneapolis, MN (Alexander et al., 2012).

21   The epidemiology studies of people exposed to LAA were primarily identified through

22   EPA's specific knowledge of the research endeavors that have taken place since recognition in

23   the 1970s of the asbestos contamination from the vermiculite mined around Libby, MT. These

24   studies were conducted by NIOSH, McGill University, University of Cincinnati, and the

25   ATSDR. Analyses by other researchers using the data collected through these studies as well as

26   other studies of people exposed to LAA were also identified through contacts with these research

27   groups and through "forward searching" through Web of Science for references citing the key

28   publications describing the initial studies (i.e., Peipins et al., 2003; Amandus et al., 1987b;

29   Amandus et al., 1987a; McDonald et al., 1986a; Lockey et al., 1984).

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

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1   Figure 4-1 depicts the sets of studies conducted by different groups of researchers in
2 Libby, MT and in two areas with plants that used Libby vermiculite in various production
3 processes (fertilizer and other lawn products in Marysville, OH and insulation materials in
4 Minneapolis, MN). These studies have examined cancer and noncancer mortality, pulmonary
5 effects detected through x-ray examinations, pulmonary function tests, or respiratory symptoms,
6 autoimmune diseases, and prevalence of autoantibodies.
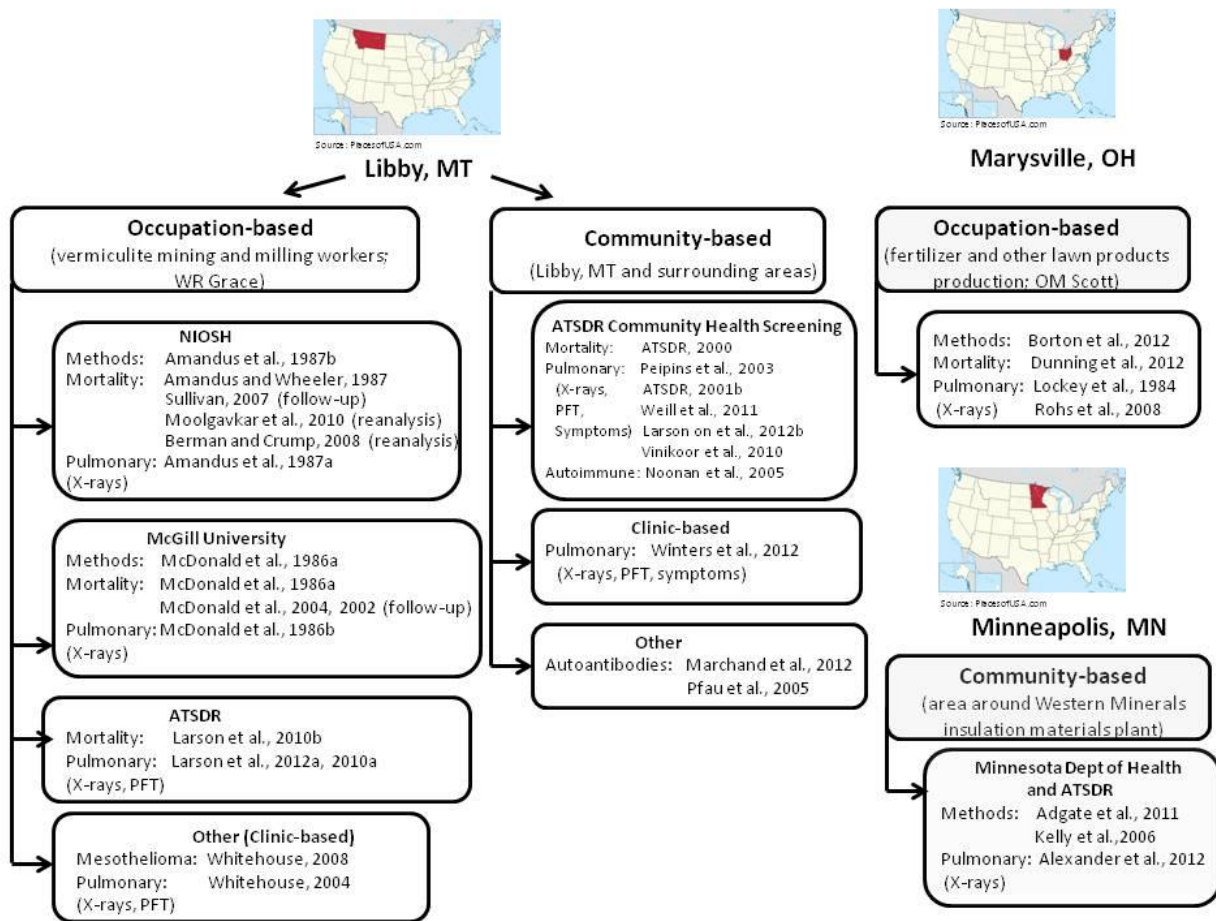
Figure 4-1. Investigations of populations exposed to LAA. Moolgavkar et al. (2010) and Berman and Crump (2008) used the Libby worker cohort assembled by Sullivan (2007) to estimate cancer potency factors; these analyses are summarized in Section 5.4.5.3.1.

PFT = pulmonary function testing.

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

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4.1.1. Overview of Primary Studies

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

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

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

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

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

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

4.1.1.1.2. *Descriptions of cohorts of Libby, MT vermiculite mining and milling operations workers.* The two cohort studies conducted in the 1980s (by NIOSH and McGill University) were similar in terms of populations and study design. For example, both studies included workers who had worked for at least 1 year. Amandus and Wheeler (1987) included men hired before 1970 ($n = 575$), with follow-up through December 31, 1981, while McDonald et al. (1986a) included men hired before 1963 ($n = 406$) with follow-up through 1983. A subsequent analysis extended this follow-up through 1999 (McDonald et al., 2004). Another analysis of the Libby, MT workers expanded the NIOSH cohort to include all workers, regardless of duration of employment (Sullivan, 2007). The total sample ($n = 1,672$ white men) included 808 workers who had worked for less than 1 year. These short-term workers had been excluded from the previous studies. Analyses presented in the report were based on follow-up from 1960−2001. Larson et al. (2010b) reconstructed a worker cohort based on company records and analyzed mortality risks through 2006. This study included 1,862 workers (including a small number of women).

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

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

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

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

1 **4.1.1.1.3.1.** *Asbestos fiber quantification and development of job-exposure matrices.*

2   Before 1970, exposure estimates were based on midget impinger samples taken primarily

3 in the dry mill by state and federal inspectors (*n* samples = 336). Total dust samples were

4 measured as million particles per cubic foot (mppcf); these samples included mineral dust and

5 vermiculite particles and scrolls as well as asbestos fibers. Membrane-filter air samples for

6 fibers, taken at various locations within the operations, began in 1967, and data are available

7 from company records as well as State and Federal Agencies (see Table 4-2). Stationary and

8 short-term (i.e., 20-minute to less than 4-hour) measurements were primarily used before 1974.

9 Air samples collected through membrane filters (*n* = 4,116) were analyzed by PCM to visually

10 count fibers greater than 5-μm long and having an aspect ratio >3:1 (Amandus et al., 1987b).[9]

11 PCM methods from the 1960s allowed reliable characterization of fibers with widths greater than

12 approximately 0.4 μm (Amandus et al., 1987b; Rendall and Skikne, 1980). Further

13 standardization of the PCM method and improved quality of microscopes provided better

14 visualization of thinner fibers; a 0.25-μm width was considered the limit of resolution for fiber

15 width in the 1980s (IPCS, 1986), with subsequent improvements in resolution to 0.20 μm in

16 width.

17

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

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

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

 Source; Amandus et al. (1987a).

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

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1   The samples taken from specific work locations within the operations were used to

2 estimate exposures in specific jobs and time periods based on industrial hygienist consideration

3 of temporal changes in facilities, equipment, and job activities. These were defined to categorize

4 tasks and locations across the mining, milling, and shipping operations to group-like tasks with

5 respect to exposure potential. Both research groups established similar location operations for

6 the Libby cohort. Because measures from sample filters were not available before 1968,

7 different procedures had to be used to estimate exposures at the various locations for this earlier

8 period. Amandus et al. (1987b) and McDonald et al. (1986a) provide high and low estimates for

9 several locations to address the uncertainties in assumptions used in these estimates. Both

10 researchers also applied a conversion factor to estimate asbestos exposures at the dry mill before

11 1967: the conversion factor was 4.0 in Amandus et al. (1987a) and 4.6 in McDonald et al.

12 (1986a).[10]

13   Jobs were mapped to operation/location based on estimated time spent in different job

14 tasks, thus estimating an 8-hour time-weighted average exposure for each job during several

15 calendar time periods. Job histories from date of first employment to 1982 were used with the

16 job-exposure matrix to develop cumulative exposure estimates for each worker.

17

18 *Additional considerations*

19   The resulting exposure estimates presented by both research groups, and the job-exposure

20 matrices used in calculating cumulative exposure for the cohort, were based on fiber counts by

21 PCM analysis of air filters. As discussed in Section 2 (see Section 2.4.4), PCM analysis does not

22 distinguish between fiber mineralogy or morphology, and all fibers >5 μm in length with an

23 aspect ratio of 3:1 or greater are included. Both researcher groups analyzed fibers available at

24 the facility in order to identify the mineral fibers in the air samples.

25   TEM[11] analysis of airborne asbestos fibers indicated a range of fiber

26 morphologies―including long fibers with parallel sides, needlelike fibers, and curved fibers

---

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

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

1   ([McDonald et al., 1986a](#)). Of the fibers examined by TEM, >62% were >5 μm in length and a

2   wide range of dimensional characteristic were noted: length (1−70 μm), width (0.1−2 μm), and

3   aspect ratios from 3:1−100:1. Energy dispersive spectroscopy used to determine the mineral

4   analysis indicated that the fibers were in the actinolite-tremolite solid solution series, but sodium

5   rich ([McDonald et al., 1986a](#)). This analysis is consistent with the current understanding of

6   amphibole asbestos found in the Libby mine (see Section 2.2.3).

7   At the time of their study, when exposure concentrations were reduced to generally less

8   than 1 fiber/cc, [Amandus et al. (1987b)](#) obtained eight air filters from area air samples collected

9   in the new wet mill and screening plant (provided by the mining company). These samples were

10   analyzed by PCM using the appropriate analytical method for the time (NIOSH Physical and

11   Chemical Analytical Method No. 239). From early method development through current PCM

12   analytical techniques, the Public Health Service, Occupational Safety and Health Administration

13   and NIOSH methods have defined a fiber by PCM analysis as having an aspect ratio ≥3:1

14   ([NIOSH, 1994](#); [Edwards and Lynch, 1968](#)). [Amandus et al. (1987b)](#) reported the dimensional

15   characteristics of the fibers from these filters including aspect ratio, width, and length (see

16   Table 4-3). Data for 599 fibers from the eight area air samples collected in the wet mill and

17   screening plant are provided. These data are limited in one sense by the minimum diameter and

18   length cutoffs (>4.98-μm long, >0.44-μm wide, aspect ratio >3:1);[12] 16% had an aspect ratio

19   ≥50:1. Only 7% of the fibers had a width greater than 0.88 μm, with one fiber reported of the

20   559 with a width greater than 1.76 μm. It should be noted that these data do not give the full

21   fiber-size distribution of LAA fibers because NIOSH was examining only PCM visible fibers

22   (see Section 2.3.1).

---

[12]See footnote 9, page 4−6.

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

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

[a]Fibers were viewed and counted by phase contrast microscopy.

Source: Amandus et al. (1987b).

1 **4.1.1.2. *Studies of O.M. Scott, Marysville, OH Plant Workers***

2 **4.1.1.2.1. *Descriptions of cohorts of O.M. Scott, Marysville, OH plant workers.*** The first study

3 of pulmonary effects in the Ohio plant workers was conducted in 1980 and involved 512 workers

4 (97% of the 530 workers previously identified with past vermiculite exposure; Lockey et al.,

5 1984; see Tables 4-4 and 4-6). The Rohs et al. (2008) study is a follow-up of respiratory effects

6 in this cohort conducted approximately 25 years later; chest x-rays and interview data were

7 collected from 280 of the 431 workers known to be alive at this time. Dunning et al. (2012)

8 examined mortality rates in the cohort, using an updated exposure analysis described by Borton

9 et al. (2012). In this analysis, vital status through June 2011 was ascertained.

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

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

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

1 **4.1.1.2.1.1. *Exposure estimation: O.M. Scott, Marysville, OH plant.*** The plant that processed

2 vermiculite ore in Marysville, OH had eight main departments in the processing facility,

3 employing approximately 530 workers, with 232 employed in production and packaging of the

4 commercial products and 99 in maintenance; other divisions included research, the front office,

5 and the polyform plant (Lockey, 1985). Six departments were located at the main facility

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

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

Cumulative fiber exposure indexes, expressed as fibers/cc-yr, were derived for each worker from available industrial hygiene data and individual work histories; three categories of exposure levels were defined (97% of the 530 workers previously identified with past vermiculite exposure; Lockey et al., 1984; see Table 4-6). Group I was considered to be the nonexposed group and consisted of the chemical processing, research, and front office workers, as well as other workers with an estimated cumulative exposure <1 fiber/cc-yr. Group II was the low-exposure category and included central maintenance, packing, and warehouse workers. The 8-hour time-weighted average fiber exposure in this group was estimated as approximately 0.1−0.4 fiber/cc before 1974 and 0.03−0.13 fiber/cc in and after 1974. Group III was the high-exposure category and included expander, plant maintenance, and pilot plant workers. The 8-hour time-weighted average fiber exposures in this group were approximately 1.2−1.5 fibers/cc before 1974 and 0.2−0.375 fiber/cc in and after 1974. The estimated cumulative exposure for the work force, including Group I workers, ranged from 0.01 to 28.1 fibers/cc-yr using an 8-hour workday and an assumed 365 days of exposure per year.[14] Exposure was assumed to occur from 1957 to 1980 in this study. Exposure outside of work hours was assumed to be zero.

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

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[13]Subsequent exposure assessment efforts by this team of investigators are described in Borton et al. (2012) and in Appendix F.
[14]Lockey et al. (1984) reported the maximum value for this group as 39.9 fibers/cc-yr, but this estimate was later corrected to exclude work from 1947 to 1956, before the use of vermiculite at the plant. Information provided in Benson (2014).

1   **4.1.1.3.** *Community-Based Studies Around Libby, MT Conducted by Agency for Toxic*
2   *Substances and Disease Registry (ATSDR)*

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

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

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

24

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

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

LPT = localized pleural thickening.

4.1.2. Respiratory Effects, Noncancer

4.1.2.1. *Asbestosis and Other Nonmalignant Respiratory Disease Mortality*

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

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

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

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

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

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

Community-based studies in Libby, MT

Reference(s)	Respiratory disease	SMR	(95% CI)	SMR	(95% CI)
ATSDR (2000)	Asbestosis (n = 11)	SMR	(95% CI)	SMR	(95% CI)
	Comparison area (Montana reference rates):			Comparison area (U.S. reference rates):	
	Libby city limits	40.8	(13.2, 95.3)	Libby city limits	63.5	(20.5, 148)
	Extended Libby boundary	47.3	(18.9, 97.5)	Extended Libby boundary	74.9	(30.0, 154)
	Air modeling	44.3	(19.1, 87.2)	Air modeling	71.0	(30.6, 140)
	Medical screening	40.6	(18.5, 77.1)	Medical screening	66.1	(30.2, 125)
	Libby valley	38.7	(19.3, 69.2)	Libby valley	63.7	(31.7, 114)
	Central Lincoln County	36.3	(18.1, 64.9)	Central Lincoln County	59.8	(29.8, 107)

Occupational studies of O.M. Scott, Marysville, OH plant workers

Reference(s)	Respiratory disease
Dunning et al. (2012)	Asbestosis (n = 1) SMR: 15.4 (0.4, 86)

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

CI = confidence interval, SRR = standardized rate ratio.

[a]Libby, MT mining and milling operations includes miners, millers, and processors; workers in the screening plant, loading docks, and expansion plants; and office workers.

[b]SMR based on external referent group.

[c]In Sullivan (2007), the SRR is a ratio of sums of weighted rates in which the weight for each stratum-specific rate is the combined person-yr for the observed cohort across all duration (or cumulative level of exposure) categories. The Life Table Analysis System provides the SRR for each duration (or cumulative level of exposure) group compared to the referent group. The cutoff points for the categories are specified by the user. Taylor-series-based confidence intervals (Rothman, 1986) are given for each specific SRR.

[d]In McDonald et al. (2004), the RR is based on Poisson analysis using an internal referent group.

[e]In Larson et al. (2010b), the RR is based on Cox proportional hazards modeling using an internal referent group.

1 **4.1.2.2.** *Pathological Alterations of the Parenchyma and Pleura, Pulmonary Function, and*
2 *Respiratory Symptoms*

3 **4.1.2.2.1.** *Definition of outcomes*

4 **4.1.2.2.1.1.** *Pathological alterations of the parenchyma and pleura*

Text Box 4-1. Pathological Alterations of the Parenchyma 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 classification guidelines provide a scheme for grading the severity of the small opacities; the size, shape, and profusion of the small opacities are recorded, as well as the affected zone of the lung.

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

Pleural thickening: The pleural lining around the lungs (visceral pleura) and along the chest wall and diaphragm (parietal pleura) may thicken due to fibrosis and collagen deposits. Pleural thickening (all sites) is reported as either 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." Localized pleural thickening may also be viewed in-profile or face-on and is generally a pleural plaque (parietal). Calcification is noted where present.

Source: ILO (2002) (describing the ILO 2000 revision).

1　　　　Respiratory disease risk can be evidenced by pleural and parenchymal abnormalities
2　(pathological, structural alterations) detected through radiographic or other types of imaging (see
3　Text Box 4-1). These types of effects are usually classified using criteria developed by the
4　International Labour Organization (ILO) of the United Nations to standardize descriptions of
5　effects and improve inter-rater agreement and accuracy for reading chest radiographs in
6　pneumoconiosis. The guidelines were initially developed in 1950 with several subsequent
7　revisions. A key component of the guidelines is the use of a set of standard films illustrating
8　different types of findings; these films are used by "B Readers" as a reference for comparison to
9　films collected in a research or clinical setting. The B Reader program was initiated in 1974 to
10　reduce variability in readings; B Readers are physicians who pass an examination, recertifying
11　every 4 years, in the adherence to detailed criteria when reading radiographs in individuals with
12　pneumoconiosis. The criteria provide for the exclusion of anomalies potentially due to
13　nonasbestos-related causes (e.g., trauma, tuberculosis).

14　　　　Parenchymal (the inner structure of the lungs) abnormalities include opacities; these
15　abnormalities are defined as small (≤10 mm diameter) or large (>10 mm diameter). Small
16　opacities are assigned a score based on the concentration of opacities in a given area (profusion),
17　zone(s) of the lung(s) affected, shape, and size. Small opacity profusion is graded on a 4-point
18　scale (0 = absence of opacity, 3 = highest level of opacity). Two ratings are given (e.g., 0/1, or
19　2/2), with the second number indicating a grade that was seriously considered as an alternative to
20　the first grade. Large opacities are scored based on dimensions within the lung zone(s) they
21　occupy. The scarring of the parenchymal tissue of the lung contributes to measurable
22　decrements in pulmonary function, including obstructive pulmonary deficits from narrowing
23　airways, restrictive pulmonary deficits from the decreased elasticity of the lung, and decrements
24　in gas exchange (ATS, 2004).

25　　　　According to the 2000 ILO guidelines (ILO, 2002), pleural abnormalities are classified as
26　(a) localized pleural thickening (LPT) or (b) diffuse pleural thickening (DPT), defined as pleural
27　thickening that is present "only in the presence of and in continuity with an obliterated
28　costophrenic angle (CPA)." Previous ILO guidelines (ILO, 1980, 1971) defined DPT without
29　the requirement for CPA obliteration; thus, under the 2000 ILO guidelines, the LPT category
30　includes what was previously defined as DPT without an obliterated costophrenic angle. The
31　2000 ILO category of LPT also includes what previous ILO guidelines defined as "plaques."
32　Different researchers implementing the earlier ILO guidelines variously used terms such as
33　"discrete" or "circumscribed" or "pleural" to describe these plaques. Both LPT and DPT are
34　scored based on their location, extent, and whether calcification is seen. LPT is a change in
35　tissue structure, and is not known to be an adaptive response to toxicity generally or to asbestos
36　specifically. Examples of pleural plaques (a subset of LPT) as visualized on autopsy are shown
37　in Figures 4-2A and 4-2B from Official Journal of the ATS (2004). Additional discussion of the
38　adversity of LPT is included in Section 5.2.2.3 (*Selection of Critical Effect*) and Appendix I.
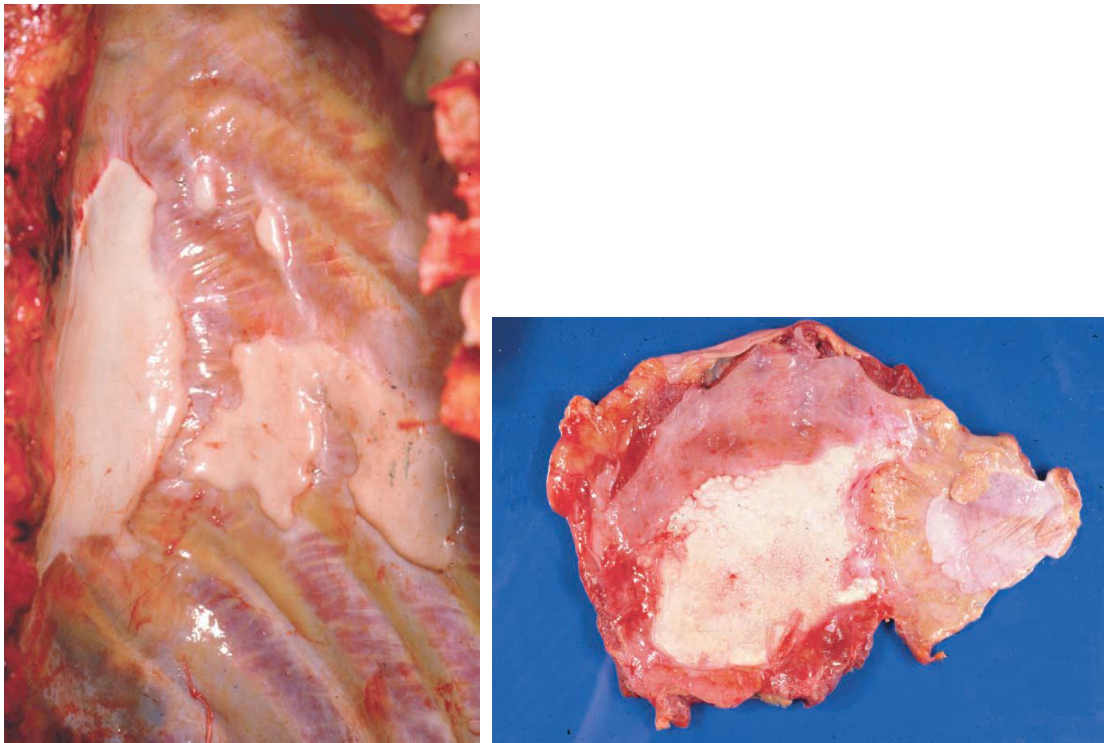
Figure 4-2. A (left). Gross appearance at autopsy of asbestos-associated pleural plaques overlying the lateral thoracic wall. (ATS, 2004, Figure 12)

Figure 4-2B (right). Gross appearance of large asbestos-related pleural plaque over the dome of the diaphragm.(ATS, 2004, Figure 13)

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

1   The latency period for the initial detection of pleural or parenchymal abnormalities varies
2   by type of lesion. Larson et al. (2010a) examined x-rays of 84 workers from the Libby, MT
3   mining and milling operations for whom pleural and/or parenchymal abnormalities were seen
4   and who had one or more previous x-rays covering a span of at least 4 years available for
5   comparison. Circumscribed pleural plaques was seen in 83 of these 84 workers at a median
6   latency of 8.6 years. Any pleural calcification was seen in 37 workers, with a median latency of
7   17.5 years, and DPT was seen in 12 workers (median latency: 27.0 years). The latency period
8   for small opacities indicating parenchymal changes (e.g., asbestosis) increased with increasing
9   profusion categories, from a median of 18.9 years for $\geq 1/0$, 33.3 years for progression to $\geq 2/1$,
10   and 36.9 years for progression to $\geq 3/2$.

Pulmonary function

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

Combinations of various functional measurements may be indicative of specific types of abnormalities affecting lung function. For example, restrictive lung function (or restrictive ventilatory defect) refers to reduced lung volume. Both FEV_1 and FVC would be reduced, but the reduction in FVC would be greater than that for FEV_1 (e.g., FEV_1/FVC ratio >0.8). Restrictive lung function can result from inflammation or scarring of the parenchyma, interstitial lung disease, fibrosis, or other conditions that restrict the ability of the lungs to expand. Obstructive lung function (or obstructive ventilatory defect) refers to reduced airflow, and is characterized by inflammation or obstruction of the airways. It is indicated by a reduction in FEV_1 without an accompanying change in FVC (e.g., the ratio of $FEV_1/FVC < 0.7$, or $FEV_1/FVC < 5^{th}$ percentile). Both restrictive and obstructive conditions can result in dyspnea (shortness of breath), cough, and chest pain.

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

Libby, MT vermiculite mine and mill workers

Studies examining pleural and parenchymal abnormalities in the Libby, MT worker cohorts are shown in Table 4-7. In the McDonald et al. (1986b) and Amandus et al. (1987a) studies, x-ray films for each worker, which NIOSH obtained from the Libby hospital that performed the screening, were independently read by three qualified readers using the 1980 ILO classification system. For the analysis, the classification indicating pleural abnormalities by at least two of the three readers was used to determine the presence of pleural abnormalities, while the median reading was used to determine the profusion category of small opacities. Although both research groups used the ILO 1980 guidelines, McDonald et al. (1986b) reported pleural thickening on the chest wall (both pleural plaques and diffuse) but not in other sites. Amandus et al. (1987a) examined "any unilateral or bilateral pleural change", which included "…pleural plaque, diffuse pleural thickening of the chest wall, diaphragm or other site, but excluded costophrenic angle obliteration." This classification would be equivalent to the LPT classification used in the revised ILO guidelines (ILO, 2002); however, the results reported in the paper are for thickening on the chest wall only (rather than including other sites) are not equivalent to the 2000 ILO LPT classification.

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

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

1   Amandus et al. (1987a) reported pleural thickening of the chest wall in 13% and small

2   opacities (≥1/0) in 9.1% of current employees. Similar data were reported by McDonald et al.

3   (1986b), with 15.9 and 10% with pleural thickening of the chest wall and small opacities,

4   respectively. In both studies, prevalence of these abnormalities increased with increasing

5   cumulative exposure. McDonald et al. (1986b) also included 80 former employees in their

6   study. The prevalence of pleural thickening of the chest wall (52.5%) and small opacities

7   (37.5%) was higher in former employees compared with current workers. These groups differed

8   by age, with only one of the 80 former workers being less than 40 years of age while 80 of

9   164 current workers were under 40 years of age. Both overall and within age categories,

10   however, the prevalence is higher among former employees, and this is attributed to higher

11   cumulative exposure in this group.

12   Both Amandus et al. (1987a) and McDonald et al. (1986b) provided categorical

13   exposure-response data as well as logistic models for various endpoints (e.g., small opacities,

14   pleural calcification, pleural thickening of the chest wall, and "any pleural change"). In

15   McDonald et al. (1986b), exposure and age were both predictive of pleural thickening along the

16   chest wall; the regression coefficient for cumulative exposure (fibers/cc-yr) was 0.0024 per unit

17   increase in cumulative exposure for the log odds of the presence of pleural thickening, adjusting

18   for age and smoking. Cumulative exposure, age, and smoking status were all predictive of small

19   opacities; the parameter for cumulative exposure had a regression coefficient of 0.0035 per unit

20   increase in cumulative exposure. In contrast, although the categorical analysis reported by

21   Amandus et al. (1987a) indicated a positive exposure response relationship for both "any pleural

22   change" and pleural thickening along the chest wall, cumulative exposure was not a significant

23   predictor in regression analysis adjusting for age (regardless of smoking status). The lack of

24   statistical significance in these models may reflect a nonlinearity resulting from the lower

25   prevalence in expose Category 2 compared to exposure Category 1. The estimated relationship

26   between exposure and prevalence of small opacities in Amandus et al. (1987a) was similar to

27   that reported by McDonald et al. (1986b).

28   Larson et al. (2012a) used data collected as part of the community screening program

29   conducted in 2001 (ATSDR, 2001b; see Section 4.1.1.3) to examine the pleural and pulmonary

30   outcomes based on chest radiographs, spirometry results, and self-reported symptoms in relation

31   to cumulative exposure among 336 workers. Diffuse pleural thickening (in the presence of

32   costrophenic angle obliteration) and parenchymal lesions (profusion ≥1/0) were each detected in

33   5% of the workers. Risk increased monotonically with increasing cumulative exposure for each

34   of these outcomes; however, the slope was shallower for diffuse pleural thickening and was not

35   statistically significant. Localized pleural thickening (only) was found in 35% of the workers

36   with an elevated risk associated with cumulative exposures as low as 1 fiber/cc-yr. For a

37   diagnosis of restrictive spirometry (prevalence = 16%), risk began to increase at 26 fibers/cc-yr

38   and reached statistical significance at 166 fibers/cc-yr. Chronic bronchitis defined as coughing

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1   up phlegm "for at least 3 months of the year for the past 2 years" was reported in 8% of the
2   workers, and a statistically significant increased risk was calculated at 24 fibers/cc-yr.
3
4   *O.M. Scott, Marysville, OH plant workers*
5   The first study of the O.M. Scott, Marysville, OH plant workers was conducted by
6   Lockey et al. (1984); see Table 4-12. Physical examination (for detection of pulmonary rales
7   and nail clubbing), pulmonary function (spirometry and DLCO), and chest x-rays were
8   performed, and information pertaining to smoking history, work history at the plant, and other
9   relevant work exposures was collected using a trained interviewer. Approximately 44% of the
10   512 workers in the study were current smokers, 20% former smokers, and 35% lifetime
11   nonsmokers, but smoking history (i.e., smoking status, pack-years) did not differ by exposure
12   group. An increased risk of costophrenic angle blunting ($n = 11$), other pleural and parenchymal
13   abnormalities ($n = 11$), or any of these outcomes ($n = 22$) was observed in relation to exposure
14   assessed by job title and area (see description of exposure groups in Section 4.1.1.2.2) and
15   categorized into groups based on the cumulative fiber estimates. The prevalence of any
16   radiographic change was 2.8% in Group I, 3.9% in Group II, and 5.8% in Group III. Using the
17   cumulative fiber metric, the prevalence of any radiographic change was 2.4% in the
18   <1 fiber/cc-yr group, 5.0% in 1−10 fibers/cc-yr group, and 12.5% in the >10 fibers/cc-yr group.
19   Lockey et al. (1984) used a modification of the ILO 1971 guidelines; one modification was that
20   costophrenic angle blunting was considered a category separate from other pleural lesions. The
21   results in Lockey et al. (1984) are presented in sufficient detail to allow interpretation according
22   to the ILO 2000 guidelines (ILO, 2002).
23   A follow-up study of this cohort was conducted in 2002−2005 (Rohs et al., 2008; see
24   Table 4-8). This study included 298 workers, of which 280 completed the study interview (with
25   work history and smoking history) and chest x-ray. The evaluation of each worker included an
26   interview to determine work and health history, pulmonary examination, and chest x-ray.
27   Exposure was estimated using the procedure previously described (Lockey et al., 1984).
28   Exposure was assumed to occur from 1963 to 1980 in this study, assuming an 8-hour workday
29   and 365 days of exposure per year (Benson, 2014). Each worker supplied a detailed work
30   history (start and end date for each area within the facility). The exposure reconstruction
31   resulted in a cumulative exposure estimate for each individual. The estimated cumulative
32   exposure for this follow-up study ranged from 0.01 to 19.03 fibers/cc-yr (mean = 2.48). The
33   time from first exposure ranged from 23 to 47 years. Exposure outside of work was assumed to
34   be zero.

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

Reference(s)	Inclusion criteria and design details			Results
Lockey ([1985](#)) Locket et al. ([1984](#))[a]	1980, $n = 512$ Three exposure groups, based on jobs and area: Mean cumulative exposure[b]			Cumulative fiber exposure related to history of pleuritic chest pain and shortness of breath. No relation between cumulative exposure and forced vital capacity, forced expiratory volume, or diffusing capacity. Costophrenic angle blunting ($n = 11$); other pleural thickening or plaques in ($n = 10$); bilateral, small opacities ($n = 1$). Abnormality (combined outcomes) increased with increasing cumulative exposure.
	Group I	0.45 fiber/cc-yr	($n = 112$)	
	Group II	1.13 fibers/cc-yr	($n = 206$)	
	Group III	6.16 fibers/cc-yr	($n = 194$)	
	Radiographs read independently by two board-certified radiologists (B Readers), with a reading by a third reader when the initial two readings did not agree. Modification of ILO 1971 classification guidelines (e.g., separated costophrenic angle blunting from other pleural thickening) (see Table 4-4 for additional details)			
Rohs et al. ([2008](#))	2002−2005, interviews and chest x-rays conducted, $n = 298$; 280 with interviews and readable chest x-rays; Three B Readers based on 2000 ILO classification guidelines (see Table 4-4 for additional details)			Pleural abnormalities in 80 workers (28.7%). Small opacities ($\geq 1/0$) in eight workers (2.9%). Increasing risk of pleural abnormalities with increasing cumulative fiber exposure: odds ratios (adjusting for age, date of hire, body mass index) by exposure quartile were 1.0 (referent), 2.7, 3.5, and 6.9.

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

1   Three board-certified radiologists, blinded to all identifiers, independently classified the
2   radiographs using the 2000 ILO classification system (ILO, 2002). Pleural thickening (all sites)
3   was reported as either localized pleural thickening or diffuse pleural thickening. Diffuse pleural
4   thickening of the chest wall was recorded on the lateral chest wall "only in the presence of and in
5   continuity with, an obliterated costophrenic angle" (ILO, 2002). Localized pleural thickening
6   was described by Rohs et al. (2008) as "…*(pleural)* thickening with or without calcification,
7   excluding solitary costophrenic angle blunting," consistent with current ILO classification.
8   Interstitial abnormalities indicative of asbestosis were considered present if the reader identified
9   irregular opacities of profusion 1/0 or greater. A chest x-ray was defined as positive for pleural
10 abnormality and/or interstitial abnormality when the median classification from the
11 three readings was consistent with such effects. Radiographs classified as unreadable were not
12 used (n not reported).
13   Pleural thickening was observed in 80 workers (28.7%), and small opacities ($\geq 1/0$) were
14 observed in 8 (2.9%). The 80 workers with pleural thickening include 68 with LPT (85%) and
15 12 with DPT (15%). Six of the eight participants with small opacities also had pleural

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1   thickening (four as LPT, two as DPT). The prevalence of pleural thickening increased across

2   exposure quartiles from 7.1% in the first quartile to 24.6, 29.4, and 54.3% in the second, third,

3   and fourth quartiles, respectively (see Table 4-9; Rohs et al., 2008).

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

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

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

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

4   Pleural thickening was strongly associated with hire on or before 1973 and age at time of

5   interview, but not with body mass index (BMI) or smoking history (ever smoked; see

6   Table 4-10); BMI is a potentially important confounder because fat pads can sometime be

7   misclassified as localized pleural thickening. A hire date of on or before 1973 and age at time of

8   interview are each highly correlated with cumulative exposure to fibers. The small number of

9   females ($n = 16$) in the cohort limits the analysis of the association with gender.

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

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

[a]*n* = 239 for BMI due to 38 persons undergoing phone interview and 3 persons with onsite interviews who were not measured for height and weight.

[b]Smoking history as recorded in 2004 questionnaire. Of these 280 participants, 20 persons reported never smoking in the 1980 questionnaire but subsequently reported a history of smoking in the 2004 questionnaire (either current or ex-smoker).

Source: Rohs et al. (2008).

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

1   There was potential coexposure to a number of herbicides, pesticides, and other

2   chemicals in the facility ([Smith, 2014](#)).[15] No quantitative information on exposure to these

3   chemicals is available. However, the addition of the other chemicals to the vermiculite carrier

4   occurred in a different part of the facility after expansion of the vermiculite ore. Industrial

5   hygiene monitoring in these areas showed very low levels of fibers in the air. In addition, none

6   of these other chemicals is volatile. Thus, it is unlikely that workers would be coexposed by

7   inhalation to these other chemicals. In addition, EPA has no information indicating that

8   exposure to any of these individual chemicals causes pleural thickening or small opacities typical

9   of those found in workers employed in the Marysville facility, and thus EPA does not consider

10   the presence of these coexposures likely to produce any confounding in the observed

11   associations between LAA exposure and the pulmonary effects seen in this cohort.

12   The [Rohs et al. (2008)](#) study demonstrates that exposure to LAA can cause radiographic

13   evidence of pleural thickening and parenchymal abnormalities (small opacities) in exposed

14   workers. The prevalence of pleural pathological alterations was 28.7% in 2004 (80/280),

15   compared to a 2% prevalence observed in 1984 (10/501). This increase in prevalence is most

16   likely due to the additional time between the two studies giving additional time for the

17   abnormalities to become apparent in conventional x-rays. The follow-up study also shows an

18   increasing prevalence of pleural thickening with increasing cumulative exposure to LAA.

19   The influence of some potential sources of selection bias in [Rohs et al. (2008)](#) is difficult

20   to qualitatively or quantitatively assess. One type of conceivable selection bias is the loss of

21   participants due to the death of 84 of the 513 (16%) workers in the first study; this group may

22   represent a less healthy or more susceptible population. Exclusion of the very sick or susceptible

23   may imply that the population of eligible participants was somewhat healthier than the whole

24   population of workers; this exclusion may result in an underestimation of risk. Another type of

25   selection is the loss due to nonparticipation among the 431 individuals identified as alive in 2004

26   ($n = 135$ refusals and nonresponders; 31%). Participation rates in epidemiologic studies can be

27   associated with better health status, and participation is often higher among nonsmokers

28   compared with smokers. This type of selection of a relatively healthier group (among the living)

29   could also result in an underestimation of the risk of observed abnormalities within the whole

30   exposed population. However, if participation was related differentially based on exposure and

31   outcome (i.e., if workers experiencing pulmonary effects and who were more highly exposed

32   were more likely to participate than the highly exposed workers who were not experiencing

---

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

1 pulmonary effects), the result would be to overestimate the exposure response relationship. This
2 latter scenario is less likely to occur for asymptomatic effects (i.e., abnormalities detected by
3 chest x-ray), such as those that are the focus of this study, than for symptoms such as shortness
4 of breath or chest pain.
5   Some information is available on differences by participation status in the Rohs et al.
6 (2008) study. Although current age was similar (mean: 59.1 and 59.4 years, respectively, in
7 participants and living nonparticipant groups, $p = 0.53$), participants were more likely to have
8 been hired before or during 1973 (66.4 and 49.7%, respectively, $p = 0.001$) and were also
9 somewhat less likely to ever be smokers (58.6%) compared with the living nonparticipants
10 (66.2%). Participants had higher mean exposure levels (mean cumulative exposure: 2.48 and
11 1.76 fibers/cc-yr, respectively, in participants and nonparticipants, $p = 0.06$), but when
12 combining living and deceased nonparticipants, there is no evidence of major differences in
13 exposure distribution in participants compared with the original full population.
14

15 **4.1.2.2.3. *Results: pathological alterations of parenchema and pleura, pulmonary function,***
16 ***and respiratory symptoms—community-based studies***
17 *Pathological alterations of parenchema and pleura*
18   In the ATSDR community health screening (ATSDR, 2001b; see Table 4-15), two
19 board-certified radiologists (B Readers) examined each radiograph, and a third reader was used
20 in cases of disagreement (see Tables 4-5 and 4-11). Readers were aware that the radiographs
21 were from participants in the Libby, MT health screening but were not made aware of exposure
22 histories and other participant characteristics (Peipins et al., 2004a; Price, 2004; Peipins et al.,
23 2003). The radiographs revealed pleural abnormalities in 17.9% of participants, with prevalence
24 increasing with increasing number of "exposure pathways" (defined on the basis of potential
25 work-related and residential exposure to asbestos within Libby and from other sources). The
26 authors noted that the relationship between number of exposure pathways and increasing
27 prevalence of pleural abnormalities was somewhat attenuated after excluding former workers
28 from the vermiculite mining and milling operations. The prevalence of pleural anomalies
29 decreased from approximately 35 to 30% in individuals with 12 or more exposure pathways
30 when these workers were excluded from the analysis. Among individuals with no defined
31 exposure pathways, the prevalence of pleural anomalies was 6.7%, which the authors report is
32 higher than reported in other population studies (Peipins et al., 2004a; Price, 2004). The direct
33 comparability between study estimates is difficult to make; the possibility of over- or under
34 ascertainment of findings from the x-rays based on knowledge of conditions in Libby was not
35 assessed in this study. No information is provided regarding analyses excluding all potential
36 work-related asbestos exposures.
37   Weill et al. (2011) used the ATSDR community health screening data to analyze the
38 prevalence of x-ray abnormalities in relation to age, smoking history, and types of exposures (see

1   Tables 4-5 and 4-11). Analysis was based on five exposure categories in $n = 4,397$ participants

2   ages 25 to 90 years. The prevalence of x-ray abnormalities (plaques, or diffuse pleural

3   thickening, and/or costophrenic angle obliteration) also generally increased with age (divided

4   into 25−40, 41−50, 51−60, and 61−90 years) within each of the exposure categories, with the

5   highest prevalence seen among former workers in the vermiculite mining and milling operations.

6   Among those with environmental exposure only (i.e., no household or occupational exposures),

7   the prevalence increased from approximately 2% at ages 41−50 years to 12% at ages

8   61−90 years.

9   The community-based study by Alexander et al. (2012) was conducted in an area other

10   than Libby, MT. The Western Minerals plant in Minneapolis, MN processed Libby vermiculite

11   ore to produce insulation material from 1939 to 1989. The plant was surrounded by residential

12   neighborhoods, and the waste material from the plant was offered to community residents for use

13   as filler in their yards and driveways. The Minnesota Department of Health and ATSDR

14   initiated a study of community exposures in 2000, including a baseline survey of

15   >6,400 residents. Residential history information was combined with period-specific air

16   dispersion models and data on facility emissions to classify the level of background exposure

17   (Kelly et al., 2006); details pertaining to the input parameters and modeling assumptions are

18   limited and result in considerable uncertainty in exposure estimates.[16] Intermittent high

19   exposures were estimated for specific activities (e.g., playing on waste piles, moving waste from

20   the plant), based on experiments reconstructing exposure occurring during these activities

21   (Adgate et al., 2011). In a follow-up study of people who had not worked in the plant (or lived

22   with a worker), measures of background exposure and activity-based (intermittent) exposure

23   were associated with increased prevalence of pleural abnormalities (Alexander et al., 2012; see

24   Table 4-11).

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[16]Based on review of supporting documentation provided by Gregory Pratt (Minnesota Department of Pollution Control).

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

Reference(s)	Inclusion criteria and design details	Results
Libby, MT community		
Peipins et al. (2003) ATSDR (2001b)	Participants in ATSDR community health screening, $n = 6,668$ with chest x-rays (see Table 4-5). 19 "exposure pathways" including Libby mining company work, contractor work, dust exposure at other jobs, vermiculite exposure at other jobs, potential asbestos exposure at other jobs or in the military, cohabitation with Libby mining company worker, and residential and recreational use of vermiculite. Pleural abnormality: (a) any unilateral or bilateral pleural calcification on the diaphragm, chest wall, or other site or (b) any unilateral or bilateral pleural thickening or plaque on the chest wall, diaphragm, or costophrenic angle site, consistent with asbestos-related pleural disease.	Peipins et al. (2003) and ATSDR (2001b): Pleural abnormalities seen in 17.9% of participants; increasing prevalence with increasing number of exposure pathways (6.7% among those with no specific pathways, 34.6% among those with 12 or more pathways). ATSDR (2001b): Moderate-to-severe FVC_1 restriction (FVC <70% predicted): 2.2% of men >17 yr old; 1.6% of women >17 yr old

Reference(s)	Inclusion criteria and design details	Exposure Source	Prevalence (%)		
				Profusion	
			≥1/0	Plaque	DPT/CAO
Weill et al. (2011)	Participants in ATSDR community health screening, $n = 4,397$ ages 25 to 90 yr (see Table 4-5). Analysis based on five exposure categories: (1) Vermiculite mining or milling workers employed directly by the company (W.R. Grace; $n = 255$), (2) other vermiculite worker (contractor work; $n = 664$), (3) dusty occupation ($n = 831$), (4) household (combination of three household categories; $n = 880$), and (5 environment ("no" to work and household exposures in Categories 1−4; $n = 1,894$). Profusion ≥1/0: defined as "any two readers reporting any profusion ≥1/0 Plaque: defined as "any two readers reporting any diaphragm or wall, or other site plaques, even if the readers did not agree on specifics. DPT or CAO: defined as "any two readers reporting any DPT or CAO, even if the readers did not agree on specifics.	*Age 25−40 ($n = 1,075$)*			
		Vermiculite worker by company	0.0	20.0	5.0
		Other vermiculite worker	0.8	0.8	0.0
		Dusty work	0.0	3.8	0.4
		Household	0.0	2.2	0.0
		Environment	0.0	0.4	0.0
		Age 41−50 ($n = 1,187$)			
		Vermiculite worker by company	0.0	26.2	5.0
		Other vermiculite worker	0.5	7.8	1.0
		Dusty work	0.0	3.8	0.9
		Household	0.0	11.1	0.4
		Environment	0.0	1.9	0.2

1

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

Reference(s)	Inclusion criteria and design details	Results			
Weill et al. (2011) (continued)			Prevalence (%)		
			Profusion		
		Exposure Source	≥1/0	Plaque	DPT/CAO
		Age 51−60 (*n* = 1,034)			
		Vermiculite worker by company	3.2	34.9	3.2
		Other vermiculite worker	0.6	13.7	0.6
		Dusty work	1.0	12.6	0.0
		Household	1.0	20.1	1.5
		Environment	0.0	7.7	0.9
		Age 61−90 (*n* = 1,101)			
		Vermiculite worker by company	11.0	45.7	8.6
		Other vermiculite worker	0.6	24.8	8.5
		Dusty work	1.1	21.9	3.3
		Household	2.4	38.3	5.7
		Environment	1.3	12.7	2.2

Minneapolis, MN community

Reference(s)	Inclusion criteria and design details	Results	
Alexander et al. (2012)	Participants with personal or family work history at the plant; 1,765 of 2,222 individuals randomly chosen within three strata based on exposure scenarios, (intense intermittent, long-term high ambient background, and low ambient background); *n* = 461completed the study. Clinical examination, chest x-rays read by 2000 ILO classification guidelines (posterior-anterior). Participants more likely than nonparticipants to report exposure-related activities (48 and 32%, respectively), but similar history of occupational asbestos exposure (28 and 27%, respectively). Exposure based on modeling by Kelly et al. (2006) and Adgate et al. (2011).		Prevalence
		Pleural abnormality (any)	49 (10.6%)
		DPT	5 (1.1%)
		LPT (referred to as "pleural plaques" by study authors	45 (9.9%)
		Regression analysis:	
		Exposure type Beta(±SE)	OR (95% CI)
		Background 0.322 (±0.125)	1.38 (1.08, 1.77)
		Intermittent 0.063 (±0.039)	1.07 (0.99, 1.15)
		Per unit increase in exposure measure; adjusted for yr of birth, history of asbestos-related job, gender, and the other exposure measure.	

SE = standard error

Respiratory symptoms

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

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1   that could result in vermiculite or dust exposure (see Tables 4-5 and 4-12). The potential for

2   vermiculite exposure outside of the workplace was classified based on responses to questions

3   about six activities (e.g., handling vermiculite insulation, playing in vermiculite piles, "popping"

4   vermiculite by heating it to make it expand). The medical history questionnaire included

5   information on three respiratory symptoms: (1) usually have a cough ($n = 108$, 10.8%);

6   (2) troubled by shortness of breath when walking up a slight hill or when hurrying on level

7   ground ($n = 145$, 14.5%); or (3) coughed up phlegm that was bloody in the past year

8   ($n = 59$, 5.9%). A question on history of physician-diagnosed lung disease ($n = 51$, 5.1%) was

9   also included. The pulmonary function results were classified as normal in 896 (90.5%),

10   obstructive in 62 (6.3%), restrictive in 30 (3.0%), and mixed in 2 (0.2%). There was little

11   variation in prevalence of shortness of breath, physician-diagnosed lung disease, or abnormal

12   spirometry across the exposure categories; for two other symptoms, the highest relative risk was

13   seen in the highest exposure group, but neither of these estimates was statistically significant

14   (OR 2.93, 95% confidence interval (CI) 0.93, 9.25 for usually having a cough and OR 1.49, 95%

15   CI: 0.41, 5.43 for coughing up bloody phlegm).

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

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

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Pathological alterations of parenchema and pleura in relation to pulmonary function

Two studies that examined LAA specifically provide insight into the question of the relation between specific types pleural or parenchymal lesions and pulmonary function (see Table 4-13). These studies, based on data from the community health screening conducted by ATSDR, reported an association between the presence of pleural plaques and a mean decrement (approximately 5%) in FVC measures (Weill et al., 2011), and of an increased risk of restrictive pulmonary function (Larson et al., 2012b). The authors of the first study (Weill et al., 2011) concluded that the change in FVC was "probably clinically insignificant." The second study (Larson et al., 2012b), focused on the likelihood of an "abnormal" pulmonary function test (restrictive lung function), rather than on a difference in the mean of the distribution. Although the association with a restrictive pulmonary function was weaker for circumscribed pleural plaques (OR = 1.4) than for DPT (OR = 4.1), increasing risk was seen with increasing size and across categories of pulmonary impairment (OR 1.7, 2.1, and 2.3, respectively, for mild, moderate and severe). These two analyses, using essentially the same data set, illustrate that the clinical perspective of an "insignificant" decrement in lung function (i.e., a small mean difference) is compatible with a population perspective of an increased risk of an adverse outcome.

4.1.2.2.4. *Clinic-based reports and case reports of respiratory disease (noncancer).*
Whitehouse (2004) examined changes in pulmonary function measures in 123 patients (86 former employees of the vermiculite operations, 27 family members of employees, 10 Libby residents with only environmental exposures) seen in a pulmonary disease practice serving the Libby, MT area. The mean age of study participants was 66 years, and the mean follow-up time was 35 months. Chest x-rays or high resolution computed tomography scans revealed no evidence of interstitial changes in 67 (55%) of the 123 patients, and 56 patients (45%) were found to have interstitial changes at profusion Category 0/1 or 1/0. The average yearly loss of pulmonary function was 2.2% for FVC, 2.3% for total lung capacity, and 3.0% for DLCO.

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

Reference(s)	Inclusion criteria and design details	Results		

Weill et al. (2011) row:

			% Predicted FVC		
Radiographic results	n	Mean	(±SE)
DPT, CAO	33	78.76	(±3.64)
Profusion ≥1/0	40	82.16	(±3.34)
Other pleural abnormality	482	95.63	(±0.76)
None of above	4,065	103.15	(±0.25)

Weill et al. (2011) — Participants in ATSDR community health screening, n = 4,397, ages 25 to 90 yr. ILO 1980 classification guidelines. Profusion ≥1/0: any two readers reporting any profusion ≥1/0. Plaque: any two readers reporting any diaphragm or wall, or other site plaques, even if the readers did not agree on specifics. DPT or CAO: defined as any two readers reporting any DPT or CAO, even if the readers did not agree on specifics.

Larson et al. (2012b) — Participants in the ATSDR community health screening, n = 6,476, ages ≥18 yr. Pulmonary function classified as normal, restrictive only (FVC < lower limit of normal and FEV_1/FVC > lower limit of normal), obstructive only, (FVC ≥ lower limit of normal and FEV_1/FVC < lower limit of normal) or mixed based on reference values for FVC and FEV_1/FVC for the U.S. population (Hankinson et al., 1999). Analysis adjusted for parenchymal abnormalities, age, gender, smoking history, BMI, exposure group, number of exposure pathways, duration of residence in Libby, and shortness of breath; referent group = "normal" pulmonary function. ILO 1980 classification guidelines modified such that plaques definition was equivalent to ILO 2000 LPT guidelines.

Radiographic results	n	Risk of restriction OR	(95% CI)
DPT, CAO	58	4.1	(2.1, 7.8)
Profusion ≥1/0	50	2.9	(1.4, 6.0)
Calcification	254	2.7	(1.2, 2.4)
Circumscribed plaques	708	1.4	(1.1, 1.8)

By index of degree of abnormality (median = 3.0 for DPT, 2.5 for LPT)

DPT Only

	n	OR	(95% CI)
≤ median	78	2.1	(1.1, 3.7)
> median	57	5.6	(2.7, 11.6)

Index of plaque size

	n	OR	(95% CI)
≤ median	562	1.3	(1.0, 1.7)
> median	499	1.9	(1.5, 2.5)

By severity of impairment, for index of plaque size > median

	n	OR	(95% CI)
Mild (FEV_1 > 70%)	63	1.7	(1.3, 2.5)
Moderate (50% ≤ FEV_1 < 69%)	50	2.1	(1.4, 3.2)
Severe (FEV_1 < 50%)	6	2.3	(0.8, 6.7)

A study by Winters et al. (2012) was conducted among patients seen for annual examinations at a clinic in Libby, MT specializing in the diagnosis and treatment of asbestos-related disease (see Table 4-14). The x-rays (posterior-anterior and lateral views) were read by one radiologist. In this clinic sample, 60 individuals were considered to have no abnormality, 182 had pleural abnormality only, 18 had interstitial abnormality, and 69 had both pleural and interstitial abnormalities. FVC was lower among those with pleural abnormalities

1 compared with the no abnormalities group, and the decrement in FEV_1 was similar for the
2 pleural and the interstitial abnormalities groups. Higher scores on the respiratory quality of life
3 scale (indicating increased impairment) were also seen in relation the presence of pleural
4 abnormalities. One limitation of this study is that the ILO classification criteria were not used
5 and a description or definition of the classification categories was not provided; in addition,
6 factors influencing the decision of residents (and past residents) to receive asbestos-related health
7 care through this clinic introduces additional challenges to the interpretation of these data.
8

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

Reference(s)	Inclusion criteria and design details	Results			
			Mean (SD), by group		
				Abnormalities	
		Normal (n = 60)	Pleural (n = 182)	Interstitial (n = 18)	Both (n = 69)
Winters et al. (2012)	Patients seen at Center for Asbestos-Related Disease clinic in Libby, MT. N = 329 (2/3 local, 1/3 distant), seen for annual examination; 70% between ages 50−69 yr. (156 other patients excluded because of missing data). Analysis of chest x-ray (diagnostic criteria not provided), pulmonary function, and respiratory health quality of life (questionnaire).	**Pulmonary function**			
		FVC	103.8 (15.0)	94.9 (20.2)[a]	95.6 (12.0)	88.8 (16.3)
		FEV_1	92.8 (21.8)	87.7 (20.0)	86.4 (16.5)	80.4 (18.6)
		FEV_1/FVC_1	94.8 (13.6)	95.9 (10.8)	94.7 (12.6)	95.6 (13.5)
		DLCO	90.2 (19.5)	85.7 (20.1)	68.1 (24.5)	73.7 (22.4)
		Respiratory symptoms and quality of life[b]			
		Total score	29.8 (20.8)	39.1 (22.5)[a]	41.3 (21.5)	43.8 (20.4)
		Symptoms	47.1 (24.2)	51.8 (25.1)	54.5 (27.0)	56.3 (23.8)
		Activity	36.5 (26.8)	49.9 (27.4)[a]	54.6 (22.3)	57.7 (23.0)
		Impact	20.1 (19.2)	28.4 (21.2)[a]	28.5 (23.4)	31.4 (21.8)

[a] $p < 0.05$ for comparison with no abnormality ("normal") group.
[b] Measured with St. George Respiratory Questionnaire; total score from 0 (better health) to 100 (worse health); symptoms = frequency and severity of respiratory symptoms; activity = activities that cause or are limited by breathlessness; impact = social function and psychological disturbances related to respiratory problems.

9   Additional studies in the form of case reports provide ancillary evidence that exposure to
10 LAA may lead to respiratory disease. Progressive disease from exposure to LAA was noted in a
11 case report of fatal asbestosis in an individual who died 50 years after working at a vermiculite
12 processing plant for a few months at about age 17 (Wright et al., 2002). In another case report,
13 exposures that stemmed from playing for a few years as a child in contaminated vermiculite
14 waste materials around a former Libby vermiculite processing facility was reportedly associated

1   with the development of asbestosis and fatal lung cancer (Srebro and Roggli, 1994). Although
2   these case reports do not provide quantitative exposure measures, they do illustrate the potential
3   for demonstrable health effects from exposures of short duration and from exposures in a
4   community setting.

5   **4.1.2.2.5. *Summary of respiratory effects, other than cancer.*** Epidemiology studies
6   demonstrate consistent results pertaining to the association between LAA exposure and various
7   forms of respiratory effects, with effects seen in worker populations and in populations with
8   residential (nonoccupational) routes of exposure. The risk of mortality related to asbestosis and
9   other forms of nonmalignant respiratory disease is elevated in the Libby vermiculite mining and
10 processing operations, with a pattern of increasing risk with increasing cumulative exposure
11 (more than a 10-fold increased risk of asbestosis and a 1.5- to 3-fold increased risk of
12 nonmalignant respiratory disease) in the analyses using internal, referent groups in McDonald et
13 al. (2004), Sullivan (2007), and Larson et al. (2010b). Radiographic evidence of small opacities
14 (evidence of parenchymal damage) and pleural thickening (pleural plaques, LPT, and DPT) has
15 also been shown in studies of Libby workers (Larson et al., 2012a; Larson et al., 2010a;
16 Whitehouse, 2004; Amandus et al., 1987a; McDonald et al., 1986b), and in the studies of
17 workers in the Marysville, OH plant (Rohs et al., 2008; Lockey et al., 1984). In the Marysville
18 cohort, the prevalence of small opacities (interstitial changes in the lung) increased from 0.2% in
19 the original study to 2.9% in the follow-up study, and the prevalence of pleural thickening
20 increased from 2 to 28.6%. No effects on lung function were found in the original study (Lockey
21 et al., 1984), and lung function was not reported for the Rohs et al. (2008) analysis of the cohort
22 follow-up. Data from the ATSDR community health screening study in Libby, MT indicate that
23 the prevalence of pleural abnormalities, identified by radiographic examination, increases
24 substantially with increasing number of exposure pathways (Peipins et al., 2003). The presence
25 of pleural plaques is associated with a small decrement in lung function (approximately 5%)
26 when evaluated based on mean values (Weill et al., 2011), and presence of LPT is associated
27 with an increased risk of restrictive lung function (Larson et al., 2012b). Additional evidence of
28 respiratory effects of LAA exposure comes from the study of residents in an area surrounding a
29 processing plant in Minneapolis, MN (Alexander et al., 2012).
30
31 **4.1.3. Other Effects, Noncancer**
32 **4.1.3.1. *Cardiovascular Disease***
33   Larson et al. (2010b) presents data on mortality due to cardiovascular diseases (CVDs)
34 among the Libby cohort of vermiculite workers, with SMRs of 0.9 (95% CI: 0.9, 1.0) for heart
35 disease ($n = 552$) and 1.4 (95% CI: 1.2, 1.6) for circulatory system diseases ($n = 258$). Deaths
36 due to heart diseases were further categorized into ischemic heart disease ($n = 247$) and other

1   heart disease (n = 120, for pericarditis, endocarditis, heart failure, and ill-defined descriptions
2   and complications of heart disease), with SMRs of 0.7 (95% CI: 0.6, 0.8) and 1.5 (95% 1.2, 1.8),
3   respectively. Circulatory diseases included hypertension without heart disease (n = 42), with an
4   SMR of 1.7 (95% CI: 1.2, 2.4) and diseases of arteries, veins, or lymphatic vessels (n = 136),
5   SMR = 1.6 (95% CI: 1.4, 2.0). The combined category of cardiovascular-related mortality
6   resulted in modestly increased risks across quartiles of exposure, with RRs of 1.0 (referent), 1.3
7   (95% CI: 1.0, 1.6), 1.3 (95% CI: 1.0, 1.6), and 1.5 (95% CI: 1.1, 2.0) with exposure groups of
8   <1.4, 1.4 to <8.6, 8.6 to <44.0, and ≥44.0 fibers/cc-yr, respectively. In the Monte Carlo
9   simulation used to estimate the potential bias in cardiovascular disease risk that could have been
10 introduced by differences in smoking patterns between exposed and unexposed workers in the
11 cohort, the bias adjustment factor was relatively small ($RR_{unadjusted}/RR_{adjusted}$ = 1.1), reducing the
12 overall RR estimate from 1.6 to 1.5. The observed association between asbestos exposure and
13 cardiovascular disease-related mortality may reflect, at least in part, a consequence of an
14 underlying respiratory disease.
15
16 **4.1.3.2. *Autoimmune Disease and Autoantibodies***
17   Three epidemiology studies have examined the potential role of LAA and autoimmunity.
18 Noonan et al. (2006) used the data from the community health screening to examine
19 self-reported histories of autoimmune diseases (rheumatoid arthritis, scleroderma, or lupus) in
20 relation to the asbestos exposure pathways described above (see Tables 4-5 and 4-15). To
21 provide more specificity in the self-reported history of these diseases, a follow-up questionnaire
22 was mailed to participants to confirm the initial report and obtain clarifying information
23 regarding the type of disease, whether the condition had been diagnosed by a physician, and
24 whether the participant was currently taking medication for the disease. Responses were
25 obtained from 208 (42%) of the 494 individuals who had reported these conditions. Of these
26 208 responses, 129 repeated the initial report of the diagnosis of rheumatoid arthritis, and
27 161 repeated the initial report of the diagnosis of one of the three diseases (rheumatoid arthritis,
28 scleroderma, or lupus); approximately 70% of those confirming the diagnosis also reported
29 taking medication for the condition. Among people aged 65 and over (n = 34 rheumatoid
30 arthritis cases, determined using responses from the follow-up questionnaire), a twofold to
31 threefold increase in risk was observed in association with several measures reflecting potential
32 exposure to asbestos (e.g., asbestos exposure in the military) or specifically to LAA (e.g., past
33 work in mining and milling operations, use of vermiculite in gardening, and frequent playing on
34 vermiculite piles when young). Restricted forced vital capacity (defined as FVC <80% predicted
35 and a ratio of FEV_1 to FVC ≥70% predicted), presence of parenchymal abnormalities, playing
36 on vermiculite piles, and other dust or vermiculite exposures were also associated with
37 rheumatoid arthritis in the group younger than 65 years (n = 95 cases). For all participants, an
38 increased risk of rheumatoid arthritis was observed with increasing number of exposure

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1   pathways. Although the information gathered in the follow-up questionnaire and repeated

2   reports of certain diagnoses decreased the false-positive reports of disease, the reliance of

3   self-reported data is a limitation of this study. Considerable misclassification (over-reporting

4   and under-reporting) is likely, given the relatively low confirmation rate of self-reports of

5   physician-diagnosed rheumatoid arthritis (and other autoimmune diseases) seen in other studies

6   (Karlson et al., 2003; Rasch et al., 2003; Ling et al., 2000).

7   Another study examined serological measures of autoantibodies in 50 residents of Libby,

8   MT, and a comparison group of residents of Missoula, MT (Pfau et al., 2005; see Table 4-16).

9   The Libby residents were recruited for a study of genetic susceptibility to asbestos-related lung

10   disease, and the Missoula residents were participants in a study of immune function. None of the

11   50 Missoula residents and three of the Libby participants reported a history of a rheumatoid

12   arthritis, systemic lupus erythematosus, or other systemic autoimmune disease (SAID). Libby

13   residents exhibited an increased prevalence (22%) of high-titer (≥1:320) antinuclear antibodies

14   when compared to Missoula residents (6%), and similar increases were seen in the Libby

15   samples for rheumatoid factor, antiribonucleoprotein (RNP), anti-Scl-60, anti-Sm, anti-Ro

16   (SSA), and anti-La (SSB) antibodies. Although neither sampling approach was based on a

17   random selection from the community residents, an individual's interest in participating in a gene

18   and lung-disease study would not likely be influenced by the presence of autoimmune disease or

19   autoantibodies in that individual. Thus selection bias would not be considered likely in this

20   study.

21   In a follow-up study, Marchand et al. (2012) examined the association of autoantibodies

22   with asbestos-related lung disease in 124 Libby residents (65 female, 59 male). Serum samples

23   were tested for the presence of antimesothelial cell antibodies (MCAA) to determine if the

24   mesothelial cells of the pleural lining are targets for autoimmune responses. Mean

25   concentrations of MCAA were increased in Libby residents, particularly in those with lung or

26   pleural lesions compared to a reference population of Missoula residents. In addition, Libby

27   residents positive for antinuclear antibodies or MCAA had an increased odds ratio of also

28   presenting with pleural abnormalities (odds ratio 3.60 and 4.88, respectively). However, the

29   cross-sectional nature of this study design makes it difficult to determine if these autoantibodies

30   were a principal mechanism for inducing pleural disease, or if their presence is an indication of

31   tissue damage.

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

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

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

1 ### 4.1.4. Cancer Effects

2 ### 4.1.4.1. *Lung Cancer*

3   Several analyses of the mortality experience of Libby vermiculite workers have been

4 conducted (see Section 4.1.1 for a summary of exposure measures and cohort descriptions for

5 these studies). The studies of the Libby worker cohort by Amandus and Wheeler (1987),

6 Sullivan (2007), and Larson et al. (2010b) defined lung cancer mortality based on a more

7 specific cause of death codes (e.g., cancers of the trachea, bronchus, and lung) compared to the

8 broader classification of "all respiratory cancer" used by McDonald et al. (2004; 1986a), which

9 would include laryngeal and "other" respiratory cancers. In the national Surveillance,

10 Epidemiology, and End Results cancer data from 2003−2007, the age-adjusted mortality rate for

11 cancer of the larynx was 1.2 per 100,000 person-year, compared to 52.5 per 100,000 person-year

12 for lung and bronchial cancer (NCI, 2011). Thus, these additional categories (larynx and "other"

13 respiratory cancers) represent a relatively small proportion of respiratory cancers. Although they

14 could also be a source of some misclassification of the outcome if these other cancers are not

15 related to asbestos exposure, the magnitude of this bias would be small.

16   In the more recent study by McDonald et al. (2004), 44 respiratory cancers were observed

17 among 406 men who had worked at least 1 year in the vermiculite mining and milling facilities.

18 Sullivan (2007) and Larson et al. (2010b) included workers with less than 1 year of work,

19 resulting in a larger sample size (approximately 1,700) and more than 80 lung cancer deaths.

20 Each of these studies observed an increased overall risk, with SMRs of 1.4, 16, and 2.4,

21 respectively in Sullivan (2007), Larson et al. (2010b), and McDonald et al. (2004).

22 Exposure-response analyses from these studies demonstrated increasing mortality with

23 increasing exposure, using categorical and continuous measures of exposure, different lag

24 periods, and different exposure metrics, with approximately a twofold to threefold increased risk

25 in the highest exposure group (see Table 4-16 and Figure 4-3).

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

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

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

Reference(s)	Inclusion criteria and design details	Standardized mortality ratio (95% CI)	Exposure-response analyses—lung cancer			
McDonald et al. (2004; 1986a)	Men, hired before 1963, worked at least 1 yr ($n = 406$); follow-up through 1999 (McDonald et al., 2004); 165 deaths before July 1983 (163 with death certificates); 120 deaths July 1983−1998 coded by nosologists using ICD-8 classifications; cause of death for deaths from 1983−1998 obtained from National Death Index. Mean duration: 8.7 yr Mean fiber-yr: 144.6	Respiratory ($n = 44$) SMR: 2.4 (1.7, 3.2)	*Excluding first 10 yr of follow-up:*			
			Cumulative exposure	n	RR (95% CI)[d]	
			0.0−11.6 fibers/cc-yr	5	1.0 (referent)	
			11.7−25.1 fibers/cc-yr	9	1.7 (0.58, 5.2)	
			25.2−113.7 fibers/cc-yr	10	1.9 (0.63, 5.5)	
			≥113.8 fibers/cc-yr	16	3.2 (1.2, 8.8)	
			per 100 fibers/cc-yr increase (linear model, RR = 1 + b*exposure) 0.36 (0.03, 1.2) ($p = 0.02$) Similar patterns were reported for analyses of intensity and residence-weighted exposure, but results not presented in paper.			
Sullivan (2007)	White men, enumerated in 1982, alive in 1960 or hired after 1960, worked at least 1 d, follow-up 1960−2001 ($n = 1,672$); 767 deaths (95% with known cause of death) Mean duration: 4.0 yr (808, ~50% worked less than 1 yr) Median fibers/cc-yr: 8.7 Underlying cause of death data from death certificates or National Death Index-Plus.	*15-yr exposure lag:* All cancer ($n = 202$) SMR: 1.4 (1.2, 1.6) Lung ($n = 89$) SMR: 1.7 (1.4, 2.1)	*15-yr exposure lag:*			
			Cumulative exposure	n	SMR (95% CI)[b]	SRR (95% CI)[c]
			0.0−4.49 fibers/cc-yr	19	1.5 (0.9, 2.3)	1.0 (referent)
			4.5−22.9 fibers/cc-yr	24	1.6 (1.1, 2.5)	1.1 (0.6, 2.0)
			23.0−99.0 fibers/cc-yr	23	1.8 (1.1, 2.7)	1.4 (0.7, 2.7)
			≥100 fibers/cc-yr	23	1.9 (1.2, 2.9)	1.5 (0.8, 2.8)
			Linear trend test			($p < 0.001$)
			Duration	n	SMR (95% CI)[b]	SRR (95% CI)[c]
			<1 yr	41	1.6 (1.1, 2.1)	1.0 (referent)
			1−9.9 yr	34	1.7 (1.1, 2.3)	1.1 (0.7, 1.8)
			≥10 yr	14	2.5 (1.4, 4.3)	1.8 (0.9, 3.4)

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

Reference(s)	Inclusion criteria and design details	Standardized mortality ratio (95% CI)	Exposure-response analyses—lung cancer			
Larson et al. (2010b)	Inclusion criteria not described ($n = 1,862$); follow-up through 2006; 952 deaths (80% with known cause of death). Median duration: 0.8 yr Median fibers/cc-yr = 4.3 Immediate and underlying cause of death data (i.e., multiple cause of death) from death certificates or National Death Index-Plus.	Lung ($n = 104$) SMR: 1.6 (1.3, 2.0)	*20-yr exposure lag:*			
			Cumulative exposure	n	SMR (95% CI)[b]	RR (95% CI)[e]
			0.0−<1.4 fibers/cc-yr	19	(not reported)	1.0 (referent)
			1.4 to <8.6 fibers/cc-yr	20	(not reported)	1.1 (0.6, 2.1)
			8.6 to <44.0 fibers/cc-yr	21	(not reported)	1.7 (1.0, 3.0)
			≥44.0 fibers/cc-yr	38	(not reported)	3.2 (1.8, 5.3)
			Per 100 fibers/cc-yr increase			1.11 (1.05, 1.18)
						($p = 0.006$)

[a]Includes miners, millers, and processors; workers in the screening plant, loading docks, and expansion plants; and office workers.
[b]SMR based on external referent group.
[c]In Sullivan (2007), the SRR is a ratio of sums of weighted rates in which the weight for each stratum-specific rate is the combined person-yr for the observed cohort across all duration (or cumulative level of exposure) categories. The Life Table Analysis System provides the SRR for each duration (or cumulative level of exposure) group compared to the referent group. The cutoff points for the categories are specified by the user. Taylor-series-based confidence intervals are given for each specific SRR.
[d]In McDonald et al. (2004), the RR is based on Poisson analysis using an internal referent group.
[e]In Larson et al. (2010b), the RR is based on Cox proportional hazards modeling using an internal referent group.
SMR = standardized mortality ratio; CI = confidence interval; SRR = standardized rate ratio; RR = relative risk.
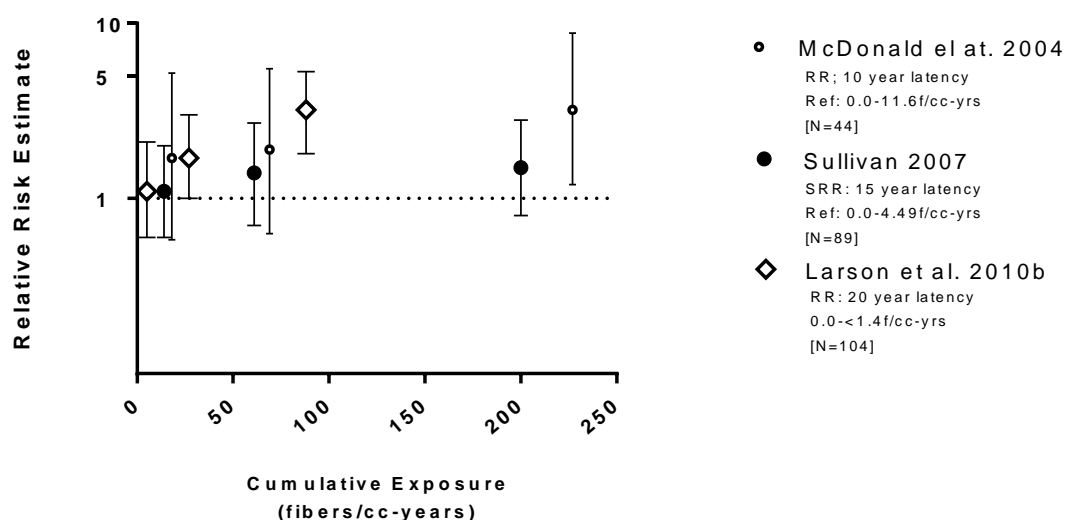
Figure 4-3. Lung cancer mortality risk among workers in the Libby, MT vermiculite mine and mill workers. Data from the three studies with updated follow-up (through 1998, 2001, and 2006, respectively, in McDonald et al. (2004), Sullivan (2007), and Larson et al. (2010b). Size of symbols is proportional to number of observed cases. Midpoint of the highest exposure category in each group is estimated as twice the value of the lower cut-point.

1   Two of these studies included data addressing the question of the extent to which the
2   results could be confounded by smoking (Larson et al., 2010b; Amandus and Wheeler, 1987).
3   Amandus and Wheeler (1987) provide some information on the smoking history of a sample of
4   161 male workers employed during 1975−1982 with at least 5 years of employment in the Libby
5   cohort study and comparison data based on surveys conducted in the United States from
6   1955−1978. Among the workers, 35% were current smokers and 49% were former smokers.
7   This smoking information was obtained from questionnaires the company administered to
8   workers after 1975. Assuming the definitions are similar to those of the national surveys, the
9   prevalence of current smokers is similar in the worker cohort compared to the U.S. white male
10   population data (ranging from 37.5−41.9% current smokers between 1975 and 1978). The only
11   year in this range with data on former smokers in the national survey is 1975, and at that time,
12   the prevalence of former smokers in the population data was 29.2%, about 20% lower than
13   among the workers. Using an estimated RR of lung cancer of 14 among smokers, Amandus and
14   Wheeler (1987) estimated that the difference in smoking rates between workers and the
15   comparison population could have resulted in a 23% increase in the observed risk ratio and
16   commented that the increased risk observed in the lower dose range (<50 fiber-year) could be the
17   result of confounding by smoking status.
18   Smoking patterns in the U.S. population changed considerably over the period
19   corresponding to the data reported by Amandus and Wheeler (1987). In the National Health

1   Interview Surveys conducted between 1974 and 1983, the prevalence of smoking in males

2   age 20 and older decreased from 42.1 to 35.5% (HHS, 1990). In addition, the prevalence of

3   former smokers can depend on the definition used. Based on 1986 survey data, the percentage of

4   adults age 17 and older classified as former smokers varied between 14.7 and 25.8% using

5   different definitions for time since last smoked (e.g., from quitting 5 or more years ago to

6   quitting within the past 3 months; HHS, 1990). Thus, given the lack of information pertaining to

7   the period in which smoking information was collected and the specifics of the sources that were

8   used, EPA concludes there is considerable uncertainty regarding the evidence for differences in

9   smoking rates between the workers and the external comparison population.

10   Larson et al. (2010b) used data from the ATSDR community health screening in Libby

11 (described in Section 4.1.1.3) pertaining to smoking history to estimate that the proportion of

12 smokers ranged from 50 to 66% in the unexposed group (defined as exposure <8.6 fibers/cc-yr)

13 and between 66 and 85% among the exposed (defined as ≥8.6 fibers/cc-yr). Larson et al.

14 (2010b) used these estimates in a Monte Carlo simulation to estimate the potential bias in lung

15 cancer risks that could have been introduced by differences in smoking patterns. The bias

16 adjustment factor ($RR_{unadjusted}/RR_{adjusted} = 1.3$) reduced the overall RR estimate for lung cancer

17 from 2.4 to 2.0.

18

19 *O.M. Scott, Marysville, OH plant workers*

20   There was no evidence of an increased risk of lung cancer in the analysis of mortality

21 among the 465 Marysville, OH plant workers (Dunning et al.). The SMR was 0.9 (95%

22 CI: 0.5−1.5), based on 16 observed lung cancer deaths, and there was no indication of an

23 increased risk in analyses stratifying by tertiles of cumulative exposure (SMRs varying between

24 0.8 and 1.0, and standardized rate ratios (SRRs) varying between 0.9 and 1.0).

25

26 *Geographic mortality analysis*

27   In the geographic mortality analysis (1979−1998) conducted by ATSDR (2000), the

28 SMR for lung cancer ranged from 0.9−1.1 and 0.8−1.0 for each of the six geographic boundaries

29 using Montana and U.S. reference rates, respectively. These analyses did not distinguish

30 between deaths among workers and deaths among other community members.

31

32 **4.1.4.2. *Mesothelioma***

33   Prior to the 10th revision of the ICD, which was implemented in the United States in

34 1999, there was no unique ICD code for mesothelioma. The updated NIOSH study by Sullivan

35 (2007) identified 15 deaths for which mesothelioma was mentioned on the death certificate.

36 Only two of these deaths occurred between 1999 and 2001, which were coded using the ICD-10

37 mesothelioma coding (C45). Larson et al. (2010b) classified all death certificates listing

38 mesothelioma as ICD-10 code C45. The updated McGill study (McDonald et al., 2004; with

1   analysis through 1998) noted that the classification of mesothelioma was based on a nosologist's
2   review of death certificates; only 5 of the 12 cases classified as mesothelioma had a cause of
3   death listed as pleural cancer (ICD-9 code 163).
4   Data pertaining to mesothelioma risk from the available occupational studies are
5   summarized in Table 4-17. McDonald et al. (2004) presented dose-response modeling using
6   Poisson regression of mesothelioma risk based on 12 cases. Note that the referent group was
7   also at excess risk of dying from mesothelioma; that is, one to three cases of mesothelioma were
8   observed in the referent group, depending on the exposure index. Three exposure indices were
9   used in the analysis: average intensity over the first 5 years of employment, cumulative
10   exposure, and residence-weighted cumulative exposure. Because of the requirement for 5 years
11   of employment data, 199 individuals (including three mesothelioma cases) were excluded from
12   the analysis of average intensity. The residence-weighted cumulative exposure was based on the
13   summation of exposure by year, weighted by years since the exposure. This metric gives greater
14   weight to exposures that occurred a longer time ago. Although evidence of an excess risk of
15   dying from mesothelioma was seen in all groups, only the residence-weighted cumulative
16   exposure metric exhibited a monotonically increasing pattern, with an RR of 1.57 among those
17   with 500.1−1,826.8 fibers/cc-yr exposure, and an RR of 1.95 among workers with higher
18   residence-weighted cumulative exposure. In the study by Sullivan (2007), which identified
19   15 deaths from mesothelioma through a manual review of death certificates, the SMR for
20   mesothelioma was 14.1 (95% CI: 1.8, 54.4), based on the two mesothelioma deaths occurring
21   between 1999 and 2001, the period for which comparison data using the ICD-10 classification
22   criteria were available.

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

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

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

Reference(s)	Inclusion criteria and design details	Results		

Sullivan (2007)	White men, enumerated in 1982, alive in 1960 or hired after 1960, worked at least 1 d, follow-up 1960−2001 ($n = 1,672$); 767 deaths (95% with known cause of death)
	Mean duration: 4.0 yr (808, ~50% worked less than 1 yr)
	Median fibers/cc-yr: 8.7
	Underlying cause of death data from death certificates or National Death Index-Plus. SMR analysis limited to 1999−2001 because this is the period for which comparison data from ICD-10 are available.
		15 mesothelioma deaths observed; 2% of all deaths
		$N = 2$ for 1999−2001:
		  SMR: 15.1 (95% CI: 1.8, 54.4)
		Pleural ($n = 4$)
		  SMR: 23.3 (95% CI: 6.3, 59.5)		

Larson et al. (2010b)	Inclusion criteria not described ($n = 1,862$); follow-up through 2006; 952 deaths (80% with known cause of death). Median duration: 0.8 yr 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		
		20-yr exposure lag:		
		Cumulative exposure	n	RR (95% CI)[c]
		<1.4 fibers/cc-yr	1	1.0 (referent)
		1.4 to <8.6 fibers/cc-yr	2	1.9 (0.31, 13.6)
		8.6 to <440 fibers/cc-yr	5	4.5 (0.8, 24.6)
		≥44.0 fibers/cc-yr	11	17.1 (3.7, 78.1)
		per 100 fibers/cc-yr increase		1.15 (1.03, 1.28)
				($p = 0.0134$)

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

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

1   pathology reports were obtained for 10 of the 11 patients. The Centers for Disease Control and

2   Prevention estimated the death rate from mesothelioma, using 1999 to 2005 data, as

3   approximately 14 per million per year (CDC, 2009), approximately three to four times lower

4   than the Libby-area rate estimated by EPA using the observation of seven cases without known

5   personal or familial occupational exposure, over a 15-year observation period and an estimated

6   Libby area (Lincoln Country) population of 9,500 (142,000 person-year). Whitehouse et al.

7   (2008) stated that a W.R. Grace unpublished report of measures taken in 1975 indicated that

8   exposure levels of 1.1 fibers/cc were found in Libby, and 1.5 fibers/cc were found near the mill

9   and railroad facilities. Because the mining and milling operations continued to 1990, and

10   because of the expected latency period for mesothelioma, Whitehouse et al. (2008) suggested

11   that additional cases can be expected to occur within this population, as well as in transitory

12   workers and in workers who had left the area.

13

14   **4.1.4.2.1. *O.M. Scott, Marysville, OH plant workers.*** In the analysis of mortality among the

15   Marysville, OH plant workers, 2 of the 465 workers died of mesothelioma compared to an

16   expected 0.2 cases (SMR 10.5, 95% CI 1.3, 38; Dunning et al., 2012). The cumulative exposure

17   for each of these two cases was approximately 45 fibers/cc-yr. One other incident mesothelioma

18   case was identified in the cohort. This case was alive at the time of the study, and so is not

19   included in the mortality analysis, but the cumulative exposure of the individual was

20   5.73 fibers/cc-yr.

21

22   **4.1.4.3. *Other Cancers***

23   Larson et al. (2010b) presented data on cancers other than respiratory tract and

24   mesothelioma. The category of malignant neoplasms of digestive organs and peritoneum

25   included 39 observed deaths, for an SMR of 0.8 (95% CI: 0.6, 1.1). No risk in relation to

26   asbestos exposure was seen with a 20-year lag.

27

28   **4.1.4.4. *Summary of Cancer Mortality Risk in Populations Exposed to Libby Amphibole***
29   ***Asbestos***

30   The studies conducted in the 1980s (Amandus and Wheeler, 1987; McDonald et al.,

31   1986a) as well as the extended follow-up studies published in more recent years (Larson et al.,

32   2010b; Sullivan, 2007; McDonald et al., 2004) provide consistent evidence of an increased risk

33   of lung cancer mortality and of mesothelioma mortality among the workers in the Libby

34   vermiculite mining and processing operations. The lung cancer analyses using an internal

35   referent group in the larger follow-up studies (Larson et al., 2010b; Sullivan, 2007; McDonald et

36   al., 2004) observed increasing risks with increasing cumulative exposure when analyzed using

37   quartiles or as a continuous measure. Increased risks are also seen in the studies reporting

38   analyses using an external referent group (i.e., standardized mortality ratios; Sullivan, 2007;

1   Amandus and Wheeler, 1987; McDonald et al., 1986a). Although an increased lung cancer risk

2   was not observed in the Marysville, OH plant workers, three cases of mesothelioma (two of

3   which resulted in death) have been identified as of June, 2011. These observations further

4   support the identification of cancer (specifically, lung cancer and mesothelioma) as a hazard of

5   LAA.

6

7   **4.1.5. Comparison With Other Asbestos Studies—Environmental Exposure Settings**

8   The literature pertaining to risks of asbestos is extensive; of particular interest is the set of

9   studies examining environmental exposures to constituents of LAA (e.g., tremolite) or other

10 amphiboles. This literature provides findings consistent with those identified for LAA.

11   Several communities have been exposed in environmental or residential settings to

12 tremolite or tremolite-chrysotile mixtures from natural soils and outcroppings as well as

13 construction materials found in the home (see Table 4-18). Studies on these affected populations

14 (published as early as 1979) reported an increased risk of pleural and peritoneal malignant

15 mesothelioma (Sichletidis et al., 1992b; Baris et al., 1987; Langer et al., 1987; Baris et al., 1979).

16 Clinical observations include a bilateral increase in pleural calcification accompanied by

17 restrictive lung function decrements as the disease progresses, a condition known as "Metsovo

18 lung," named after a town in Greece (Constantopoulos et al., 1985). These health effects are

19 consistent with the health effects documented for workers exposed to commercial forms of

20 asbestos.

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

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

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

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

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

1   Although it is not a constituent of LAA, crocidolite is another type of amphibole asbestos
2   that has been studied with respect to health effects arising from environmental exposures.
3   Several studies have examined cancer risk and pneumoconiosis risk among nonworker residents
4   of Wittenoom, Australia, an area surrounding a crocidolite asbestos mine and mill (Reid et al.,
5   2007; Hansen et al., 1998; see Table 4-18). Increased risk of mesothelioma and pneumoconiosis
6   and more modestly increased risk of lung cancer were reported in these studies.

7   **4.2. SUBCHRONIC- AND CHONIC-DURATION STUDIES AND CANCER**
8   **BIOASSAYS IN ANIMALS—ORAL, INHALATION, AND OTHER ROUTES OF**
9   **EXPOSURE**

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

1 summarized below to potentially increase understanding of the effects and mechanisms of LAA.

2 Detailed study summaries can be found in Appendix D and summarized in Tables 4-19 and 4-20.

3 As noted in Section 3, the primary route of human exposure is inhalation. Thus, studies that

4 expose animals through a pulmonary route are the most relevant for hazard identification. No

5 inhalation studies have been performed for LAA, but chronic intrapleural injection studies in

6 hamsters demonstrate carcinogenicity following exposure. The chronic inhalation and

7 intrapleural injection laboratory animal studies with tremolite asbestos demonstrated pleural

8 pathology and carcinogenicity in rats. These studies support the epidemiology studies of LAA

9 exposure (see Section 4.1) and aid in informing the mechanisms of LAA-induced disease.

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

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

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

Species (gender)	Exposure route	Fiber type	Mean fiber length	Mean fiber diameter	Effects[a]	Reference
SH (M) (n = 8/group)	Intratracheal instillation (once) 4 h, 1 d 1.0 mg DEF; 21 µg FeCl₃; 0.5 mg LAA, 0.5 mg FeLAA; 0.5 mg LAA + 1 mg DEF in 300 µL saline	LAA (Six Mix)	5.0 ± 4.5 µm	0.29 ± 0.19 µm	Statistically significant increases in neutrophils was observed in BALF in animals exposed to LAA, FeLAA, and LAA + DEF with the greatest increase observed in the LAA + DEF animals.	Shannahan et al. (2011b)
Fischer 344 rats (M) (n = 8/group)	Intratracheal instillation (once) 1 d, 3 d, 7 d, 2 wk, 3 mo 0.65 or 6.5 mg/rat LAA; 0.65 mg amosite in 250 µL saline	LAA (Six Mix) Amosite	5.0 ± 4.5 µm	0.29 ± 0.19 µm	Statistically significant increases in inflammatory markers were observed following exposure to LAA and amosite, including increased neutrophils and inflammatory gene expression, with the greatest increase in amosite-exposed rats.	Padilla-Carlin et al. (2011)

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

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

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

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

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

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

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

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

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

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

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

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

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

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

4.2.1. Inhalation

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

1   observed in the controls. These results show that Wistar rats exposed to tremolite exhibited

2   increased numbers of pulmonary lesions and possibly tumors.

3

4   **4.2.2. Intratracheal Instillation Studies**

5   Intratracheal instillation has been used to examine the effect of exposure to Libby

6   Amphibole (Cyphert et al., 2012b; Cyphert et al., 2012a; Shannahan et al., 2012a; Shannahan et

7   al., 2012c; Shannahan et al., 2012b; Shannahan et al., 2012d; Padilla-Carlin et al., 2011;

8   Shannahan et al., 2011a; Shannahan et al., 2011b; Smartt et al., 2010; Putnam et al., 2008) and

9   tremolite asbestos (Blake et al., 2008; Pfau et al., 2008; Sahu et al., 1975). These studies

10 exposed C57Bl/6 mice (100 μg/mouse), Wistar-Kyoto (WKY) rats (0.25 or 1 mg/rat) or Fischer

11 344 rats (0.25 or 6.5 mg/rat) once to LAA and analyzed the results up to 2 years postexposure.

12 Putnam et al. (2008) observed statistically nonsignificant increases in collagen following

13 exposure to LAA, as well as gene expression alterations related to membrane transport, signal

14 transduction, epidermal growth factor signaling, and calcium regulation. Smartt et al. (2010)

15 followed up this study by analyzing specific genes by quantitative reverse transcription

16 polymerase chain reaction for genes involved in collagen accumulation and scar formation

17 (Col1A1, Col1A2, Col3A1). LAA exposure led to increased gene expression of Col1A2 at

18 1 week postinstillation and Col3A1 at 1 month postexposure. Both studies observed increased

19 inflammation; however, LAA exposure demonstrated minimal inflammation that did not

20 progress in the time points examined. These studies demonstrate that exposure to LAA may lead

21 to inflammation and fibrosis.

22   Shannahan et al. (2011a) exposed two rat models of human cardiovascular disease to

23 LAA to determine if the preexisting CVD in these models would impact the lung injury and

24 inflammation following exposure. Healthy WKY rats were compared to spontaneously

25 hypertensive (SH) and spontaneously hypertensive-heart failure (SHHF) rats following exposure.

26 All rats (male only) were exposed to 0, 0.25, or 1.0 mg/rat via intratracheal instillation and were

27 examined at 1 day, 1 week, and 1 month postexposure. No changes were observed

28 histopathologically; however, changes were observed in markers of homeostasis, inflammation,

29 and oxidative stress. While inflammation and cell injury were observed in all strains, no

30 strain-related differences were observed following exposure to LAA (Shannahan et al., 2011a).

31   A series of studies further examined SH, SHHF, and WKY rats over several durations of

32 exposure to identify potential biomarkers of LAA exposure and determine if asbestos exposure

33 shifts biomarker expression in healthy rats to resemble CVD (Shannahan et al., 2012a;

34 Shannahan et al., 2012d). Acute-phase response molecules involved in inflammatory responses

35 such as α2-macroglobulin and α1-acid glycoprotein, as well as the metabolic molecule

36 lipocalin-2 were generally increased 1 day after exposure regardless of duration (Shannahan et

37 al., 2012a). In addition, LAA generally did not change biomarker expression similarly to the

38 CVD rat strains (Shannahan et al., 2012b). However, the expression of two vasoconstriction

1   genes, eNOS and ETR-A, were altered in Libby Amphibole-exposed WKY rats to resemble

2   untreated SH and SHHF rats (Shannahan et al., 2012b). Biomarkers for cancer were largely

3   unaffected in all three strains following LAA exposure (Shannahan et al., 2012a).

4   In a follow-up study to further examine the role of iron in the inflammatory response to

5   LAA exposure, Shannahan et al. (2011b) exposed SH rats to LAA alone and with bound Fe as

6   well as with an iron chelator (deferoxamine [DEF]). Exposure to LAA led to significant

7   increases in inflammatory markers (e.g., neutrophils, interleukin [IL]-8) with the greatest

8   increase occurring in the presence of DEF. Iron bound to LAA was not released following

9   instillation except in the presence of DEF as supported by the lack of increase of iron in

10   bronchoalveolar lavage fluid (BALF). These results suggest that chelation of iron bound to LAA

11   as well as endogenous proteins increases the toxicity of LAA in vivo.

12   A pair of studies further examined the effect of iron in the context of Libby

13   Amphibole-induced lung injury and inflammasome activation. DEF treatment in addition to

14   LAA significantly affected cyclooxygenase-2 (COX-2), IL-6, and CCL-11 in lung tissue

15   compared to LAA treatment alone (Shannahan et al., 2012c). Addition of iron to LAA

16   significantly altered NF-kβ and IL-1β compared to LAA alone (Shannahan et al., 2012c).

17   However, iron overload and DEF treatment generally were not significantly changed from each

18   other, suggesting that iron has little impact on the inflammasome cascade. Histological

19   examination and gene array analysis of inflammatory genes in WKY, SH, and SHHF rats did not

20   identify significant differences in the progression of pulmonary fibrosis between the three strains

21   (Shannahan et al., 2012d). These data do not indicate that the iron overload conditions that are

22   characteristic of the cardiovascular disease-rat strains amplify the pulmonary effects of LAA.

23   Padilla-Carlin et al. (2011) exposed Fischer 344 rats (male only) to LAA (0.65 or 6.5 mg/rat) or

24   amosite (0.65 mg/rat; positive control) by intratracheal instillation to examine inflammatory

25   response for 3 months postexposure. LAA exposure led to statistically significant increases of

26   neutrophils in BALF as early as 1 day postexposure, with other inflammatory markers (e.g.,

27   protein, lactate dehydrogenase [LDH], gamma-glutamyl transpeptidase [GGT]) increased

28   statistically significantly at different time points during the 3-month-period postexposure.

29   However, on a mass basis, amosite produced a greater inflammatory response as measured by

30   inflammatory markers (e.g., neutrophil influx, gene expression changes) and histopathological

31   analysis demonstrating interstitial fibrosis. Examination of male Fischer 344 rats from this study

32   at 2 years postexposure demonstrated that LAA induced a significant fibrogenic (but not

33   carcinogenic) effect (Cyphert et al., 2012b). Response to LAA exposure in this study was less

34   potent than amosite on a mass basis. Further comparison of LAA to other fiber types (Sumas

35   Mountain chrysotile [SM], El Dorado tremolite [ED], and Ontario ferroactinolite [ON])

36   demonstrated that LAA exposure increased inflammatory markers at 1 day postexposure which

37   returned to control levels by 3 months (Cyphert et al., 2012a). LAA exposure also led to an

38   increased fibrogenic response at 3 months postexposure. As compared to other fibers tested,

1   fibrogenic response was correlated with the fiber length and width of each fiber, with

2   SM-exposed rats demonstrating the greatest fibrogenic response (SM > LAA > ON > ED).

3   These studies demonstrate a statistically significant increase in inflammatory response to LAA in

4   mice and rats as measured in BALF by cytology, histopathology, and gene expression analysis.

5   Follow-up studies are needed to inform the chronic effects of exposure to LAA.

6   Laboratory animal studies of tremolite intratracheal instillation exposure have been

7   performed in mice in doses ranging from 60 μg to 5 mg. Male Swiss albino mice exposed to

8   tremolite (5 mg) via intratracheal instillation demonstrated histological changes (Sahu et al.,

9   1975). Microscopic results following exposure to tremolite showed acute inflammation of the

10 lungs at 7 days postexposure, including macrophage proliferation and phagocytosis similar to

11 that observed with amosite and anthophyllite. Limited progression of fibrotic response was

12 observed at 60 and 90 days postexposure, with no further progression of fibrotic response.

13

14 **4.2.3. Injection/Implantation Studies**

15   There are no laboratory animal studies examining intraperitoneal injection or

16 implantation of LAA. Biological effects following exposure to tremolite have been examined in

17 five intraperitoneal injection studies (Roller et al., 1997, 1996; Davis et al., 1991; Wagner et al.,

18 1982; Smith et al., 1979; Smith, 1978) and one implantation study (Stanton et al., 1981).

19   Studies by Smith and colleagues (Smith et al., 1979; Smith, 1978), Wagner et al. (1982),

20 Davis et al. (1991), and Roller et al. (1997, 1996) demonstrated that intrapleural injections of

21 tremolite asbestos[17] is associated with an increase in pleural fibrosis and mesothelioma in

22 hamsters and rats compared to controls or animals injected with less fibrous materials. Doses

23 ranged from 10−25 mg/animal for each study, and although carcinogenesis was observed in these

24 studies, there was a variable level of response to the different tremolite forms examined.

25 Although these studies clearly show the carcinogenic potential of Libby Amphibole or tremolite

26 asbestos fibers, intrapleural injections bypass the clearance and dissolution of fibers from the

27 lung after inhalation exposures. Further, limited information was provided confirming the

28 presence or absence of particles or fibers less than 5 μm in length in these studies, limiting the

29 interpretation of results.

30   One laboratory animal study examined the effect of tremolite exposure following

31 implantation of fibers in the pleural cavity. Stanton et al. (1981) examined tremolite and

32 described a series of studies on various forms of asbestos. Fibers embedded in hardened gelatin

33 were placed against the lung pleura. As an intrapleural exposure, results might not be

34 comparable to inhalation exposures, as the dynamics of fiber deposition and pulmonary

35 clearance mechanisms are not accounted for in the study design. Studies using two tremolite

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

asbestos samples from the same lot were described as being in the optimal size range for carcinogenesis; the fibers were distinctly smaller in diameter than the tremolite fibers Smith et al. (1979) used. These samples both had a high number of fibers in the size range (>8-μm long and <0.25 μm in diameter; i.e., "Stanton fibers"). Exposure to both tremolite samples led to mesotheliomas in 21 and 22 of 28 rats exposed. The Stanton et al. (1981) study also used talc, which did not lead to mesothelioma production.

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

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

4.2.4. Oral

No studies in laboratory animals with oral exposure to Libby Amphibole were found in the literature. However, one chronic cancer bioassay was performed following oral exposure to tremolite. McConnell et al. (1983a) describe part of a National Toxicology Program study (NTP, 1990b) performed to evaluate the toxicity and carcinogenicity of ingestion of several minerals, including tremolite. The tremolite (Governeur Talc Co, Governeur, NY) used was not fibrous. No significant tumor induction was observed in the animals with oral exposure to tremolite animals. Although nonneoplastic lesions were observed in many of the aging rats, these were

1   mostly in the stomach and occurred in both controls and exposed animals. The observed lesions

2   included chronic inflammation, ulceration, and necrosis of the stomach (McConnell et al.,

3   1983a). McConnell et al. (1983a) suggested that nonfibrous nature of this tremolite sample

4   could account for the lack of toxicity following exposure in this group of animals. Also, oral

5   studies of asbestos, in general, show decreased toxicity and carcinogenicity as compared to

6   inhalation and implantation/injection studies (Condie, 1983).

7

8   **4.2.5. Summary of Animal Studies for Libby Amphibole and Tremolite Asbestos**

9   Tables 4-19 and 4-20 summarize the studies described in this section, with full study

10   details available in Appendix D. Limited in vivo studies have been performed exposing

11   laboratory animals to LAA. One intrapleural injection study using tremolite from the Libby, MT

12   area is included in this section under LAA since earlier terminology for LAA was often tremolite

13   (Smith, 1978). Hamsters in this study exposed to LAA developed fibrosis and mesothelioma

14   following exposure. Intratracheal instillation studies of LAA in rats showed increased collagen

15   gene expression at 2-years postexposure (Cyphert et al., 2012a). Subchronic-duration studies in

16   mice (Smartt et al., 2010; Putnam et al., 2008) demonstrated gene and protein expression

17   changes related to fibrosis production following exposure to LAA. Finally, short-term-duration

18   studies in rats demonstrated an increase in inflammatory and cardiovascular disease markers

19   following exposure to LAA (Padilla-Carlin et al., 2011; Shannahan et al., 2011a; Shannahan et

20   al., 2011b).

21   Because tremolite is part of LAA, results from tremolite studies were also described. In

22   general, fibrous tremolite has been shown to cause pulmonary inflammation, fibrosis, and/or

23   mesothelioma or lung cancer in rats (Bernstein et al., 2005; Bernstein et al., 2003; Davis et al.,

24   1991; Davis et al., 1985; Wagner et al., 1982) and hamsters (Smith et al., 1979). The single

25   short-term-duration study on mice showed limited response to tremolite (Sahu et al., 1975). The

26   one chronic-duration oral study (McConnell et al., 1983a) did not show increased toxicity or

27   carcinogenicity; this study, however, used only nonfibrous tremolite, which later studies showed

28   to be less toxic and carcinogenic than fibrous tremolite (Davis et al., 1991).

29   Chronic inflammation is hypothesized to lead to a carcinogenic response through the

30   production of reactive oxygen species and increased cellular proliferation (Hanahan and

31   Weinberg, 2011). Although limited, the data described in Section 4.2 suggest an increase in

32   inflammatory response following exposure to LAA and tremolite asbestos similar to that

33   observed for other durable mineral fibers (reviewed in Mossman et al., 2007). Whether this

34   inflammatory response then leads to cancer is unknown. Studies examining other types of

35   asbestos (e.g., crocidolite, chrysotile, and amosite) have demonstrated an increase in chronic

36   inflammation as well as respiratory cancer related to exposure (reviewed in Kamp and

37   Weitzman, 1999). Chronic inflammation has also been linked to genotoxicity and mutagenicity

38   following exposure to some particles and fibers (Driscoll et al., 1997; Driscoll et al., 1996;

1 Driscoll et al., 1995). The evidence described above suggests chronic inflammation is observed

2 following LAA and tremolite asbestos exposure; however, the role of inflammation and whether

3 it leads to lung cancer or mesothelioma following exposure to LAA is unknown.

4 　　　　ROS production has been measured in response to both LAA and tremolite asbestos

5 exposure. Blake et al. (2007) demonstrated an increase in the production of superoxide anions

6 following exposure to LAA. Blake et al. (2007) also demonstrated that total superoxide

7 dismutase (SOD) was inhibited, along with a decrease in intracellular glutathione (GSH), both of

8 which are associated with increased levels of ROS. These results are supported by a recent study

9 in human mesothelial cells (Hillegass et al., 2010; described in Section 4.4 and Appendix D).

10 Increased ROS production was also observed in human airway epithelial cells (HAECs)

11 following exposure to LAA (Duncan et al., 2010; described in Section 4.4 and Appendix D).

12 This increase in ROS and decrease in glutathione are common effects following exposure to

13 asbestos fibers and particulate matter. Pfau et al. (2012) examined the role of the amino acid

14 transport system x^-_c, which is one of the pathways murine macrophages use to detect and

15 respond to stressful conditions. This study demonstrated that ROS production increase system

16 x^-_c activity. Although ROS production is relevant to humans, based on similar human responses

17 as compared to animals, information on the specifics of ROS production following exposure to

18 LAA is limited to the available data described here. Therefore, the role of ROS production in

19 lung cancer and mesothelioma following exposure to LAA is unknown.

20 　　　　Recent studies have also examined the role of the inflammasome and iron in the

21 development of fibrosis in male SH-rats. The role of inflammasome activation and iron in the

22 development of LAA-induced fibrosis was studied in Shannahan et al. (2012c). Lung tissue

23 expression of inflammatory cytokines CCL-7, Cox-2, CCL-2, and CXCL-3 was increased

24 4 hours following LAA exposure. Conversely, LAA exposure reduced IL-4 and CXCl-1 in the

25 BALF. Finally, the ratio of phosphorylated ERK (pERK)/extracellular signal-related kinases

26 (ERK), which is an upstream activator of the inflammasome cascade, was increased in the lung

27 of LAA exposed rats 1 day post exposure. Rats treated with LAA + DEF or LAA + Fe had

28 significantly different levels of Cox-2 in the BALF and IL-6 in lung tissue but all other endpoints

29 were not significantly different. These data suggest that the concentration of iron does not

30 impact the activation of the inflammasome cascade and cytokines downstream of the pathway in

31 LAA-exposed animals.

32 　　　　In another study examining the role of iron in lung disease, Shannahan et al. (2012d)

33 valuated the effect of Fe overload on LAA-induced lung injury in rats with cardiovascular

34 disease. Gene array analysis demonstrated that LAA exposure upregulated inflammatory-related

35 genes such as NF-kβ and cell cycle regulating genes such as matrix metalloproteinase-9 in WKY

36 rats but inhibited these same cluster of genes in SH and SHHF animals 3 months after

37 instillation. Histological examination of lung sections observed greater Fe staining of

38 macrophages in SHHF rats compared to WKY and SH rats 1 and 3 months post exposure;

1 however, no differences in the progression of pulmonary fibrosis were noted between the three

2 strains. Altogether, these data do not suggest that the iron overload conditions that are

3 characteristic of the cardiovascular disease strains amplify the pulmonary effects of LAA.

4

4.3. OTHER DURATION- OR ENDPOINT-SPECIFIC STUDIES

4.3.1. Immunological

7 Salazar et al. (2013; 2012), Rasmussen and Pfau (2012), Blake et al. (2008), Pfau et al.

8 (2008), Serve et al. (2013) and Hamilton et al. (2004) examined the role of asbestos in

9 autoimmunity in laboratory animal or in vitro studies. Blake et al. (2008) performed in vitro

10 assays with LAA (see Section 4.4), and both studies performed the in vivo assays with tremolite.

11 C57BL/6 mice were instilled intratracheally for a total of two doses each of 60-μg saline and

12 wollastonite or Korean tremolite sonicated in sterile phosphate buffered saline (PBS), given

13 1 week apart in the first 2 weeks of a 7-month experiment. Sera from mice exposed to tremolite

14 showed antibody binding colocalized with SSA/Ro52 on the surface of apoptotic blebs (Blake et

15 al., 2008). In Pfau et al. (2008), by 26 weeks, the tremolite-exposed animals had a significantly

16 higher frequency of positive antinuclear antibody (ANA) tests compared to wollastinate and

17 saline. Most of the tests were positive for double-stranded DNA (dsDNA) and SSA/Ro52.

18 Serum isotyping showed no major changes in immunoglobulin (Ig) subclasses (IgG, IgA, IgM),

19 but serum IgG in tremolite-exposed mice decreased overall. Further, IgG immune complex

20 deposition in the kidneys increased, with abnormalities suggestive of glomerulonephritis. No

21 increased proteinuria was observed during the course of the study. Local immunologic response

22 was further studied on the cervical lymph nodes. Although total cell numbers and lymph-node

23 sizes were significantly increased following exposure to tremolite, percentages of T- and B-cells

24 did not significantly change.

25 Hamilton et al. (2004) investigated the ability of Libby Amphibole, crocidolite, and

26 particulate matter 2.5 μm in diameter or less (PM$_{2.5}$, collected over a 6-month period in Houston,

27 TX, from EPA site 48-201-1035) to alter the antigen-presenting cell (APC) function in cultured

28 human alveolar macrophages. Asbestos exposure (regardless of type) and PM$_{2.5}$ up-regulated a

29 Th1 lymphocyte-derived cytokine, interferon gamma (IFNγ), and the Th2 lymphocyte-derived

30 cytokines IL-4 and IL-13. However, extreme variation among subjects was noted in the amount

31 of response. In addition, no correlation was present between an individual's cells' response to

32 asbestos versus particulate matter, suggesting that more than one possible mechanism exists for a

33 particle-induced APC effect and individual differential sensitivities to inhaled bioactive particles.

34 Rasmussen and Pfau (2012) examined the role of macrophages in the development of

35 autoantibody production following exposure to LAA. LAA exposure alone did not affect cell

36 proliferation or antibody production; however, culturing lymphocytes with macrophage medium

37 following exposure to LAA did lead to increased cellular proliferation and antibody production.

1 Serve et al. (2013) examined a possible role of autoimmunity in fibrosis by an in vitro
2 examination of potential mechanisms of MCAA leading to collagen deposition, a precursor to
3 fibrosis. This study demonstrated MCAA binding leads to increased collagen deposition through
4 altering matrix metalloproteinase (MMP) expression.
5   In two studies examining potential autoimmune effects of LAA exposure, Salazar et al.
6 (2013; 2012) examined the potential impact of LAA exposure on rheumatoid arthritis and on
7 ANA increases associated with systemic autoimmune disease. Salazar et al. (2013; 2012)
8 conducted a series of studies to establish the effects of LAA exposure on autoimmune disease.
9 The first set of studies utilized the collagen-induced arthritis and peptidoglycan-polysaccharide
10 (PG-PS) models of rheumatoid arthritis to determine whether LAA exposure increased the onset,
11 prolonged, or intensified the joint inflammation characteristic of the disease (Salazar et al.,
12 2012). Female Lewis rats were instilled biweekly for 13 weeks with a total dose of 0, 0.15, 0.5,
13 1.5, and 5.0 mg LAA followed by induction with either model of arthritis. LAA 5.0 mg reduced
14 the magnitude of the swelling response in the cell-mediated PG-PS model; however, neither the
15 onset nor the duration of swelling was affected by LAA exposure. LAA 1.5 and 5.0 mg and
16 amosite 0.5 and 1.5 mg reduced total serum IgM. LAA 5.0 mg and amosite 1.5 mg reduced
17 anti-PG-PS IgG in the serum 17 weeks after the final instillation. Finally, the number of rats
18 positive for ANA was increased only at the low exposure concentrations of LAA in PG-PS-
19 treated and nonarthritic rats. These results suggest that LAA may have a modest inhibitory effect
20 on the PG-PS rat model but may enhance responses to other systemic autoimmune diseases.
21   In a follow-up study, Salazar et al. (2013) explored in greater detail the effect of LAA
22 exposure on ANA over time and the antigen specificity of the ANA. Female Lewis rats were
23 intratracheallyinstilled under the conditions in the previous study (Salazar et al., 2012). Serum
24 samples were analyzed every 4 weeks from the beginning of the instillations up to termination at
25 Week 28. Since elevated ANA are commonly associated with kidney disease, proteinuria was
26 assessed every 3 weeks beginning at Week 6 until termination of the experiment.
27 Histopathological analysis was also performed on the kidneys. ANA was increased 8 weeks
28 postexposure to LAA 5.0 mg. By Week 28, all doses of LAA except 1.5 mg increased ANA in
29 the serum. Analysis of the antigen specificity found that only the LAA at 1.5 mg significantly
30 increased antibodies specific for extractable nuclear antigens and the Jo-1 antigen. Urinalysis
31 found that all doses of LAA exposure induce moderate levels of proteinuria, but this effect was
32 not dose responsive. No dose-related histopathological effects were observed. Altogether, these
33 data suggest that LAA exposure increases autoimmune antibodies in the serum, but no evidence
34 of autoimmune disease was identified. However, the lack of SAID in the Lewis rat may be due
35 to strain-specific factors and suggests that other animal models may be more appropriate for
36 studying autoimmune effects of LAA.

1   Although the number of studies is limited, the results suggest a possible effect on

2 autoimmunity following exposure to LAA. Further studies are needed to increase understanding

3 of this potential effect.

4

5 **4.4. MECHANISTIC DATA AND OTHER STUDIES IN SUPPORT OF THE MODE OF**

6   **ACTION**

7   For asbestos in general, International Agency for Research on Cancer (IARC) has

8 proposed a mechanism for the carcinogenicity of asbestos fibers (see Figure 4-4; IARC, 2012).

9 Asbestos fibers lead to oxidant production through interactions with macrophages and through

10 hydroxyl radical generation from surface iron. Inhaled fibers that are phagocytosed by

11 macrophages may be cleared or lead to frustrated phagocytosis, which results in macrophage

12 activation, release of oxidants, and increased inflammatory response, in part due to

13 inflammasome activation. Free radicals may also be released by interaction with the iron on the

14 surface of fibers. Increased oxidant production may result in epithelial cell injury, including

15 DNA damage. Frustrated phagocytosis may also lead to impaired clearance of fibers, with fibers

16 being available for translocation to other sites (e.g., pleura). Mineral fibers may also lead to

17 direct genotoxicity by interfering with the mitotic spindle and leading to chromosomal

18 aberrations. Asbestos exposure also leads to the activation of intracellular signaling pathways,

19 which in turn may result in increased cellular proliferation, decreased DNA damage repair, and

20 activation of oncogenes. Research on various types of mineral fibers supports a complex

21 mechanism involving multiple biologic responses following exposure to asbestos (i.e.,

22 genotoxicity, chronic inflammation/cytotoxicity leading to oxidant release, and cellular

23 proliferation) in the carcinogenic response to mineral fibers (see Figure 4-4, reviewed in IARC,

24 2012). These complexities of fiber toxicity need to be considered when analyzing MOA for

25 asbestos (as reviewed in Aust et al., 2011; Broaddus et al., 2011; Bunderson-Schelvan et al.,

26 2011; Huang et al., 2011; Mossman et al., 2011).
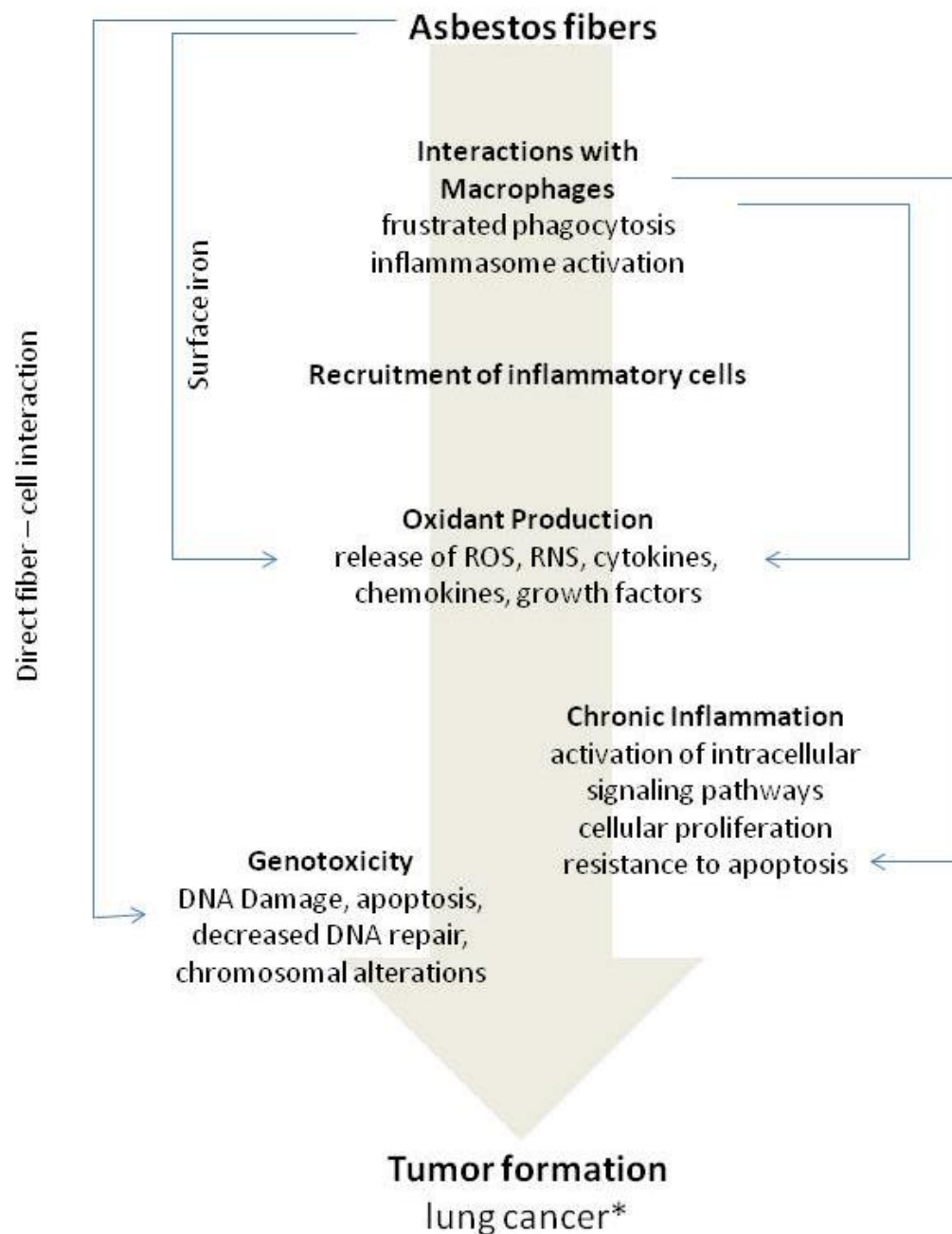
Figure 4-4. Proposed mechanistic events for carcinogenicity of asbestos fibers.

Adapted from IARC (2012).

1   Important considerations in evaluating the available mechanism and MOA data are fiber
2   characteristics, route of exposure, dose metric, as well as study design and interpretation.
3   Specific fiber characteristics impact the fiber toxicokinetics (reviewed in Section 3), and in turn
4   the biologic response to fibers. For example, fiber length is an important determinant of fiber
5   clearance, with shorter fibers generally being cleared more efficiently as longer fibers result in
6   frustrated phagocytosis. Mechanisms of carcinogenesis may accordingly vary based on fiber
7   characteristics. The biologic response to respirable fibers is also influenced by the route of
8   exposure. Inhalation exposure studies are the most informative. Intratracheal instillation and
9   aspiration exposures bypass normal clearance mechanisms, and therefore affect fiber dosimetry.
10   Concerning dose metric, some studies suggest that the dose should be determined based on fiber
11   length, width, number, or surface area (Case et al., 2011; Mossman et al., 2011). However, the
12   majority of studies of fibers have been performed using mass as a dose. Finally, an important
13   consideration in analysis of in vitro studies is the cell types used, particularly related to the
14   ability to internalize fibers and produce an oxidative stress response. The discussions below
15   highlight these considerations in presenting the available mechanistic evidence for LAA.
16   Limited in vitro studies have been conducted with LAA from the Zonolite Mountain
17   mine. These studies demonstrated an effect of LAA on inflammation and immune function
18   (Duncan et al., 2014; Duncan et al., 2010; Blake et al., 2008; Blake et al., 2007; Hamilton et al.,
19   2004), oxidative stress (Hillegass et al., 2010), and genotoxicity (Pietruska et al., 2010). Similar
20   endpoints have been examined in vitro following exposure to tremolite asbestos (Okayasu et al.,
21   1999; Wylie et al., 1997; Suzuki and Hei, 1996; Athanasiou et al., 1992; Wagner et al., 1982).
22   Results from in vitro studies have demonstrated potential biological mechanisms of oxidative
23   stress and inflammation in response to exposure to Libby Amphibole and tremolite asbestos. As
24   discussed in Section 4.2, laboratory animal studies examining the effects of tremolite exposure
25   have been reviewed and are summarized to potentially increase understanding of the effects and
26   mechanisms of LAA, because tremolite is a component of LAA (~6%). These studies are
27   summarized below and in Tables 4-21 and 4-22, with detailed study descriptions available in
28   Appendix D.

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

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

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

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

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

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

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

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

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

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

4.4.1. Inflammation and Immune Function

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

Increased cytokine and chemokine production has been observed following exposure to LAA as well as other amphibole asbestos. Hamilton et al. (2004) showed an increase in Th1 and Th2 cytokines following exposure to LAA, crocidolite, and particulate matter, suggesting a similar effect of exposure to these materials on immune function. Analysis of these results is limited, as the use of primary cells in culture led to an extremely variable response. Two studies by Blake et al. (2008) and Blake et al. (2007) further examined the effect of LAA on immune response in vitro in mouse macrophages. These studies demonstrated that the size of the LAA material is such that it was able to be internalized by macrophages (<10 μm), and this internalization resulted in an increase in ROS production. These studies also showed a variable cytotoxic response, because LAA exposure did not result in a statistically significant increase in cytotoxicity, while crocidolite did. DNA damage also was increased in crocidolite-exposed cells but not in LAA-exposed cells. An increase (relative to controls) in autoantibody formation following exposure to LAA was also observed. Studies that examined cellular response to tremolite also found that fiber characteristics (length and width) play a role in determining ROS production, toxicity, and mutagenicity (Okayasu et al., 1999; Wagner et al., 1982).

Gene expression alterations of *IL-8*, *COX-2*, *heme oxygenase (HO)-1*, as well as other stress-responsive genes as compared to amosite was observed in primary HAEC following exposure to LAA. Comparisons were made with both fractionated (aerodynamic diameter ≤2.5 μm) and unfractionated fiber samples (Duncan et al., 2010). Crocidolite fibers (UICC) were also included in some portions of this study for comparison. Primary HAECs were exposed to 0, 2.64, 13.2, and 26.4 μg/cm^2 of crocidolite, amosite, amosite 2.5 (fractionated), LAA, or LAA 2.5 (fractionated) for 2 or 24 hours in cell culture. Minimal increases in gene expression of IL-8, COX-2, or HO-1 were observed at 2 hours postexposure to all five fiber types; at 24 hour postexposure, however, a dose-response was observed following exposure to all fiber types with the results showing a proinflammatory gene expression response (Duncan et al., 2010). Cytotoxicity was determined by measuring LDH from the maximum dose (26.4 μg/cm^2) of both amosite and LAA samples, with less than 10% LDH present following exposure to all four samples. A follow-up study with the same design by (Duncan et al. (2014)) was performed to examine the in vitro determinants of asbestos fiber toxicity, comparing two samples each of

LAA (LA2000, LA2007) and amosite (UICC, RTI) asbestos. Primary human airway epithelial cells (HAEC) were exposed for 24 hours to 2.64, 13.2 or 26.4 ug/cm^2 LAA and amosite asbestos that had been analyzed for fiber size distribution, surface area, and surface-conjugated iron (see Table D-11). Most characteristics were similar, except RTI amosite consisted of longer fibers. Fiber toxicity was measured by cytotoxicity (LDH assay), levels of ROS production, as well as IL-8 mRNA levels as a measure of relative proinflammatory responses. Cytotoxicity levels were similar for all four samples at the highest dose, but statistically significant compared to the no-treatment control. Results on an equal mass basis demonstrated a statistically significant increase in IL-8, IL-6, COX-2, and TNF mRNA levels for all four amphiboles at the highest two doses. The greatest increase in IL-8 mRNA levels was following exposure to the RTI amosite sample, while both LAA samples and the UICC amosite resulted in a similar level of response to each other. Therefore, IL-8 was used to further analyze the dose metrics for this response. Surface iron concentrations and surface reactivity was quantified with respect to hydroxyl radical production to assess the effect of these properties on IL-8 mRNA expression. Surface iron concentrations were similar for the two LAA samples and for the two amosite samples, but the amosite samples had much greater surface iron as compared to the LAA samples. UICC amosite had slightly greater iron as compared to RTI. A strong correlation was observed between fiber dose metrics of length and external surface area. When these metrics were used in place of equal mass dose, the differential IL-8 mRNA expression following exposure to these four samples was eliminated. These results support a limited cytotoxicity and increased inflammatory cytokine response of both amosite and LAA under these concentrations and time frames.

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

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

LAA[18] as compared to the nonpathogenic control (75×10^6 $\mu m^2/cm^2$ glass beads) in the human mesothelial cell line LP9/TERT-1 for 8 and 24 hours. Gene ontology of these results demonstrated alterations in genes related to signal transduction, immune response, apoptosis, cellular proliferation, extracellular matrix, cell adhesion, and motility, and only in one gene related to reactive oxygen species processing. Oxidative stress was observed to be both dose- and time-dependent in cells exposed to LAA. GSH levels were transiently depleted following 2−8 hours exposure to the higher dose of LAA, with a gradual recovery up to 48 hours in LP9/TERT-1 cells (HKNM-2 not analyzed). These studies demonstrate that LAA exposure leads to increases in oxidative stress as measured by ROS production, gene expression, protein and functional changes in oxidative stress proteins (SOD), and GSH level alterations in human mesothelial cells.

The role of inflammasome activation and iron in the development of LAA-induced fibrosis was studied in Shannahan et al. (2012d). Male SH rats were instilled with a single exposure to 0 or 0.5 mg LAA, DEF, 21 µg $FeCl_3$, 0.5 mg LAA + 21 µg $FeCl_3$, or 0.5 mg LAA + 1 mg DEF. Tissues were collected 4 hours and 1 day postexposure. LAA instillation increased lung expression of the inflammasome-related molecules cathepsin B, Nalp3, NF-kβ, apoptosis-associated speck-like protein containing a CARD (ASC), IL-1β, and IL-6 expression 4 hours postexposure. Lung tissue expression of inflammatory cytokines CCL-7, Cox-2, CCL-2, and CXCL-3 was increased 4 hours following LAA exposure. These data suggest that LAA exposures leads to the activation of the inflammasome cascade and cytokines downstream of the pathway in LAA-exposed animals. Li et al. (2012) also studied LAA inflammasome activation and demonstrated in vitro in THP-1 cells that LAA activated the NLRP3 inflammasome but to a lesser degree than chrysotile. However, this study showed that LAA exposure generated more ROS production as compared to chrysotile. Although not studied, the authors suggest that differences in fiber length and surface area may play a role in this differential inflammatory response.

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

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4.4.2. Genotoxicity

Genotoxicity, and more specifically, mutagenicity, are associated with tumor formation through alterations in genetic material.[19] Mutagenicity refers to a permanent effect on the structure and/or amount of genetic material that can lead to heritable changes in function, while genotoxicity is a broader term including all adverse effects on the genetic information (Eastmond et al., 2009). Results of standard mutation assays like the Ames test, which analyze for point mutations, have found asbestos and other mineral fibers to be negative or only marginally positive (Walker et al., 1992). Several other studies, however, have shown that asbestos exposure can result in a variety of chromosomal alterations, which are briefly discussed below. Genotoxicity following exposure to asbestos fibers has been described as the result of two distinct mechanisms, either ROS production leading to DNA damage, or physical interference of mitosis by the fibers. For both DNA damage and mitotic interference, the fibers must first enter the cell. Some studies have shown that a direct interaction between fibers and cellular receptors might also lead to increased ROS production. ROS production is also related to surface iron on fibers, with increased surface iron leading to increased ROS production (IARC, 2012). ROS production is possibly a key event in fiber-induced direct DNA damage, as observed following exposure to other forms of asbestos, while the indirect DNA damage requires fiber interaction with cellular components (e.g., mitotic spindle, chromosomes).

ROS production and genotoxicity (micronuclei induction) following exposure to LAA has been demonstrated in x-ray repair cross complementing protein 1 (XRCC1)-deficient human lung epithelial H460 cells (Pietruska et al., 2010). XRCC1 is involved in the repair mechanisms for oxidative DNA damage, particularly single strand breaks. Micronuclei induction was measured following treatment of cells by controls (positive, hydrogen peroxide; negative, paclitaxel) and by 5 μg/cm^2 fibers or TiO$_2$ particles for 24 hours. Spontaneous micronuclei induction was increased in XRCC1-deficient cells in a dose-dependent manner following exposure to crocidolite and LAA as compared to unexposed cells. These results support a potential genotoxic effect of exposure to both crocidolite and LAA.

Athanasiou et al. (1992) performed a series of experiments to measure genotoxicity following exposure to tremolite, including the Ames mutagenicity assay, micronuclei induction, chromosomal aberrations, and gap-junction intercellular communication. Although a useful test system for mutagenicity screening for many agents, the Ames assay is not the most effective test

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

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1   to detect mutations induced by mineral fibers. Mineral fibers can cause mutation through
2   generation of ROS or direct disruption of the spindle apparatus during chromatid segregation.
3   Fibers do not induce ROS in the Ames system, however, and the *Salmonella typhimurium* strains
4   do not endocytose the fibers. Only one study was found in the published literature that used the
5   Ames assay to measure mutagenicity of tremolite. Metsovo tremolite asbestos has been shown
6   to be the causative agent of endemic pleural calcification and an increased level of malignant
7   pleural mesothelioma (see Section 4.1). To measure the mutagenicity of Metsovo tremolite,
8   *S. typhimurium* strains (TA98, TA100, and TA102) were exposed to 0−500 µg/plate of asbestos
9   (Athanasiou et al., 1992). Metsovo tremolite did not yield a statistically significant increase in
10   revertants in the Ames assay, including in the TA102 *Salmonella* strain, which is generally
11   sensitive to oxidative damage. This study demonstrated clastogenic effects of tremolite,
12   including chromosomal aberrations and micronuclei induction. Tremolite exposure in Syrian
13   hamster embryo (SHE) cells did lead to a dose-dependent increase in chromosome aberrations
14   that was statistically significant at the highest doses tested ($1.0−3.0$ µg/cm^2; $p < 0.01$;
15   Athanasiou et al., 1992). A statistically significant, dose-dependent increase in levels of
16   micronuclei was demonstrated following tremolite exposure at concentrations as low as
17   0.5 µg/cm^2 ($p < 0.01$) in BPNi cells after 24-hour exposure. Literature searches did not find
18   tremolite tested for clastogenicity in other cell types, but the results of this study suggest
19   interference with the spindle apparatus by these fibers. No analysis was performed to determine
20   whether fiber interference of the spindle apparatus could be observed, which would have
21   supported these results. No effect on the gap-junctional intercellular communication following
22   tremolite exposure was observed in both Chinese hamster lung fibroblasts (V79) and Syrian
23   hamster embryo BPNi cells, which are sensitive to transformation (Athanasiou et al., 1992).
24   Okayasu et al. (1999) analyzed the mutagenicity of Metsovo tremolite, erionite, and the
25   man-made refractory ceramic fiber (RCF-1). Human-hamster hybrid A$_L$ cells contain a full set
26   of hamster chromosomes and a single copy of human chromosome 11. Mutagenesis of the CD59
27   locus on this chromosome is quantifiable by an antibody complement-mediated cytotoxicity
28   assay. The study authors state that this is a highly sensitive mutagenicity assay, and previous
29   studies have demonstrated mutagenicity of both crocidolite and chrysotile (Hei et al., 1992). The
30   cytotoxicity analysis for mutagenicity was performed by exposing 1×10^5 A$_L$ cells to a range of
31   concentrations of fibers as measured by weight (0−400 µg/mL or 0−80 µg/cm^2) for 24 hours at
32   37°C. A dose-dependent increase in CD59 mutant induction was observed following exposure
33   to erionite and tremolite, but not RCF-1.
34   In summary, one in vitro study examined genotoxicity of LAA by measuring DNA
35   adduct formation following exposure via murine macrophages (primary and immortalized; Blake
36   et al., 2007). The data showed no increase in adduct formation as compared to unexposed
37   controls. A second study observed increases in micronuclei induction in both normal human
38   lung epithelial cells and XRCC1-deficient cells for both LAA and crocidolite asbestos (Pietruska

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

4.4.3. Cytotoxicity and Cellular Proliferation

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

Wagner et al. (1982) examined the in vitro cytotoxicity of three forms of tremolite used in their in vivo studies. LDH and β-glucuronidase were measured in the medium following incubation of unactivated primary murine macrophages to 50, 100, and 150 μg/mL of each sample for 18 hours. The Korean tremolite (Sample C) produced results similar to the positive control: increased toxicity of primary murine macrophages, increased cytoxicity of Chinese hamster ovary cells, and increased formation of cells >25 um diameter from the A549 cell line. The tremolite sample from Greenland (Sample B) did result in increased toxicity over controls; although to a lesser degree (statistics are not given). Although differential toxicity of these samples was noted on a mass basis, data were not normalized for fiber content or size. The inference is that differential results may be due, at least in part, to differential fiber counts.

Wylie et al. (1997) examined the mineralogical features associated with cytotoxic and proliferative effects of asbestos in hamster tracheal epithelial (HTE) and rat pleural mesothelial (RPM) cells with a colony-forming efficiency assay. HTE cells are used because they give rise to tracheobronchial carcinoma, while RPM cells give rise to mesotheliomas. The results of the

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1   analysis with fiber exposure by mass (μg/cm^2) show elevated colonies in HTE cells following

2   exposures to both asbestos fibers ($p < 0.05$) at the lowest concentrations, while significant

3   decreases were observed for both asbestos fibers at the higher concentrations (0.5 μg/cm^2,

4    $p < 0.05$; Wylie et al., 1997). No proliferation was observed for either chrysotile or crocidolite

5   asbestos fibers in RPM cells, but cytotoxicity was observed at concentrations greater than

6   0.05 μg/cm^2 ($p < 0.05$). All talc samples were less cytotoxic in both cell types. Analyzing the

7   data for cytotoxicity and proliferation based on the exposure measurement demonstrated

8   differences in response depending solely on how the fibers were measured: by mass, number, or

9   surface area. These results show variability in interpreting the results of the same assay based on

10   the defined unit of exposure. Most early studies used mass as the measurement for exposure,

11   which can impact how the results are interpreted. When possible, further analysis of fiber

12   number and surface area would help elucidate the role of these metrics, particularly for in vivo

13   studies.

14   Tremolite and LAA exposure led to increases in both fibrosis and tumorigenicity in all

15   but one animal study, supporting a possible role for proliferation in response to these fibers (see

16   Tables 4-19 and 4-20). However, there are limited data to demonstrate that increased

17   cytotoxicity and cellular proliferation following exposure to LAA leads to lung cancer or

18   mesothelioma.

19

20   *Summary*

21   The review of these studies clearly highlights the need for more controlled studies

22   examining LAA in comparison with other forms of asbestos and for examining multiple

23   endpoints—including ROS production, DNA damage, inflammasome activation, and

24   proinflammatory gene expression alterations—to improve understanding of mechanisms

25   involved in cancer and other health effects. Data gaps still remain to determine specific

26   mechanisms involved in LAA-induced disease. Studies that examined cellular response to

27   tremolite also found that tremolite exposure may lead to increased ROS production, toxicity, and

28   genotoxicity (Okayasu et al., 1999; Wagner et al., 1982). As with the in vivo studies, the

29   definition of fibers and how the exposures were measured varies among studies.

30

31   **4.5. SYNTHESIS OF MAJOR NONCANCER EFFECTS**

32   The predominant noncancer health effects observed following inhalation exposure to

33   LAA are effects on the lungs and pleural lining surrounding the lungs. These effects have been

34   observed primarily in studies of exposed workers and community members, and are supported by

35   laboratory animal studies. Recent studies have also examined other noncancer health effects

36   following exposure to Libby Amphibole, including autoimmune effects and cardiovascular

37   disease; this research base is currently not as well developed as that of respiratory noncancer

38   effects. Adequate data are not available to differentiate the health effects of the predominant

1 mineralogical forms composing LAA. Although the adverse effects of tremolite are reported in

2 the literature, the contribution of winchite and richterite to the aggregate effects of LAA has not

3 been determined.

4

4.5.1. Pulmonary Effects

4.5.1.1. *Pulmonary Fibrosis (Asbestosis)*

7   Asbestosis is the interstitial pneumonitis (inflammation of lung tissue) and fibrosis

8 caused by inhalation of asbestos fibers and is characterized by a diffuse increase of collagen in

9 the alveolar walls (fibrosis) and the presence of asbestos fibers, either free or coated with a

10 proteinaceous material and iron (asbestos bodies). Fibrosis results from a sequence of events

11 following lung injury, which includes inflammatory cell migration, edema, cellular proliferation,

12 and accumulation of collagen. Asbestosis is associated with dyspnea (shortness of breath),

13 bibasilar rales, and changes in pulmonary function: a restrictive pattern, mixed

14 restrictive-obstructive pattern, and/or decreased diffusing capacity (ATS, 2004). Radiographic

15 evidence of small opacities in the lung is direct evidence of scarring of the lung tissue and is the

16 fibrotic scarring of lung tissue consistent with mineral dust and mineral fiber toxicity. The

17 scarring of the parenchymal tissue of the lung contributes to measured changes in pulmonary

18 function, including obstructive pulmonary deficits from narrowing airways, restrictive

19 pulmonary deficits from impacting the elasticity of the lung, as well as decrements in gas

20 exchange.

21   Workers exposed to LAA from vermiculite mining and processing facilities in Libby,

22 MT, as well as plant workers in Marysville, OH, where vermiculite ore was exfoliated and

23 processed, have an increased prevalence of small opacities on chest x-rays, which is indicative of

24 fibrotic damage to the parenchymal tissue of the lung (Rohs et al., 2008; Amandus et al., 1987a;

25 McDonald et al., 1986b; Lockey et al., 1984). Significant increases in asbestosis as a cause of

26 death have been documented in studies of the Libby worker cohort report (see Table 4-6 for

27 details; Larson et al., 2010b; Sullivan, 2007; Amandus and Wheeler, 1987; McDonald et al.,

28 1986a). For both asbestosis mortality and radiographic signs of asbestos (small opacities),

29 positive exposure-response relationships are described where these effects are greater with

30 greater cumulative exposure to LAA.

31   Deficits in pulmonary function consistent with pulmonary fibrosis have been reported in

32 individuals exposed to LAA in community-based studies.[20] Data from the ATSDR community

33 screening, which included workers, provide support for functional effects from parenchymal

34 changes. The original report of the health screening data indicated moderate to severe

---

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

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1   pulmonary restriction in 2.2% of men (Peipins et al., 2003; ATSDR, 2001b). A recent reanalysis

2   of these data show that for study participants with small opacities viewed on the radiographs

3   (grade 1/0 or greater) and DPT, the mean FVC is reduced to 78.76 ($\pm$3.64), 82.16 ($\pm$3.34),

4   respectively of the expected value (Weill et al., 2011). A mean FVC of 95.63 ($\pm$0.76) was

5   reported for those with other pleural abnormalities versus 103.15 ($\pm$0.25) in participants with no

6   radiographic abnormalities. The strongest effects of diffuse pleural thickening and/or

7   costophrenic angle obliteration on FVC were seen among men who had never smoked ($-$23.77,

8     $p < 0.05$), with smaller effects seen among men who had smoked ($-$9.77, $p < 0.05$) and women

9   who had smoked ($-$6.73, $p < 0.05$). Laboratory animal and mechanistic studies of LAA are

10   consistent with the noncancer health effects observed in both Libby workers and community

11   members. Pleural fibrosis was increased in hamsters after intrapleural injections of LAA (Smith,

12   1978). More recent studies have demonstrated increased collagen deposition consistent with

13   fibrosis following intratracheal instillation of LAA fibers in mice and rats (Padilla-Carlin et al.,

14   2011; Shannahan et al., 2011a; Shannahan et al., 2011b; Smartt et al., 2010; Putnam et al., 2008).

15   Pulmonary fibrosis, inflammation, and granulomas were observed after tremolite inhalation

16   exposure in Wistar rats (Bernstein et al., 2005; Bernstein et al., 2003) and intratracheal

17   instillation in albino Swiss mice (Sahu et al., 1975). Davis et al. (1985) also reported pulmonary

18   effects after inhalation exposure in Wistar rats, including increases in peribronchiolar fibrosis,

19   alveolar wall thickening, and interstitial fibrosis.

20

21   **4.5.1.2.** *Other Nonmalignant Respiratory Diseases*

22   Mortality studies of the Libby workers indicate increased mortality not only from

23   asbestosis, but also from other respiratory diseases. Deaths attributed to chronic obstructive

24   respiratory disease and deaths attributed to "other" nonmalignant respiratory disease were

25   elevated more than twofold (see Table 4-6; Larson et al., 2010b; Sullivan, 2007). These diseases

26   are consistent with asbestos toxicity, and the evidence of a positive exposure-response

27   relationship for mortality from all nonmalignant respiratory diseases, supports this association.

28

29   **4.5.2. Pleural Effects**

30   Pleural thickening caused by mineral fiber exposure includes two distinct biological

31   lesions: discrete pleural plaques in the parietal (outer) pleura and diffuse pleural thickening of

32   the visceral (inner) pleura. Both of these forms of pleural thickening can be viewed on standard

33   radiographs, however smaller lesions may not be detected (high resolution computed

34   tomography is a method that can detect smaller lesions than are visible on x-rays). Current ILO

35   guidelines (2002) state that pleural thickening on x-ray can be Localized (LPT) or Diffuse

36   (DPT). LPT was not defined by the ILO until the 2000 guidelines were published (ILO, 2002).

37   Previously, the 1980 ILO guidelines defined only circumscribed pleural thickening (plaques) and

diffuse pleural thickening (DPT) either with or without costophrenic angle obliteration. The 2000 ILO revision defines LPT as the union of what was previously defined as plaques found on the chest wall or in other locations (e.g., diaphragm) in the 1980 guidelines, and what was previously defined as DPT without costophrenic angle obliteration. Neither classification for pleural thickening (LPT or DPT) in the 2000 ILO guidelines corresponds with the previous ILO classification systems for pleural thickening; LPT is defined more broadly than the previous category of pleural plaques, while DPT is defined more narrowly due to the requirement for costophrenic angle obliteration. Different researchers have used different terminology for circumscribed pleural thickening or plaques when implementing the 1980 ILO guidelines, most often using the terms "pleural plaques."

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

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

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

There is limited research available on noncancer health effects occurring outside the respiratory system and pleura. Larson et al. (2010b) examined cardiovascular disease-related mortality in the cohort of exposed workers from Libby (see Section 4.1). Mechanistic studies have examined the potential role of iron and the associated inflammation for both respiratory and

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1　cardiovascular disease (Shannahan et al., 2012a; Shannahan et al., 2012c; Shannahan et al.,

2　2012b; Shannahan et al., 2012d; Shannahan et al., 2011b). Other studies examined the

3　association between asbestos exposure and autoimmune disease (Noonan et al., 2006) or

4　autoantibodies and other immune markers (Pfau et al., 2005; see Table 4-16). However,

5　limitations in the number, scope, and design of these studies make it difficult to reach

6　conclusions as to the role of asbestos exposure in either cardiovascular disease or autoimmune

7　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　LAA (Larson et al., 2010b; Sullivan, 2007; McDonald et al., 2004; Amandus and Wheeler,

13　1987). Additional studies have documented an increase in radiographic changes in the pleura

14　(pleural thickening) and parenchyma among employees of a manufacturing facility in

15　Marysville, OH that used vermiculite ore contaminated with LAA (Rohs et al., 2008; Lockey et

16　al., 1984). Radiographic evidence of pleural thickening and interstitial damage (small opacities)

17　are also well documented among employees of the Libby vermiculite mining operations (Larson

18　et al., 2012a; Larson et al., 2010a; Amandus et al., 1987a; McDonald et al., 1986b). Positive

19　exposure-response relationships for these health effects for both occupational cohorts studied, as

20　well as the observed latency, support an association between exposure to LAA and these pleural

21　and/or pulmonary effects. Studies of community members exposed to LAA have documented

22　similar pleural abnormalities and pulmonary deficits consistent with parenchymal damage (Weill

23　et al., 2011; Whitehouse, 2004; Peipins et al., 2003). Although limited, animal studies support

24　the toxicity of LAA to pleural and pulmonary tissues. Developing research supports a role of

25　inflammatory processes in the toxic action of LAA, consistent with the observed health effects

26　(Cyphert et al., 2012b; Shannahan et al., 2012c; Shannahan et al., 2011b; Duncan et al., 2010;

27　Hamilton et al., 2004). Taken together, the strong evidence in human studies, defined

28　exposure-response relationships, and supportive animal studies provide compelling evidence that

29　exposure to LAA causes nonmalignant respiratory disease, including asbestosis, pleural

30　thickening, and deficits in pulmonary function associated with mineral fiber exposures. Existing

31　data regarding cardiovascular effects and the potential for autoimmune disease are limited.

32

33　**4.5.5. Mode-of-Action Information (Noncancer)**

34　　　　The precise mechanisms causing toxic injury from inhalation exposure to LAA have not

35　been established. However, nearly all durable mineral fibers with dimensional characteristics

36　that allow penetration to the terminal bronchioles and alveoli of the lung have the capacity to

37　induce pathologic response in the lung and pleural cavity (ATSDR, 2001a; Witschi and Last,

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1   1996). The physicochemical attributes of mineral fibers are important in determining the type of

2   toxicity observed. Fiber dimension (width and length), density, and other characteristics, such as

3   chemical composition, surface area, solubility in physiological fluids, and durability, all play

4   important roles in both the type of toxicity observed and the biologically significant dose. As

5   described in Section 3, these characteristics also play a role in fiber dosimetry. Fibrosis results

6   from a sequence of events following lung injury, which includes inflammatory cell migration,

7   edema, cellular proliferation, and accumulation of collagen. Fibers do migrate to the pleural

8   space, and it has been hypothesized that a similar cascade of inflammatory events may contribute

9   to fibrotic lesions in the visceral pleura. Thickening of the visceral pleura is more often localized

10 to lobes of the lung with pronounced parenchymal changes, and it has also been hypothesized

11 that the inflammatory and fibrogenic processes within the lung parenchyma in response to

12 asbestos fibers may influence the fibrogenic process in the visceral pleura. The etiology of

13 parietal plaques is largely unknown with respect to mineral fiber exposure.

14   There is currently insufficient evidence to establish the noncancer MOA for LAA.

15 Limited in vitro studies have demonstrated oxidative stress following LAA exposures in various

16 cell types (Duncan et al., 2010; Hillegass et al., 2010; Pietruska et al., 2010; Blake et al., 2007).

17 LAA fibers increased intracellular ROS in both murine macrophages and human epithelial cells

18 (Duncan et al., 2010; Blake et al., 2007). Surface iron and inflammatory marker gene expression

19 was increased following exposure to LAA in human epithelial cells (Shannahan et al., 2012a;

20 Shannahan et al., 2012c; Shannahan et al., 2012b; Shannahan et al., 2012d; Shannahan et al.,

21 2011b; Duncan et al., 2010; Pietruska et al., 2010; see Table 4-18). Tremolite studies

22 demonstrate cytotoxicity in various cell culture systems (see Table 4-22).

23   The initial stages of any fibrotic response involve cellular proliferation, which may be

24 compensatory for cell death due to cytotoxicity. Analysis of cellular proliferation has

25 demonstrated both increases and decreases following exposure to asbestos fibers in vitro and in

26 vivo depending on the specific fiber or cell type (Mossman et al., 1985; Topping and Nettesheim,

27 1980). Other studies have focused on the activation of cell-signaling pathways that lead to

28 cellular proliferation following exposure to asbestos (Scapoli et al., 2004; Shukla et al., 2003;

29 Ding et al., 1999; Zanella et al., 1996).

30   Although slightly increased compared to controls, cytotoxicity in murine macrophage

31 cells exposed to LAA was decreased compared to other fiber types (Blake et al., 2008).

32 Cytotoxicity was slightly, but statistically significantly, increased compared to an unexposed

33 control at 24 hours postexposure to LAA, while crocidolite exposure resulted in even higher

34 levels of cytotoxicity. No other in vitro study examined cytotoxicity following exposure to

35 LAA, although an increase in apoptosis was demonstrated in this same cell system (Blake et al.,

36 2008). Recent studies in mice exposed to LAA demonstrated increased collagen deposition and

37 collagen gene expression, markers of fibrosis (Smartt et al., 2010; Putnam et al., 2008).

38 Short-term-duration studies in rats also demonstrated an increased inflammatory response

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1 ([Padilla-Carlin et al., 2011](#); [Shannahan et al., 2011a](#); [Shannahan et al., 2011b](#)). Tremolite or
2 LAA exposure both led to increases in fibrosis in all but one animal study, supporting a role for
3 proliferation in response to these fibers. Taken together with studies on other asbestos fibers,
4 these data suggest that cytotoxicity and cell proliferation may play a role in the noncancer health
5 effects following exposure to LAA.

6   Although continued research demonstrates that the LAA has biologic activity consistent
7 with the inflammatory action and cytotoxic effects seen with other forms of asbestos, the data are
8 not sufficient to establish a MOA for the pleural and/or pulmonary effects of exposure to LAA.
9

10 4.6. EVALUATION OF CARCINOGENICITY

11 4.6.1. Summary of Overall Weight of Evidence

12   Under the EPA *Guidelines for Carcinogen Risk Assessment* ([U.S. EPA, 2005a](#)), LAA is
13 *carcinogenic to humans* following inhalation exposure based on epidemiologic evidence that
14 shows a convincing association between exposure to LAA fibers and increased lung cancer and
15 mesothelioma mortality ([Larson et al., 2010b](#); [Moolgavkar et al., 2010](#); [Sullivan, 2007](#);
16 [McDonald et al., 2004](#); [Amandus and Wheeler, 1987](#); [McDonald et al., 1986a](#)). These results are
17 further supported by animal studies that demonstrate the carcinogenic potential of LAA fibers
18 and tremolite fibers in rodent bioassays (see Section 4.1, 4.2, Appendix D). As a durable mineral
19 fiber of respirable size, this conclusion is consistent with the extensive published literature that
20 documents the carcinogenicity of amphibole fibers (as reviewed in [Aust et al., 2011](#); [Broaddus et
21 al., 2011](#); [Bunderson-Schelvan et al., 2011](#); [Huang et al., 2011](#); [Mossman et al., 2011](#)).
22   EPA's *Guidelines for Carcinogenic Risk Assessment* ([U.S. EPA, 2005a](#)) indicate that for
23 tumors occurring at a site other than the initial point of contact, the weight of evidence for
24 carcinogenic potential may apply to all routes of exposure that have not been adequately tested at
25 sufficient doses. An exception occurs when there is convincing information (e.g., toxicokinetic
26 data) that absorption does not occur by other routes. Information on the carcinogenic effects of
27 LAA via the oral and dermal routes in humans or animals is absent. The increased risk of lung
28 cancer and mesothelioma following inhalation exposure to LAA has been established by studies
29 in humans, but these studies do not provide a basis for determining the risk from other routes of
30 exposure. Mesothelioma occurs in the pleural and peritoneal cavities and, therefore, is not
31 considered a portal-of-entry effect. However, the role of indirect or direct interaction of asbestos
32 fibers in disease at these extrapulmonary sites is still unknown. There is no information on the
33 translocation of LAA to extrapulmonary tissues following either oral or dermal exposure, and
34 limited studies have examined the role of these routes of exposure in cancer. Therefore, LAA is
35 considered *carcinogenic to humans* by the inhalation route of exposure.

1 **4.6.1.1.** *Synthesis of Human, Animal, and Other Supporting Evidence*

2   Libby, MT workers have been the subject of multiple mortality studies demonstrating
3 increased cancer mortality in relation to estimated fiber exposure. Occupational studies
4 conducted in the 1980s (Amandus and Wheeler, 1987; McDonald et al., 1986a) as well as the
5 extended follow-up studies published in more recent years (Larson et al., 2010b; Sullivan, 2007;
6 McDonald et al., 2004) and additional analyses of the extended follow-up (Moolgavkar et al.,
7 2010) provide evidence of an increased risk of lung cancer mortality and of mesothelioma
8 mortality among the workers exposed to LAA in the Libby vermiculite mining and processing
9 operations. This pattern is seen in the lung cancer analyses using an internal referent group in
10 the larger follow-up studies (Larson et al., 2010b; Sullivan, 2007; McDonald et al., 2004), with
11 cumulative exposure analyzed using quartiles or as a continuous measure, and in the studies
12 reporting analyses using an external referent group (i.e., standardized mortality ratios; Sullivan,
13 2007; Amandus and Wheeler, 1987; McDonald et al., 1986a). McDonald et al. (2004) also
14 reported increasing risk of mesothelioma across categories of exposure; the more limited number
15 of cases available in earlier studies precluded this type of exposure-response analysis. This
16 association is also supported by the case series of 11 mesothelioma patients among residents in
17 or around Libby, MT, and among family members of workers in the mining operations
18 (Whitehouse et al., 2008), and by the observation of three cases of mesothelioma (two of which
19 resulted in death) in the Marysville, OH worker cohort identified as of June 2011 (Dunning et al.,
20 2012).

21   Although experimental data in animals and data on toxicity mechanisms are limited for
22 LAA, tumors were observed in tissues similar to those in humans (e.g., mesotheliomas, lung
23 cancer) indicating the existing data are consistent with the cancer effects observed in humans
24 exposed to LAA. Smith (1978) reported increased incidence of mesotheliomas in hamsters after
25 intrapleural injections of LAA. Additionally, studies in laboratory animals (rats and hamsters)
26 exposed to tremolite via inhalation (Bernstein et al., 2005; Bernstein et al., 2003; Davis et al.,
27 1985), intrapleural injection (Roller et al., 1997, 1996; Davis et al., 1991; Wagner et al., 1982;
28 Smith et al., 1979), or implantation (Stanton et al., 1981) have shown increases in mesotheliomas
29 and lung cancers. Tremolite from various sources was used and varied in fiber content and
30 potency (see Section 4.2, Appendix D). The most sensitive model for mesothelioma induction is
31 the Syrian golden hamster following asbestos inhalation, with different susceptibility between
32 species attributed to more rapid translocation to the pleural space (Donaldson et al., 2010).
33 Although McConnell et al. (1983a) observed no increase in carcinogenicity following oral
34 exposure to nonfibrous tremolite, the ability of this study to inform the carcinogenic potential of
35 fibrous tremolite through inhalation is unclear, and these study results contribute little weight to
36 the evaluation of the carcinogenicity of fibrous LAA.

37   The available mechanistic information suggests LAA induces effects that may play a role
38 in carcinogenicity (see Section 4.2 Appendix D). Several in vitro studies have demonstrated

1 oxidative stress and genotoxicity following LAA exposures in various cell types (Duncan et al.,
2 2010; Hillegass et al., 2010; Pietruska et al., 2010; Blake et al., 2007). LAA increased
3 intracellular ROS in both murine macrophages and human epithelial cells (Duncan et al., 2010;
4 Blake et al., 2007). Additionally, surface iron, inflammatory marker gene expression, and
5 aneugenic micronuclei were increased following exposure to LAA in human epithelial cells
6 (Duncan et al., 2010; Pietruska et al., 2010). Tremolite studies demonstrate cytotoxic and
7 clastogenic effects (e.g., micronucleus induction and chromosomal aberrations) of the fibers in
8 various cell culture systems.

9   In summary, the epidemiologic data demonstrate an association between exposure to
10 LAA and increased cancer risk. Supporting evidence of carcinogenic potential was observed in
11 the limited number of laboratory animal studies exposed to LAA or tremolite (see Tables 4-15
12 and 4-16 summarizing in vivo studies). Overall, the available evidence supports the conclusion
13 that LAA is *carcinogenic to humans*.

14

15 **4.6.2. Mode-of-Action Information (Cancer)**

16 **4.6.2.1. *Description of the Mode-of-Action Information***

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

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

1   **4.6.2.2. *Evidence Supporting a Mutagenic Mode of Action***

2   *Strength, consistency and specificity of the association*

3   Only limited genotoxicity analysis following exposure to LAA or tremolite has been

4   reported, although studies of other types of asbestos fibers have shown increases in genotoxicity

5   both in vitro and in vivo (reviewed in Huang et al., 2011). One in vitro study examined

6   genotoxicity of LAA by measuring DNA adduct formation following exposure via murine

7   macrophages (primary and immortalized; Blake et al., 2007). The data showed no increase in

8   adduct formation as compared to unexposed controls. A second study observed increases in

9   micronuclei induction in both normal human lung epithelial cells and XRCC1-deficient cells for

10   both Libby Amphibole and crocidolite asbestos (Pietruska et al., 2010). Two studies of tremolite

11   examined genotoxicity. The first found no significant increase in revertants in the Ames assay

12   (Athanasiou et al., 1992), which is similar to results obtained for other forms of asbestos. This

13   study did find, however, that tremolite exposure led to a dose-dependent increase in chromosome

14   number and micronuclei formation, which has also been described for other asbestos fibers (as

15   reviewed in Hei et al., 2006; Jaurand, 1997). Hei and colleagues (Okayasu et al., 1999)

16   performed mutation analysis with tremolite and found a dose-dependent increase in mutations in

17   CD59 in hamster hybrid cells. Although LAA- 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.

20

21   *Dose-response concordance and temporal relationship*

22   A dose-response concordance has not been established between the development of

23   genotoxicity and exposure to LAA or other amphibole asbestos. Genotoxicity studies of other

24   amphibole asbestos have examined gene mutations and chromosomal mutations, as well as DNA

25   damage resulting from ROS production following exposure. As recently reviewed by Huang et

26   al. (2011), there are a large number of in vitro studies that support possible genotoxic

27   mechanisms following exposure to fibers. There are fewer in vivo studies of the genotoxicity of

28   amphibole asbestos, and a very limited number of these were following inhalation exposure.

29   Some of these studies were performed in nonrelevant cell types for inhalation endpoints, and

30   some also were performed at doses higher than observed in environmental or occupational

31   asbestos exposures. Temporal relationship would be impacted by direct or indirect genotoxic

32   mechanism playing a role in asbestos-induced tumorigenesis. There is insufficient data to

33   conclude whether the observed genotoxic effects following exposure to amphibole asbestos

34   result from direct (e.g., spindle interference) or indirect (e.g., reactive oxygen species

35   production) mechanisms. The available evidence suggests a role for both direct and indirect

36   genotoxicity, but requires further research (Huang et al., 2011). Therefore, although these results

37   suggest a possible role for genotoxicity in the MOA of LAA, dose-response concordance and a

38   temporal relationship are difficult to determine.

Biological plausibility and coherence

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

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

Chronic inflammation has been observed following fiber exposure, which is often followed by fibrosis at the site of inflammation if the fibers persist (reviewed in Mossman et al., 2011). Macrophages phagocytose fibers and particulate matter and are activated to trigger the release of inflammatory cytokines, ROS, and growth factors. These responses lead to a sustained inflammatory response that can result in fibrosis at the site of fiber deposition. Chronic inflammation is hypothesized to contribute to a carcinogenic response through the production of ROS and increased cellular proliferation (Hanahan and Weinberg, 2011).

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

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

1 based on similar responses in cohorts analyzed (Musk et al., 2008; Hein et al., 2007; Levin et al.,
2 1998).

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

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

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

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

1   A temporal relationship has not been established between the development of chronic

2   inflammation and inhalation exposure to LAA. Chronic inhalation studies of tremolite

3   demonstrate an increase in chronic inflammation over time (Bernstein et al., 2005; Bernstein et

4   al., 2003) that may lead to fibrosis, or possibly tumor formation. A similar pattern has also been

5   observed in inhalation studies with other amphibole asbestos (as reviewed in Mossman et al.,

6   2011).

7   Chronic inflammation following exposure to fibers has been associated with the

8   development of both malignant and nonmalignant lung and pleural diseases (Bringardner et al.,

9   2008; Mossman and Churg, 1998). In vivo and in vitro studies have shown increases in

10   inflammation and inflammatory markers following exposure to LAA and tremolite up to 1 month

11   following single intratracheal instillation exposures in animal models (see Section 4.2,

12   Appendix D). Although inhalation studies are limited, the results of those studies demonstrate an

13   increase in chronic inflammation over time, similar to studies of other amphibole asbestos fibers

14   (Mossman et al., 2011). Overall, the evidence described above suggests chronic inflammation is

15   observed following Libby Amphibole and tremolite asbestos exposure.

16   Although slightly increased compared to controls, cytotoxicity in murine macrophage

17   cells exposed to LAA was decreased compared to other fiber types (Blake et al., 2008). No other

18   in vitro study examined cytotoxicity following exposure to LAA, although an increase in

19   apoptosis was demonstrated in this same cell system (Blake et al., 2008).

20   Compensatory proliferation in epithelial cells following cytotoxicity can lead to an

21   increase in mutations (both spontaneous and induced). This increase is generally offset by

22   increased levels of apoptosis, as in Blake et al. (2008). Recent studies in mice exposed to LAA

23   demonstrated increased collagen deposition and collagen gene expression, markers of fibrosis

24   (Smartt et al., 2010; Putnam et al., 2008). Tremolite and LAA exposure led to increases in both

25   fibrosis and tumorigenicity in all but one animal study, supporting a role for proliferation in

26   response to these fibers. Taken together with studies on other asbestos fibers, these data suggest

27   that cytotoxicity and cell proliferation may play a role in tumor formation.

28   Neither a dose-response concordance nor temporal relationship has been established

29   between the development of cytotoxicity and regenerative cellular proliferation and exposure to

30   LAA. However, cytotoxicity and regenerative cellular proliferation has been observed following

31   exposure to LAA as well as other amphibole asbestos through other routes of exposure in in vivo

32   assays (e.g., intratracheal instillation). Also, increases in markers of proliferative response have

33   been observed in in vitro studies of LAA and other amphibole asbestos in epithelial cells. These

34   results suggest exposure to LAA may lead to increases in cytotoxicity and regenerative

35   proliferation; however, the data are not sufficient to determine a dose-response relationship.

36   It is generally accepted that sustained cell proliferation in response to cytotoxicity can be

37   a significant risk factor for cancer (Correa, 1996). Sustained cytotoxicity and regenerative cell

38   proliferation may result in the perpetuation of mutations (spontaneous or directly or indirectly

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induced by the chemical), resulting in uncontrolled growth. It is also possible that continuous proliferation may increase the probability that damaged DNA will not be repaired. Reparative proliferation alone is not assumed to cause cancer. Tissues with naturally high rates of turnover do not necessarily have high rates of cancer, and tissue toxicity in animal studies does not invariably lead to cancer. Nevertheless, regenerative proliferation associated with persistent cytotoxicity appears to be a risk factor of consequence.

4.6.2.4. *Conclusions About the Hypothesized Modes of Action*

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

There are a limited number of studies on the genotoxicity of LAA and/or tremolite. However, the studies described in Section 4 suggest a possible role for mutagenicity in asbestos-induced carcinogenicity. These studies showed chromosomal aberrations, increases in micronuclei induction, and increased reactive oxygen species production which has been shown to lead to mutagenicity (see Section 4, Table 4-21). One study of DNA adduct formation did not show any DNA damage or adducts following exposure to LAA. Laboratory animal studies of other amphibole asbestos have demonstrated similar results (Huang et al., 2011). Further research in this area is needed in order to inform the possibility of a mutagenic MOA for LAA.

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

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

1   *Is the hypothesized mode of action relevant to humans*

2   Although limited for LAA, the evidence discussed above demonstrates that LAA

3   exposure results in genotoxicity in in vitro and in vivo studies in test animal species. Therefore,

4   the presumption is LAA would be genotoxic in humans. The few available data from human and

5   in vivo laboratory animal studies concerning the genotoxicity of amphibole asbestos suggest

6   consistency with this mechanism, but the studies are not sufficiently conclusive to provide direct

7   supporting evidence for a mutagenic MOA. This MOA is considered relevant to humans.

8   The evidence discussed above demonstrates that exposure to LAA and/or tremolite

9   asbestos lead to chronic inflammation. The available human data following exposure to LAA

10   and other amphibole asbestos suggest consistency with this mechanism being relevant to

11   humans. Data are inadequate to determine that a cytotoxic mechanism is operative following

12   exposure to LAA in exposed populations; however, none of the available data suggest that this

13   mechanism is biologically precluded in humans. Furthermore, both animal and in vitro studies

14   suggest that LAA causes cytotoxicity at exposures that may induce pulmonary cancers,

15   constituting positive evidence of the human relevance of this hypothesized MOA.

16

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

19   A mutagenic MOA is considered relevant to all populations and life stages. According to

20   EPA's Cancer Guidelines (U.S. EPA, 2005a) and Supplemental Guidance (U.S. EPA, 2005b),

21   there may be increased susceptibility to early-life exposures for carcinogens with a mutagenic

22   MOA. The weight of evidence is insufficient to support a mutagenic MOA for LAA

23   carcinogenicity and in the absence of chemical-specific data to evaluate differences in

24   susceptibility, 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 is not recommended.

27   Populations that may be more susceptible include those that may have varied fiber

28   toxicokinetics related to potential anatomical, physiological, and biochemical differences which

29   may impact fiber dosimetry (see Section 4.7). No data are available as to whether other factors

30   may lead to different populations or life stages being more susceptible to a chronic inflammation

31   MOA for LAA-induced tumors. For instance, it is not known how the hypothesized key events

32   in chronic inflammatory response (e.g., increased oxidative stress) to fibers interact with known

33   risk factors for human pulmonary or pleural carcinomas.

34   As with chronic inflammation, populations that may be more susceptible to increased

35   cytotoxicity following exposure to LAA include those that may have varied fiber toxicokinetics

36   related to potential anatomical, physiological, and biochemical differences which may impact

37   fiber dosimety (see Section 4.7). No data are available as to whether other factors may lead to

38   different populations or life stages being more susceptible to a cytotoxic MOA for LAA-induced

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1 tumors. For instance, it is not known how the hypothesized key events (e.g., interference with

2 the spindle apparatus) in this MOA interact with known risk factors for human pulmonary or

3 pleural carcinomas.

4

5 *Summary*

6   Research on multiple types of elongate mineral fibers supports the role of multiple modes

7 of action following exposure to LAA. Of the MOAs described above, the evidence that chronic

8 inflammation, genotoxicity and cytotoxicity, and cellular proliferation may all play a role in the

9 carcinogenic response to LAA is only suggestive (see Table 4-23). In vitro studies provide

10 evidence that amphibole asbestos is capable of eliciting genotoxic and mutagenic effects in

11 mammalian respiratory cells; however, direct evidence linking mutagenicity to respiratory cells

12 following inhalation exposure is lacking. Results of the in vivo studies described here are

13 consistent with the hypothesis that some forms of amphibole asbestos act through a MOA

14 dependent on cellular toxicity. This is largely based on the observations that cytotoxicity and

15 reparative proliferation occur following subchronic exposure and bronchiolar tumors are

16 produced at exposure levels that produce cytotoxicity and reparative proliferation. However,

17 dose-response data in laboratory animal studies for damage/repair and tumor development are

18 limited because a limited number of inhalation studies exist that used multiple doses of fibers.

19 Although evidence is generally supportive of a MOA involving chronic inflammation or cellular

20 toxicity and repair, there is insufficient evidence to support these hypotheses; thus, a linear

21 approach is used to calculate the inhalation cancer unit risk in accordance with the default

22 recommendation of the 2005 *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a). It

23 is possible that multiple MOAs discussed above, or an alternative MOA, may be responsible for

24 tumor induction.

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

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

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

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

1 **4.6.2.5. *Application of the Age-Dependent Adjustment Factors***

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

3 support a mutagenic MOA for LAA carcinogenicity. Therefore, according to EPA's

4 *Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens*

5 (U.S. EPA, 2005b), the application of the age-dependent adjustment factors is not recommended.

6

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4.7. SUSCEPTIBLE POPULATIONS

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

There are also factors that may influence one's exposure potential to asbestos based on life stage or other characteristics. For example, children spend more hours outside and may engage in activities which impact exposure potential compared to adults (U.S. EPA, 2006b; NRC, 1993). Because life stage and activity patterns can increase the potential for health effects from exposure, these factors define who may be more susceptible to health effects due to greater exposure. Section 2.3 discusses this exposure potential, including how children, workers, household contacts, and residents may be exposed to LAA.

4.7.1. Influence of Different Life Stages on Susceptibility

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

1 **4.7.1.1.** *Life-Stage Susceptibility*

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

10   No in utero exposure data exist for LAA but limited observations in stillborn infants
11 indicate transplacental transfer of tremolite (Haque et al., 1998; Haque et al., 1996) and other
12 asbestos and nonasbestos fibers does occur (Haque et al., 1998; Haque et al., 1996; Haque et al.,
13 1992; Haque et al., 1991). Transplacental transfer of asbestos was also demonstrated in animals
14 following maternal exposure by gavage (Haque et al., 2001) or injection (Haque and Vrazel,
15 1998; Cunningham and Pontefract, 1974; see Section 3). These studies did not evaluate the
16 sources or levels of exposure, and injection studies are a less relevant route of exposure
17 compared to inhalation. Based on these studies, LAA fibers may be transferred through the
18 placenta, resulting in prenatal exposure at any stage of fetal development.

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

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

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1   decreased postimplantation survival in cultured embryos (Schneider and Maurer, 1977).

2   However, chrysotile ingested via drinking water did not affect embryonic survival in vivo in

3   pregnant mice (Schneider and Maurer, 1977). Altogether, the data provide no clear evidence for

4   increased susceptibility following early life or in utero asbestos exposure.

5   Several studies have examined the susceptibility of asbestos exposure on young children,

6   including how fiber deposition is affected by the physiological differences in children's lungs.

7   Evidence suggests that fiber deposition is increased in the lungs of children compared with adults

8   (Bennett et al., 2008; Isaacs and Martonen, 2005; Asgharian et al., 2004; Phalen and Oldham,

9   2001; Oldham et al., 1997; Schiller-Scotland et al., 1994; Phalen et al., 1985). Nasal deposition

10 of particles was lower in children compared to adults—particularly during exercise (Becquemin

11 et al., 1991). The lung and nasal depositional differences are partially due to structural

12 differences across life stages that change the depositional pattern of different fiber sizes, possibly

13 altering the site of action, and resulting in differential clearance and subsequent health effects.

14 However, it is unclear whether the lung surface, body weight, inhalation volume, or exposure

15 patterns are most determinative of dose.

16   There are a few studies analyzing noncancer outcomes in children exposed to Libby

17 Amphibole. A Libby medical screening program collected data on 7,307 participants, including

18 600 children aged 10−17 years, which represents 8.2% of the cohort (Peipins et al., 2003).

19 Pulmonary function tests showed that none of these children had moderate or severely restricted

20 lung function (ATSDR, 2002, 2001b). This program also studied chest radiographs for those

21 18 years or older (Noonan et al., 2006; Peipins et al., 2003; ATSDR, 2001b), but x-rays were not

22 conducted on children. Among 1,003 adolescents and young adults (ages 10 to 29) who were

23 ≤age 18 in 1990 when the mining/milling operations closed (Vinikoor et al., 2010), there was

24 little variation in prevalence of shortness of breath, physician-diagnosed lung disease, or

25 abnormal pulmonary function tests (restrictive, obstructive, or mixed, based on FEV_1 and FVC

26 values) across the exposure categories. This analysis does not directly address the issue of

27 susceptibility by age, however, because a comparison with people exposed only at older ages is

28 not included.

29   Based on limited studies described below, it is possible that early life stage exposure may

30 increase the risk of noncancer outcomes in adulthood. Altered immunity (Zerva et al., 1989) and

31 asbestosis (Voisin et al., 1994) were observed in adults following tremolite exposure during

32 childhood. No other studies of noncancer outcomes in early life stages of humans or

33 experimental animals exposed to LAA have been reported. Thus, additional research is needed

34 to establish the clinical significance of these findings and to expand understanding of the

35 progression of the adverse health effects in the community.

36   To address the potential for increased susceptibility to cancer from early lifetime

37 exposures, one needs to consider if there is evidence of differential health effects such as

38 increased potency from early lifetime exposure, changes in latency based on the age of exposure,

1 or cancers observed with early lifetime exposures not seen with adult exposures. There are no
2 published reports that can directly answer these questions for exposure to LAA. Few cancers
3 occurring in childhood have been documented in children exposed to any form of asbestos.
4 Examples of cases include a 17-year-old exposed to chrysotile and tremolite (Andrion et al.,
5 1994) and a 3-year-old exposed to chrysotile (Lieben and Pistawka, 1967), both of whom
6 developed mesothelioma. Notably, childhood mesothelioma may have an etiology that is
7 different from that of the disease seen in adults, further confounding interpretation of these data
8 (Cooper et al., 1989).
9   Studies involving populations exposed to other types of asbestos have yielded equivocal
10 results on the carcinogenic effects following exposures occurring earlier in life, and few evaluate
11 very early life exposures. One study in the United Kingdom described occupational exposure to
12 chrysotile, crocidolite, and amosite for a group of 900 women. First exposure from ages
13 15−24 years led to a higher relative mortality risk for lung and pleural cancer compared with
14 women who were first exposed at older ages (SMR 30 based on 12 observed and 0.4 expected,
15 SMR 8 based on 4 observed and 0.5 expected, and SMR 6.7 based on 6 observed and 0.9
16 expected in the first exposure at ages 15−24, 25−34, and ≥35 years, respectively; Newhouse et
17 al., 1972). In a study in Wittenoom, Western Australia, 27 individuals were diagnosed with
18 mesothelioma who had been environmentally exposed to crocidolite (i.e., residents of the town
19 but not directly employed in the area's crocidolite mining and milling industry); 11 of these
20 subjects were <15 years old at the time of exposure (Hansen et al., 1998). One-third of all the
21 subjects were younger than 40 years old when diagnosed, but the authors found no increase in
22 mesothelioma mortality rates when analyzed by age at first exposure. However, risk was
23 significantly increased based on time from the first exposure, duration of exposure, and
24 cumulative exposure (Hansen et al., 1998). Additional studies of this cohort found that the
25 mesothelioma mortality rate was lower for those first exposed (based on age residence in the area
26 began) to crocidolite at ages <15 years (n = 24; mesothelioma mortality rate 47 per
27 100,000 person-year) compared with those first exposed at ages ≥15 years (n = 43; mesothelioma
28 mortality rate 112 per 100,000 person-year; Reid et al., 2007). The hazard ratio for age at first
29 residential exposure of ≥15 years compared with <15 years was 3.83 (95% CI: 2.19, 6.71),
30 adjusting for cumulative exposure, gender, and an interaction term for gender and cumulative
31 exposure. Altogether, these studies do not clarify whether exposure during childhood yields
32 different adverse health effects compared with exposure during adulthood.
33   Relatively few studies have examined the effects of asbestos exposure in juvenile
34 animals. Oral exposure to nonfibrous tremolite did not increase tumors in the offspring of rats
35 compared to controls (NTP, 1990b; McConnell et al., 1983a). Similar studies of other forms of
36 asbestos reported an increase of various neoplasms in the offspring (NTP, 1990a, 1988, 1985;
37 McConnell et al., 1983b; McConnell et al., 1983a), but another study reported none (NTP, 1983).
38 No cancer bioassays have been performed in juvenile animals exposed to LAA. Based on these

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

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

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

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

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 et

6   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 LAA particles reported in Table 2-2. This study

9   found that, in general, women had a greater retention of particles compared to men because men

10   had higher ventilation rates compared to women; however, the overall deposition rate was higher

11   in the men (Bennett et al., 1996).

12   Most occupational studies for LAA have examined the effects of exposure only in men

13   (Moolgavkar et al., 2010; Sullivan, 2007; McDonald et al., 2004; Amandus et al., 1988;

14   Amandus et al., 1987b; Amandus and Wheeler, 1987; McDonald et al., 1986a; McDonald et al.,

15   1986b). There is limited information specifically on women exposed to LAA. 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 LAA.

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, socioeconomics, 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 gender, 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 LAA reported in Table 2-2) in African Americans compared to

31   Caucasians (Bennett and Zeman, 2005). Furthermore, nasal breathing during exercise occurred

32   less in Caucasians compared to African Americans in this study (Bennett et al., 2003).

33   Of the occupational and residential studies for LAA, the vast majority of subjects with

34   known race were white, precluding the ability to conduct an analysis of racial and

35   ethnicity-related differences in the mortality risks within the Libby worker cohort. In a study of

36   occupational exposure to chrysotile asbestos in a textile factor, lung cancer mortality risk in

37   relation to exposure was lower in nonwhite males (0.84, 95% CI: 0.52−1.27) compared to white

1   males (2.34, 95% CI: 1.94−2.79), although a statistically significant increase in SMR was

2   observed for nonwhite males at high exposure levels (≥120 fiber-yr/mL; Hein et al., 2007). This

3   observed difference could be due to a lower prevalence of smoking among nonwhite compared

4   with white males (Hein et al., 2007).

5

6   **4.7.4. Influence of Genetic Polymorphisms on Susceptibility**

7   *XRCC1* is a DNA damage repair gene. A recent study demonstrated that

8   *XRCC1*-deficient cells exposed to Libby Amphibole or crocidolite asbestos demonstrated

9   increased levels of micronuclei induction (Pietruska et al., 2010). Two other studies examined

10   *XRCC1* polymorphisms in relation to disease risk with other types of asbestos exposure. Zhao et

11   al. (2006) found no association between *XRCC1* polymorphisms and asbestosis in

12   asbestos-exposed workers. A study by Dianzani et al. (2006), however, did find an association

13   between *XRCC1* and asbestos-induced lung disease in a population exposed to asbestos

14   pollution. Further work is necessary, with clear definitions of patient populations and their

15   exposure levels, so that these studies and others can be compared to determine if *XRCC1*

16   polymorphisms increase susceptibility to adverse health effects following exposure to LAA.

17   Superoxide dismutases are free radical scavengers that dismutate superoxide anions to

18   oxygen and hydrogen peroxide. SODs are expressed in most cell types exposed to oxygen.

19   Several common forms of SODs occur and are named by the protein cofactor: copper/zinc,

20   manganese, iron, or nickel. A recent study observed no significant alterations in levels of

21   intracellular SOD following a 3-hour exposure to LAA in mice (Blake et al., 2007). Other

22   studies in humans and mice have examined SOD expression in relation to other types of asbestos

23   exposure. Manganese SOD activity was elevated in biopsies of human asbestos-associated

24   malignant mesothelioma, although no genotypic differences were found to be related to this

25   change in activity (Hirvonen et al., 2002). Other studies have focused on the role of extracellular

26   superoxide dismutase (EcSOD) and asbestos-induced pulmonary disease (Kliment et al., 2009;

27   Gao et al., 2008; Fattman et al., 2006; Tan et al., 2004). These studies have suggested a

28   protective effect of EcSOD, because mice that lack this form of SOD have increased sensitivity

29   to asbestos-induced lung injury (Fattman et al., 2006). Familial studies showing an unusually

30   high incidence of mesothelioma suggest that genetic factors might play a role in the etiology of

31   mesothelioma (Ugolini et al., 2008; Huncharek, 2002; Roushdy-Hammady et al., 2001), although

32   whether a genetic factor or a common environmental element leads to the similar responses in

33   these families is difficult to determine. Increased interest in the role of genetic factors in

34   asbestos-related health outcomes has led to several analytical studies on specific genetic

35   polymorphisms. A review of 24 published reports (19 studies) discusses the current state of

36   knowledge regarding genetic susceptibility associated with asbestos-related diseases (in

37   particular, malignant pleural mesothelioma). Results from several studies demonstrated an

38   association between asbestosis-related diseases and *GSTM1*-null polymorphism, whereas results

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

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

4.7.5. Influence of Health Status on Susceptibility

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

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

1 another study, bronchial asthma was examined as a potential confounding variable for

2 asbestos-related effects on pulmonary function, although no confounding was observed

3 (Whitehouse, 2004).

4

5 **4.7.6. Influence of Lifestyle Factors on Susceptibility**

6   Smoking can impair clearance of particles from the lung (Camner, 1980; Cohen et al.,

7 1979) and increase deposition of asbestos fibers (Sekhon et al., 1995; McFadden et al., 1986).

8 These effects could lead to the retention of more inhaled asbestos fibers and for a longer period

9 of time in smokers compared to nonsmokers, even when controlling for initial exposure.

10 Evidence of smoking-related susceptibility to pulmonary effects of asbestos was reported by

11 Christensen and Kopylev (2012) using data from the O.M. Scott, Marysville, OH plant cohort

12 described by Rohs et al. (2008). The amount of LAA exposure required to elicit the same

13 increase in risk of localized pleural thickening was considerably lower (sixfold) for smokers

14 compared with nonsmokers.

15   No studies were identified that examined lifestyle factors specifically with respect to

16 LAA and cancer susceptibility. Lifestyle factors such as exercise, nutritional status, and smoking

17 habits could affect the biological effects of asbestos exposure through various mechanisms. For

18 example, those with more physically demanding jobs or those who regularly engage in vigorous

19 exercise might experience increased lung deposition from fine particles or fibers compared to

20 those with a more sedentary lifestyle (Phalen et al., 2006; Becquemin et al., 1991). Randomized

21 controlled trials of vitamin supplementation (beta-carotene and retinol) have been conducted for

22 asbestos-related lung cancer, but results do not support a protective effect (Cullen et al., 2005).

23   For lung cancer, a synergistic relationship between cigarette smoking and asbestos

24 exposure has been demonstrated (Wraith and Mengersen, 2007; Hammond et al., 1979; Selikoff

25 and Hammond, 1979). Research has suggested that asbestos fibers might also enhance the

26 delivery of multiple carcinogens in cigarette smoke, and that cigarette smoking decreases the

27 clearance mechanisms in the lungs and could, therefore, lead to an increase in fiber presence in

28 the lungs (Nelson and Kelsey, 2002). Smoking likely causes genetic alterations associated with

29 lung cancer (Landi et al., 2008) that might increase the carcinogenic risk from exposure to

30 asbestos. Benzo[a]pyrene, a component of tobacco, also has been observed to enhance the

31 carcinogenic effects of asbestos (Loli et al., 2004; Kimizuka et al., 1987; Mossman et al., 1984;

32 DiPaolo et al., 1983; Mossman et al., 1983; Reiss et al., 1983).

33

34 **4.7.7. Susceptible Populations Summary**

35   A very limited amount of information is available on exposure to LAA early in life that

36 could lead to increased risk of asbestos-induced disease later in life. Due to the long latency

37 period of some diseases in relation to asbestos exposure in general, adverse effects may be more

1 likely to be observed with an increase in age. This assumption requires further investigation.
2 The number of women who have been occupationally exposed to LAA is very small, and health
3 risks have not been evaluated specifically for this group. Differences between men and women
4 in residential sources and types of exposure (e.g., types of activities done in the household) also
5 preclude the possibility of drawing conclusions regarding the relative susceptibility of women
6 compared with men to health effects of exposure to LAA. Similarly, sufficient data are not
7 available to draw conclusions regarding racial or ethnic variation in susceptibility to diseases
8 caused by exposure to LAA. In addition, the potential modifying effects of genetic
9 polymorphisms, preexisting health conditions, nutritional status, and other lifestyle factors have
10 not been studied, specifically as related to exposure of LAA and health outcomes.

5. EXPOSURE-RESPONSE ASSESSMENT

5.1. ORAL REFERENCE DOSE (RfD)

An oral reference dose is not derived due to a lack of data on the toxic effects of Libby

Amphibole asbestos[21] (LAA) following oral exposure.

5.2. INHALATION REFERENCE CONCENTRATION (RfC)

An RfC is defined as "an estimate of an exposure (including sensitive subgroups) that is

likely to be without an appreciable risk of adverse health effects over a lifetime" (U.S. EPA,

2002). Consequently, studies that relate these adverse health effects to exposure levels are

necessary for RfC derivation. Preferred study characteristics for RfC derivation include

adequate exposure-response information, ideally with quantitative exposure estimates to

distinguish exposure levels in the study subjects, and adequate duration of follow-up to identify

health effects of interest.

Overview of the Methodological Approach

The noncancer effects which were evaluated in populations with exposure to LAA (see

Sections 4.1.2 and 4.1.3) are pulmonary effects (including asbestosis, pleural thickening

[localized or diffuse], and other nonmalignant respiratory disease), cardiovascular disease-related

mortality, and autoimmune effects. Localized pleural thickening (LPT) was deemed the most

sensitive and was thus selected as the critical effect to derive the RfC (see Section 5.2.2.3). A

benchmark response (BMR) of 10% extra risk was selected for exposure-response modeling (see

Section 5.2.2.5.

RfCs are based on human data when appropriate epidemiologic studies are available.

The general approach to developing an RfC from human epidemiologic data is to quantitatively

evaluate the exposure-response relationship for that agent to derive a specific estimate of its

effect on the risk of the selected outcome in the studied population. For the current assessment,

the first step was to identify the most appropriate data set available to quantitatively estimate the

effects of LAA exposure on pleural effects. Studies of three different cohorts provide such

quantitative exposure-response information. Two are of occupationally exposed cohorts. The

first one is Libby Workers (Larson et al., 2012a) and the second one is Marysville workers (Rohs

et al., 2008). The third consisted of community members with nonoccupational exposure, who

resided around the Western Minerals plant in Minneapolis (Alexander et al., 2012). Upon

evaluating these three cohorts, the Marysville workers were selected as the most appropriate for

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

10   Among the Marysville workers, there were differences in the availability of exposure and
11   health outcome data over time. No industrial hygiene measurements were available before 1972.
12   Health examinations were performed at two time points, 1980 and 2002−2005, using different
13   x-ray reading protocols and different film readers. Thus, the subgroup of workers with the
14   highest quality exposure and outcome evaluation information, was determined to be those
15   workers who were hired in 1972 or later, and who had health examinations performed in
16   2002−2005; this group was selected as the primary analytic data set for derivation of the RfC
17   (see Section 5.2.2.2). Once the relevant data describing a well-defined group of individuals
18   along with their exposures and health outcomes were selected, a suite of appropriate statistical
19   model forms was evaluated. Before performing any modeling, biological and epidemiological
20   features were considered to determine a priori which variables and which models would be most
21   suitable for the given exposure and health outcome (see Section 5.2.2.6.1). Based on these
22   considerations, the Dichotomous Hill model was considered to be the most flexible and
23   potentially most suitable model form; however, all model forms suitable for dichotomous
24   epidemiological data were examined. Each model was evaluated for adequate fit to the data,
25   with each person's individual-level exposures and outcomes modeled using a variety of exposure
26   metrics. Appropriate covariates, which may be important predictors of LPT risk, were evaluated
27   for potential confounding in the statistical model.

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

1   analytic data set. However, based on the epidemiological literature, TSFE is expected to be a

2   major predictor of LPT risk and thus an important variable in evaluating the exposure-response

3   relationship with LAA. Because inclusion of TSFE in the model did not improve model fit (and

4   it was not a significant predictor), alternative strategies were explored to incorporate the effect of

5   TSFE into the exposure-response model. EPA decided to use a hybrid modeling strategy. First,

6   the effect of TSFE was estimated in a larger subset of the Marysville workers (all those with

7   health evaluations in 2002−2005, regardless of hire date) with a broader range of TSFE values,

8   using the same model as for the primary analytic data set. Next, this estimated effect was carried

9   over to the model for the primary analytic data set (workers hired in 1972 or later with health

10   examinations in 2002−2005) as a fixed regression coefficient, and the benchmark concentration

11   and lower limit of the benchmark concentration (BMCL) estimated.

12   The BMCL from the "hybrid" modeling approach was used as the point of departure.

13   Uncertainty factors were then applied to derive an RfC (see Section 5.2.3). Alternative analyses

14   are presented in Section 5.2.4 and 5.2.5 with a summary in Section 5.2.6. Uncertainties in this

15   noncancer assessment are described in detail in Section 5.3.

16

17   **5.2.1. Choice of Principal Study**

18   **5.2.1.1. *Candidate Studies***

19   While there are studies of health effects in humans, no studies in laboratory animals on

20   the inhalation route of exposure are suitable for derivation of an RfC because the available

21   animal studies lack adequate LAA exposure-response information and are of a short-term

22   duration.

23   Multiple studies have identified several noncancer health effects in humans that could be

24   considered as potential critical effects for the derivation of an RfC. The noncancer health effects

25   range in severity from mortality to pleural abnormalities. Five mortality studies of cohorts of

26   workers who mined, milled, and processed Libby vermiculite identified increased risk of

27   mortality from noncancer causes including nonmalignant respiratory disease—especially

28   asbestosis and chronic obstructive pulmonary disease (COPD) (Larson et al., 2010b; Sullivan,

29   2007; McDonald et al., 2004; Amandus and Wheeler, 1987; McDonald et al., 1986a)—as well as

30   cardiovascular disease (Larson et al., 2010b). Because an RfC is intended to be a level that is

31   likely to be without appreciable risk of deleterious effects, these mortality studies were not

32   considered as candidates for RfC derivation because other human studies exist that provide

33   evidence of an association between LAA and less severe outcomes generally occurring at lower

34   levels of exposure, such as parenchymal and pleural abnormalities. More detailed discussion of

35   the choice of the critical effect for the RfC is presented in Section 5.2.2.3 and Appendix I.

36   Studies conducted among two cohorts of occupationally exposed workers have shown

37   radiographic evidence of health effects on the lung and pleura (a thin tissue surrounding the lung

1   and lining the chest cavity). These effects include pleural thickening and fibrosis of the lung

2   (Larson et al., 2012a; Larson et al., 2012b; Larson et al., 2010b; Rohs et al., 2008; Amandus et

3   al., 1987a; McDonald et al., 1986b; Lockey et al., 1984). Studies of exposed community

4   members in Libby, MT and Minneapolis, MN have also reported evidence of health effects on

5   the lung and pleura (Alexander et al., 2012; Weill et al., 2011; Muravov et al., 2005; Peipins et

6   al., 2004b; Whitehouse, 2004; Peipins et al., 2003, see Section 4.1.2).

7   Although data exist that define exposures from some activities in the Libby, MT

8   community studies (see Section 2.3), the available exposure data were insufficient to estimate

9   exposure at the individual level. Only studies that include exposure measurement data allowing

10 estimation of individual exposures and identify appropriate health effects are considered for RfC

11 derivation (Alexander et al., 2012; Larson et al., 2012a; Rohs et al., 2008; Amandus et al., 1987a;

12 McDonald et al., 1986b; Lockey et al., 1984). Among these six candidate principal studies (see

13 Figure 5-1), one study was of the community surrounding a vermiculite processing facility in

14 Minneapolis, MN (Alexander et al., 2012), three were occupational studies of exposed workers

15 in Libby, MT (Larson et al., 2012a; Amandus et al., 1987a; McDonald et al., 1986b), and two

16 were studies in workers from the Marysville, OH facility (Rohs et al., 2008; Lockey et al., 1984).

17 The studies by Larson et al. (2012a) and Rohs et al. (2008) represent the most recent evaluations

18 of the occupational studies of exposed workers in Libby, MT and Marysville, OH workers,

19 respectively, and were considered as candidate principal studies for the derivation of the RfC,

20 along with the study of the Minneapolis community by Alexander et al. (2012).
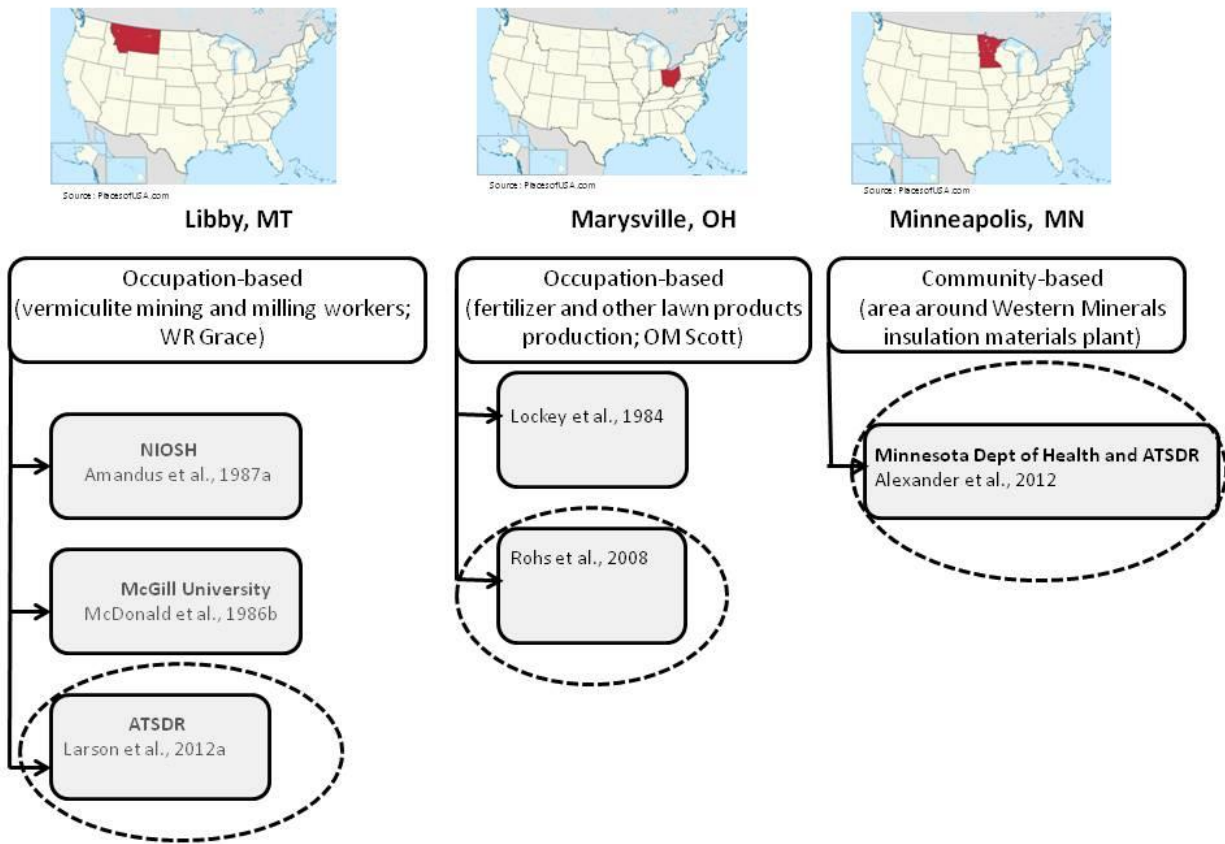
Figure 5-1. Candidate studies for derivation of the reference concentration (RfC) in three different study populations, with the most recent study of each population circled.

1   Each study has adequate reporting of the studied populations, methods of assessment of

2   health outcome(s) of interest, and statistical analyses. Each study also demonstrated associations

3   between exposure to LAA and radiographic signs of nonmalignant respiratory effects,

4   specifically pleural thickening (circumscribed and/or localized and/or diffuse) and small

5   interstitial opacities (indicative of parenchymal damage) (ILO, 2002, 1980, 1971). Table 5-1

6   summarizes the candidate principal studies. See Section 4.1.1 for detailed study information and

7   results.

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

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

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

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

[a]Although ILO 1980 guidelines were used, modifications were made such that the radiographic abnormalities were equivalent to ILO 2000 guidelines.

[b]Radiographic abnormalities were evaluated together as a group, and LPT was not modeled separately. However, in the lower exposure group, all 17 cases had pleural plaques (either alone or with another abnormality; personal communication from Bruce Alexander, 7 June 2013).

[c]Dates used in analysis by Rohs et al. (2008) are reported to be based on ATSDR (2005).

JEM = job-exposure matrix; IQR = interquartile range; PCM=phase contrast microscopy.

1   **5.2.1.2. *Evaluation of Candidate Studies and Selection of Principal Study***

2   The candidate studies were further evaluated in terms of quality attributes that would

3   support their use as a principal study in the derivation of an RfC. When selecting among

4   candidate principal studies, several factors, summarized in Table 5-2, are generally considered.

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

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

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

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

1   Two of the studies were conducted in occupationally exposed populations (Larson et al.,
2   2012a; Rohs et al., 2008), while the third was conducted in community residents without
3   occupational exposure (Alexander et al., 2012). Each of the studies provided estimates of
4   cumulative LAA exposure (in fiber/cc-yr). However, there were differences in exposure sources
5   and intensity. Of the two occupational studies, one (Larson et al., 2012a) occurred in a setting
6   where both occupational and nonoccupational exposures were relevant due to the close proximity
7   of the local vermiculite mining and milling operations to the Libby, MT community.
8   Nonoccupational exposures in the Libby, MT community were not quantified and thus were not
9   accounted for in the overall estimates of individual exposure. In the other study (Rohs et al.,
10 2008), exposures were generally lower and considered to be limited to the occupational setting
11 because most of the employees showered and changed into civilian clothes at the end of the work
12 shift. Therefore, nonoccupational exposure in the Marysville workers was assumed to be
13 minimal. However, in both cases, the exposure estimates for earlier years are subject to
14 uncertainty. For example, data on job and department were missing for the majority of the
15 workers in the Libby facility hired before 1960 (Larson et al., 2012a). In the Marysville facility,
16 no fiber measurements exist before 1972 (Rohs et al., 2008), although exposure estimates for this
17 period were constructed based on measurements taken in subsequent years (see Appendix F).
18 The third study, by Alexander et al. (2012), was conducted among Minneapolis community
19 residents (including a higher proportion of women compared to the other studies). The
20 researchers attempted to estimate individual community members' exposure based on facility
21 emissions and the individual's specific activities that were considered to be related to exposure
22 (e.g., installing or removing vermiculite insulation or playing in or around waste piles).
23 However, exposure estimates were constructed from modeled emissions based on very sparse
24 data from the facility's discharge stacks and activity-based exposure reconstruction, and as a
25 result are considered to have greater uncertainties.

1   As noted in Table 5-2, relatively lower exposure levels are advantageous for developing
2   an RfC (given sufficient numbers of individuals with the health effect of interest) due to
3   uncertainties inherent in extrapolating from high-intensity (e.g., occupational) exposure levels to
4   low-intensity (e.g., environmental) exposure levels. A limitation of the studies conducted among
5   workers at the Libby facility is that the exposure levels experienced for some job codes are high
6   compared with those in the other two studies (see Table 5-1; e.g., based on the interquartile range
7   (IQR) of exposure from the 25th percentile value of 0.4 fibers/cc-yr to the 75th percentile value of
8   15.8 fibers/cc-yr, 25% of participants had cumulative exposures above 15.8 fibers/cc-yr).
9   Another limitation of these studies for conducting exposure-response analysis for LPT is that
10   many of the Libby workers were likely to have also been residents in Libby both before and
11   during their employment at the mining and related operations, so their actual TSFE to any LAA
12   exposure may be longer than their TSFE to occupational exposure to LAA. Therefore, data on
13   this important variable is uncertain. Thus, the Libby workers study (Larson et al., 2012a) is less
14   preferable for RfC derivation. The other two studies (Alexander et al., 2012; Rohs et al., 2008)
15   had generally lower exposure levels in comparison; however, greater uncertainty exists in the
16   exposure estimates for the Minneapolis cohort because few measurements of facility emissions
17   into the ambient air (Adgate et al., 2011). Indeed, the authors estimate that the numerical
18   uncertainty in exposure estimates is likely to be at least an order of magnitude, perhaps much
19   greater. Further, it is unclear whether TSFE is well characterized for the nonoccupational
20   exposures in the Minneapolis cohort. In contrast, the study of workers at the O.M. Scott plant in
21   Marysville, OH (Rohs et al., 2008) used exposure estimates based on extensive industrial
22   hygiene sampling data, individual worker histories, and employee focus interviews. Thus, Rohs
23   et al. (2008) is the preferred study for derivation of the RfC.
24
25   **5.2.2. Methods of Analysis**
26   **5.2.2.1. *Exposure Assessment***
27   EPA collaborated with a research team at the University of Cincinnati to update the
28   exposure reconstruction for use in the job-exposure matrix (JEM) for all workers in the
29   Marysville, OH cohort, taking into account additional industrial hygiene data that were
30   unavailable for previous studies conducted in this cohort (Rohs et al., 2008; Lockey et al., 1984).
31   Exposure estimates for each worker in the O.M. Scott Marysville, OH plant were developed
32   based on the arithmetic mean of the available industrial hygiene data from the plant. The
33   exposure assessment procedure is described in Appendix F. In brief, occupational exposure was
34   estimated for each worker and adjusted to a cumulative human equivalent exposure for
35   continuous exposure, incorporating adjustments for different inhalation rates in working versus
36   nonworking time. These adjustments take into account the extensive seasonal changes in work
37   hours at the Marysville facility (see Appendix F).

1   **5.2.2.2. *Data Sets for Modeling Analyses***

2   Section 5.2.1.2 describes the selection of the Rohs et al. (2008) cohort as the principal

3   study. As explained below, EPA further considered the differential quality of exposure data for

4   different years within this data set and concluded that estimation of an RfC would be improved if

5   the primary data set for exposure-response modeling was restricted to the subset of workers hired

6   in 1972 and later, when higher quality exposure information was available.

7   As described in Section 5.2.1.2, the Marysville workers evaluated by Rohs et al. (2008)

8   formed the principal analytic group for derivation of the RfC, with exposure information updated

9   and augmented by the University of Cincinnati in collaboration with EPA. As noted in

10 Section 4.1.1.2.2 and Appendix F, the more reliable exposure estimates are considered to be

11 those from 1972 and later, as these data were based on analytical measurements. Therefore, the

12 primary modeling to derive a point of departure (POD) was conducted among the subgroup of

13 workers evaluated by Rohs et al. (2008) that began work in 1972 or later and had no previous

14 occupational exposure to asbestos (119 workers: 13 cases of localized pleural thickening and

15 106 unaffected individuals). However, information from workers who were hired before 1972,

16 as well as from workers who were evaluated only in the earlier study by Lockey et al. (1984),

17 were also considered in separate analyses (details and results of the analysis are in Appendix E).

18 In each case, to avoid any potential bias from previous unmeasured occupational exposure to

19 asbestos, only the data from those who did not report any previous occupational exposure to

20 asbestos were used.

21   Table 5-3 and Figure 5-2 present summary characteristics for the three analytic groups.

22 The first is the combined information for the 1980 (Lockey et al., 1984) and 2002−2005 (Rohs et

23 al., 2008) evaluations, comprising all workers without previous exposure to asbestos; a detailed

24 description of how these data were combined is in Appendix E. The second group is all workers

25 evaluated in 2002−2005 without previous exposure to asbestos (as described by (Rohs et al.,

26 2008). The third group is a subset of the workers evaluated in 2002−2005, hired in 1972 or later,

27 without previous exposure to asbestos (primary analytic group). For the groups comprising only

28 individuals evaluated in 2002−2005, exposure estimates covered the period from start of work

29 through the date of job stop or at the time vermiculite ceased to be used in 2000, whichever

30 occurred earlier.

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

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

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

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

[b]Data on smoking status were missing for five individuals in the full cohort. Data on body mass index (BMI) was unavailable for 216 individuals in the full cohort, 34 individuals examined in 2002−2005, and 21 individuals examined in 2002−2005 who were hired in 1972 or later.

[c]RTW exposures are calculated using midpoint of each work season.

All individuals evaluated in 1980 and/or in 2002-2005
Total $n = 434$
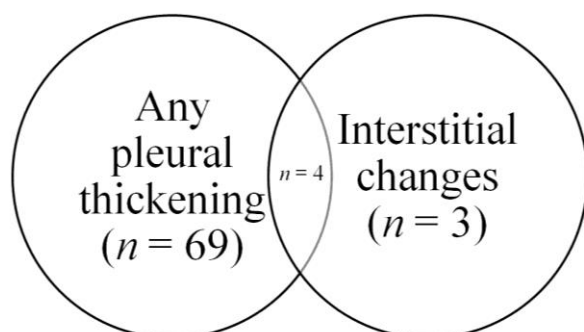
Individuals evaluated in 2002-2005
Total $n = 252$
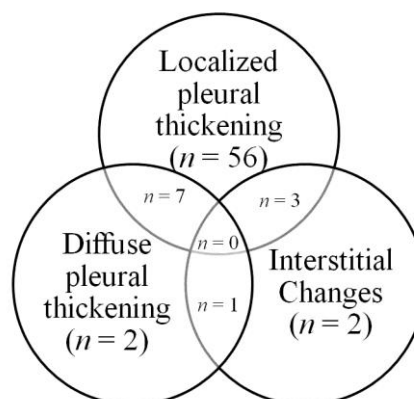
Individuals evaluated in 2002-2005, hired in 1972 or later
Total $n = 119$
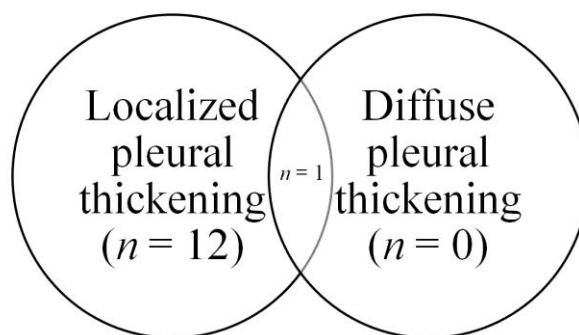
Figure 5-2. Radiographic outcomes among Marysville, OH workers. Numbers of individuals in each category are exclusive (e.g., there are 69 individuals among the total $n = 434$ with pleural thickening only, and an additional four individuals have pleural thickening in addition to interstitial changes).

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1   As stated previously, fiber measurements started in the Marysville plant in 1972, and
2   exposures before this time were estimated by University of Cincinnati scientists, based on focus
3   group interviews with 15 long-term former workers and the times when engineering changes
4   were made to control dust in the facility (see Appendix F). Exposure estimates for the period
5   before 1972 can be considered less certain compared with those estimates more directly based on
6   industrial hygine data. The University of Cincinnati analysis assumed that early exposure levels
7   in the plant are twice those measured in 1972 (see Appendix F). The greater uncertainty of the
8   pre-1972 exposure estimates led to EPA's decision to focus the analysis on the group of workers
9   hired in 1972 or later. Although it is generally true that the use of more data is an advantage for
10 statistical analyses because it allows for the computation of more statistically precise effect
11 estimates, this increased precision can be offset by a negative impact on the accuracy of the
12 effect estimate if an increase in sample size is accompanied by greater exposure misclassification
13 or other biases.
14   In summary, the primary analytic group was the Marysville workers evaluated by Rohs et
15 al. (2008) who were hired in 1972 or later; however, additional information from workers hired
16 before that date was also used in modeling and sensitivity analyses.
17
18 **5.2.2.3.** *Selection of Critical Effect*
19   A critical effect is defined as "The first adverse effect, or its known precursor, that occurs
20 to the most sensitive species as the dose rate of an agent increases" (U.S. EPA, 2011). Three
21 endpoints are suitable for consideration as critical effects for the derivation of an RfC for LAA
22 where health effects data and exposure information are available in the principal study (Rohs et
23 al., 2008): (1) parenchymal changes viewed as small interstitial opacities in the lung,
24 (2) localized pleural thickening (LPT), or (3) diffuse pleural thickening (DPT) as defined in ILO
25 (2000). Each of these represents persistent changes to normal tissue structure.
26   Small interstitial opacities (asbestosis) are widely accepted as adverse; the American
27 Thoracic Society (ATS) states that "asbestosis is usually associated with dyspnea, bibasilar rales,
28 and changes in pulmonary function: a restrictive pattern, mixed restrictive-obstructive pattern,
29 and/or decreased diffusing capacity" (ATS, 2004). Similarly, DPT is also widely accepted as
30 adverse, with the ATS stating that "decrements associated with diffuse pleural thickening reflect
31 pulmonary restriction as a result of adhesions of the parietal with the visceral pleura. Restrictive
32 impairment is characteristic, with relative preservation of diffusing capacity (pattern of entrapped
33 lung)" (ATS, 2004).
34   Statements from the concensus groups vary as to whether pleural plaques (a subset of
35 LPT) impact lung function. Regarding pleural plaques, the ATS notes that this endpoint is also
36 associated with decrements in lung function:
37

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

However, the statement goes on to note that findings of significant pulmonary deficits are not consistent, and that "most people with pleural plaques alone have well-preserved lung function." In addition to the ATS document, the American College of Chest Physicians (ACCP; Banks et al., 2009) published a Delphi study conducted to gauge consensus among published asbestos researchers, and found that these researchers statistically rejected the statement that "Pleural plaques alter pulmonary function to a clinically significant degree" (although noting that some researchers strongly agreed with the statement, and the response rate was relatively low at <40%). Therefore, EPA undertook a systematic review to evaluate the magnitude and extent of the pulmonary function deficits associated with LPT, described in Appendix I. The review demonstrates that these deficits can be considered adverse. Based on the association of LPT with pulmonary function decrease, LPT is an appropriate health effect for derivation of an RfC. Because interstitial opacities, DPT, and LPT are all appropriate candidate endpoints, the critical effect was chosen as that which is the first to appear, or which occurs at the lowest levels of exposure. A summary of the systematic review of the pleural plaque data is discussed below.

Larson et al. (2012a) evaluated the timing of appearance and exposure levels at which pleural and parenchymal abnormalities occur on chest radiographs of vermiculite workers at the Libby facility relative to hire date (i.e., time since first occupational exposure). In this retrospective analysis, the study authors reported that the health endpoint with the shortest median time to appearance was circumscribed pleural plaques (a subset of LPT) with a median latency of 8.6 years, compared to median latency times of 27.0 years for DPT and 18.9 years for parenchymal changes (small interstitial opacity profusion scores of 1/0 or greater). Although all workers experienced generally high exposure, cumulative fiber levels were lowest for those with circumscribed pleural plaques (median of 44.1 fibers/cc-yr), compared to those with DPT (median of 317.8 fibers/cc-yr) and highest for those with parenchymal changes (median of 235.7 fibers/cc-yr for those with major profusion Category 1 abnormalities, 678.4 for Category ≥2/1, and 1,303.4 for Category ≥3/2). Similarly, Rohs et al. (2008) found that for all workers in that study, on average the cumulative fiber exposure for those workers with LPT only (3.45 fibers/cc-yr) was lower compared to those with DPT only (8.99 fibers/cc-yr) or with any interstitial changes (alone or with either LPT or DPT; 11.86 fibers/cc-yr). These results indicate that LPT may be the most sensitive of the effects examined, as the radiographic outcome most likely to occur soonest after first occupational exposure, and the outcome most likely to appear at

1   relatively lower cumulative exposure levels. The clinical perspective suggests that pleural

2   plaques do not clinically impede lung function for most people. This perspective was stated by

3   the American College of Chest Physicians (Banks et al., 2009) regarding the 2004 ATS

4   statement: "Data were cited showing that large studies of workers with pleural plaques had

5   approximately a 5% mean decline in FVC compared to asbestos workers without pleural plaques.

6   In this report, the experts concluded that the presence of pleural plaques did not decrease lung

7   function to a significant extent"—that is, they concluded that the observed decrements were not

8   clinically significant to an individual patient. EPA's systematic review of the literature and

9   formal meta-analysis found decrements in the same range—statistically significant decreases in

10   FVC of 4.09% (4.08% when studies without limitations are used) and in FEV_1 of 1.99% (3.87%

11   when studies without limitations are used). In addition, although few of the studies evaluated

12   reported results for diffusing capacity (as evaluated by DL_{CO}, the diffusing capacity of the lung

13   for carbon monoxide), these studies did observe statistically significant or nearly significant

14   decreases between those with no radiographic abnormalities and those with LPT or pleural

15   plaques.

16   As stated by ATS (2004), the majority of individuals with pleural plaques (subset of

17   LPT) may have well-preserved lung function. However, this may not be the case for individuals

18   who are already at the lower end of the "normal" range of function, already have compromised

19   function, or have increased vulnerability or susceptibility due to other factors (such as chronic

20   disease, other environmental exposures, smoking, etc.). For any of these individuals, even a

21   small decrease in lung function may be important, but once averaged into the whole study

22   population (i.e., looking at only average changes in the whole group) the sensitive individuals'

23   contribution to the population-wide change in mean pulmonary function measures is muted.

24   Accordingly, there is a difference in considering what is significant from a clinical

25   perspective compared to an epidemiological perspective. The clinician's focus is the individual

26   patient, and decisions made in that context (i.e., benefits/risks of medical treatments or tests). In

27   contrast, the population-level (risk assessment) perspective considers any changes in the

28   population distribution of pulmonary function and the potentially increased risks of adversity to

29   subpopulations of the general population. When considering an entire population with a

30   distribution of lung function parameters, even small changes in the average of that distribution

31   means that a much larger proportion of the exposed population is shifted down into the lower

32   "tail" of the lung function distribution. This line of thinking is well understood in the recent

33   examples of lead and IQ (U.S. EPA, 2013a) and respiratory function and ozone (U.S. EPA,

34   2013b). Early childhood exposure to lead can lead to decrements in intelligence as measured by

35   IQ. Depending on the exposure level to lead, a mean deficit of 2 IQ points would not be

36   measurable nor lead to a clinical finding of harm in individuals, but from a epidemiologic or

37   population-level perspective, a downward shift in a portion of the entire IQ distribution by 2 IQ

38   points would be expected to push many individuals already in deficit further into a more clearly

1   "adverse" state. Similarly, even small decrements in lung function on the population level could

2   push "borderline" individuals into a state of clinically significant decreased lung function.

3   In addition, ATS (2004) stated "The presence of plaques is associated with a greater risk

4   of mesothelioma and of lung cancer compared with subjects with comparable histories of

5   asbestos exposure who do not have plaques." While references provided in the ATS (2004)

6   statement (Hillerdal and Henderson, 1997; Hillerdal, 1994b) do not directly address the ATS

7   (2004) statement, a recent large (5,287 retired workers, 17 mesothelioma cases) study (Pairon et

8   al., 2013) found a statistically elevated risk of mesothelioma in a group with plaques (parietal

9   and diaphragm) compared to a no-plaques group, using computer tomography (CT). The study

10 authors found that, after adjusting for cumulative exposure index and TSFE, the risk of

11 mesothelioma in the plaques (parietal or diaphragm) group was statistically elevated (hazard rate

12 (HR) = 6.8, 95% CI 2.2−21.4) compared to the risk of mesothelioma in the exposed workers

13 without pleural plaques.

14   In the Marysville workers evaluated in 2002−2005, differences in exposure patterns are

15 also apparent among outcome groups (see Table 5−4). Exposure to LAA was lower among those

16 with no radiographic abnormalities compared to those with LPT and those with DPT and/or

17 interstitial opacities. Of the candidate critical effects, LPT has the shortest TSFE, and is more

18 likely to appear at lower levels of LAA exposure. LPT is associated with adverse decrments on

19 pulmonary function. Thus, LPT is selected as the critical effect for RfC derivation.

Table 5-4. Characteristics of workers at the O.M. Scott plant in Marysville, OH, with health evaluations in 2002−2005

	No radiographic abnormalities	All LPT cases (with or without DPT/interstitial changes)	LPT cases without DPT/interstitial changes	LPT cases with DPT/interstitial changes	DPT/interstitial changes cases, without LPT
N	181	66	56	10	5
Time (years) since first exposure (TSFE), range	23.14−47.34	24.46−47.30	24.46−47.30	31.52−42.22	36.15−45.56
TSFE, median (interquartile range, IQR)	31.14 (27.56−36.30)	38.21 (34.38−45.81)	37.41 (34.36−45.53)	42.03 (37.58−46.22)	37.22 (37.16−45.04)
Mean exposure (f/cc), range	0.0067−3.7396	0.0068−4.1000	0.0068−2.6230	0.0571−4.1000	0.0692−3.0463
Median (IQR)	0.0372 (0.0167−0.0943)	0.1634 (0.0431−0.7532)	0.0953 (0.0421−0.3958)	1.9197 (0.6623−2.2848)	0.2378 (0.0954−1.7186)
Cumulative exposure (f/cc-yr), range	0.0050−95.0386	0.0233−96.9072	0.0233−96.5450	1.9080−96.9072	1.7986−81.4815
Median (IQR)	1.0188 (0.3162−2.0743)	4.5210 (1.3355−22.9072)	3.1710 (1.2472−10.0445)	47.3994 (22.9072−61.4999)	3.6659 (2.2890−28.2097)
Residence time-weighted (RTW) exposure (f/cc-yr^2), range	0.1196−3468.28	0.5313−3500.66	0.5314−3477.33	65.3771−3500.66	62.7209−3011.68
Median (IQR)	23.7297 (7.6204−50.7792)	127.4075 (36.5668−770.4642)	88.2670 (34.8638−302.5802)	1693.86 (770.4642−2365.89)	120.5295 (74.3389−944.9676)

1   Table 5-4 and Figure 5-2 both highlight a complexity in that these radiographic changes
2 are not mutually exclusive―individuals may have one or more changes simultaneously, in any
3 combination. Among the 66 individuals with LPT, 10 also had DPT or interstitial opacities, and
4 these 10 individuals are noticeably different with regards to TSFE and exposure compared to
5 LPT cases without other radiographic changes, consistent with the results of Larson et al.
6 (2012a). When restricting to the subgroup of individuals hired in 1972 or later, there are
7 106 individuals with no radiographic abnormalities, 12 individuals with LPT only, and one
8 individual with both LPT and DPT. The individual with both LPT and DPT had a TSFE of
9 31.52 years, similar to the median TSFE of 29.71 years among the 12 individuals with LPT only.
10 However, this individual had higher estimated mean exposure (0.46 fiber/cc, compared to a
11 median of 0.08 fiber/cc) and cumulative exposure (9.13 fibers/cc-yr, compared to a median of
12 1.82 fibers/cc-yr), compared to the other 12 LPT cases. The primary analysis considers as the
13 critical effect all LPT cases together, contrasted to those without radiographic abnormalities, but
14 the effect of separating out those with multiple radiographic outcomes is examined in the
15 sensitivity analyses (see Section 5.3.5).

1   In addition, an alternative critical effect of "any pleural thickening" (APT) is considered.

2   Note that in the case of the subcohort of workers evaluated in 2002−2005 and hired in 1972 or

3   later, this definition is equivalent to a critical effect of LPT because no individuals had DPT

4   alone.

5

6   **5.2.2.4. *Selection of Explanatory Variables to Include in the Modeling***

7   As with the mode of action (MOA) for carcinogenicity, the MOA for LPT and the results

8   of other asbestos epidemiology studies could potentially inform noncancer modeling decisions

9   and suggest exposure metrics to use in modeling. The following text discusses the plausibility of

10   exposure metrics proposed in the MOA/epidemiology literature.

11   As noted in Section 4.4, important considerations in evaluating the available mechanism

12   and MOA data are fiber characteristics, route of exposure, dose metric, as well as study design

13   and interpretation. Specific fiber characteristics impact the fiber toxicokinetics (reviewed in

14   Section 3), and in turn, the biologic response to fibers. Fiber dimensions play a role in

15   translocation, a clearance mechanism that may lead to inhaled fibers moving from the lung to the

16   pleura. Data gaps still remain to determine specific mechanisms involved in LAA-induced

17   pleural disease. The review of studies in Section 4.4 clearly highlights the need for more

18   controlled studies examining LAA in comparison with other forms of asbestos and for examining

19   multiple endpoints―including reactive oxygen species (ROS) production and proinflammatory

20   gene expression alterations―to improve understanding of mechanisms involved in noncancer

21   health effects. Although research demonstrates that the LAA has biologic activity consistent

22   with the inflammatory action and cytotoxic effects seen with other forms of asbestos, the

23   conclusion of Section 3 of this assessment is that the data are not sufficient to establish an MOA

24   for the pleural and/or pulmonary effects of exposure to LAA.

25   A general understanding of the biology and the epidemiology of LPT can still inform the

26   modeling as to which explanatory variables should be considered in the models, how the

27   variablesshould be considered or statistically parameterized, and whether they should be retained

28   in the model. From a general understanding of the respiratory effects of asbestos, the intensity of

29   exposure (i.e., concentration), the duration of exposure, and the timing of exposure in relation to

30   subsequent diagnosis of LPT (i.e., TSFE) have been shown to be univariate predictors of pleural

31   plaques (a subset of LTP) in multiple epidemiologic studies as discussed below and, therefore,

32   merit specific consideration in this modeling effort.

33

34   *Timing of exposure*

35   Fibrosis in the pleural tissues needs time to develop and become visible by x-ray (Larson

36   et al., 2010a). It has been shown that the prevalence of fibrotic lesions progresses as a function

37   of time (Rohs et al., 2008) and can appear long after the initial exposure (Lilis et al., 1991).

38   Many investigations of the exposure-response relationship for pleural plaques has found that

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TSFE is a significant explanatory variable (Paris et al., 2009; Paris et al., 2008; Järvholm, 1992).
This suggest that TSFE should be considered as a potential explanatory variable in the modeling.

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

Intensity of exposure

A general understanding of toxicology suggests that, for a given duration of exposure, exposure at higher intensities (concentrations) will likely results in higher burdens of fibers in the alveolar region of the lung, and potentially in the pleural tissue as well. Therefore, for a given duration of exposure, there is a reasonable expectation that people exposed at higher intensities of LAA would experience greater risk of being diagnosed with LPT than people exposed at lower exposure intensities. Similarly, from general principles, at a given intensity of exposure, greater duration of exposure results in higher tissue concentrations of fibers. Epidemiologic evidence from a large cohort of asbestos-exposed workers has reported that exposure intensity (concentration) can be an important predictor of being diagnosed with pleural plaques (a subset of LPT)—even in a multivariate model along with TSFE (Paris et al., 2009; Paris et al., 2008). Järvholm (1992) fit a mathematical model for the incidence of pleural plaques based on concentration and TSFE, which the author considered to have a biological interpretation. This suggests that exposure intensity should be considered as a potential explanatory variable in the modeling.

Duration of exposure

Important characteristics of amphibole fibers are their biodurability and biopersistence. Due to the slow clearance of amphibole fibers from the lung, the fiber burden in the alveolar region of the lung is expected to increase for a given exposure intensity as the duration of exposure increases. This may be true of the pleural tissues as well—but little scientific information is available on the time course of potential fiber accumulation in pleura. Amphibole fibers may remain biologically active for many years while the fibers are in residence in the tissues, although this biological activity may vary with time. For example, depending on the composition and structure of the fiber, certain fibers may cease to have surface activity in biological media, or may have different biological activity in this media (Pezerat, 2009). Further, some asbestos fibers can become covered with an iron-protein coat in the lungs of exposed individuals (i.e., forming ferruginois bodies; Dodson et al., 1993; Churg and Warnock, 1981). The biological effect of this coating is unclear, but may alter the activity of the fibers.

1 Epidemiologic evidence from studies of asbestos-exposed workers ([e.g., Clin et al., 2011](#))
2 indicates that cumulative exposure, a metric of exposure that encompasses both exposure
3 intensity as well as duration, can be an important predictor of the probability of being diagnosed
4 with pleural plaques. This suggests that duration of exposure should be considered in modeling.
5 Cumulative exposure (as an expression of concentration and duration) should be considered as a
6 potential explanatory variable in the modeling. Therefore, modeling results using both exposure
7 intensity, C, and cumulative exposure, CE, as the exposure metric are considered. Another
8 exposure metric related to both exposure intensity and duration is called residence time-weighted
9 exposure, a metric of exposure that can be used to more heavily weighearlier exposures.
10 Residence time-weighted exposure is also considered for modeling.
11
12 *Other explanatory variables*
13   Other explanatory variables of interest include those that may be confounders of the
14 explanatory variables' statistical relationships with the risk of LPT. These include body mass
15 index (BMI), age, and smoking (complete list from the table of potential confounders). Each of
16 these was assessed as a potential confounder prior to modeling the main explanatory variables of
17 interest.
18
19 **5.2.2.5. *Selection of the Benchmark Response***
20   Selecting a benchmark response ([BMR](#)) involves making judgments about the statistical
21 and biological characteristics of the data set and about the applications for which the resulting
22 benchmark concentration (BMCs)/lower limit of the BMC (BMCLs) will be used. An extra risk
23 of 10% is recommended as a standard reporting level for quantal data. Biological considerations
24 may warrant the use of a BMR of 5% or lower for some types of effects (e.g., frank effects), or a
25 BMR greater than 10% (e.g., for early precursor effects) as the basis of the POD for a reference
26 value ([U.S. EPA, 2012](#)).
27   LPT is a persistent change to normal tissue structure and is associated with a decrement
28 in lung function on a population level (~5 and ~2.5% decrements in percentage predicted FVC
29 and FEV_1, respectively). [Larson et al. (2012a)](#) showed a statistically significant increased risk of
30 people with LPT having "restrictive spirometry" and concluded that this abnormality may result
31 in lung function impairment. However, the available data do not lead EPA to conclude LPT
32 should be considered a frank effect and thus EPA selects a BMR of 10% extra risk for this
33 endpoint.
34   As noted in Section 5.2.3.1, an alternative critical effect of APTwas also considered as an
35 alternative analysis. For this outcome, a BMR of 10% was also used, given that (as shown in
36 Figure 5-2) a significant majority of cases were LPT.

1 **5.2.2.6.** *Exposure-Response Modeling*

2   LPT was selected as the critical effect based on the adverse health effects associated with

3 pleural thickening specific to this diagnosis (ILO, 2002). Note that for the primary analytic data

4 set (workers evaluated in 2002−2005 and hired in 1972 or later), the number of individuals with

5 LPT is the same as the number with either "any pleural thickening" or "any radiographic

6 change" (i.e., there is no difference in the number of cases or the estimates of risk) because the

7 single case with DPT also had LPT (and thus is included as an LPT case) and no cases of

8 interstitial abnormalities occurred. However, in the larger cohort of workers (all workers, and

9 those evaluated in 2002−2005 regardless of hire date), there were individuals with these more

10 severe outcomes as well as LPT (see Figure 5-2).

11   The exposure-response relationship was modeled as described below, and PODs were

12 estimated using BMC methodology. For inhalation data, the BMC is defined as the exposure

13 level that results in a specified BMR. The RfC is derived from the lower 95% confidence limit

14 of the BMC, referred to as the BMCL, which accounts for statistical uncertainty in the model fit

15 to the data. All analyses were performed using SAS® statistical software v. 9.3. BMCLs were

16 obtained by the profile likelihood method as recommended by Crump and Howe (1985) using

17 the nonlinear mixed modeling procedure (PROC NLMIXED) in SAS (Wheeler, 2005).

18

19 **5.2.2.6.1.** *Considerations of appropriate model forms and explanatory variables.* The process

20 and considerations for exposure-response modeling of the Marysville data were guided by EPA's

21 2012 Benchmark Dose Technical Guidance (U.S. EPA, 2012). As outlined in that document,

22 there are several stages of exposure-response modeling. Once the appropriate data set(s),

23 endpoint(s), explanatory variables(s), and BMR are determined, the next step is to choose an

24 appropriate statistical model form or set of model forms to evaluate (e.g., logistic, probit,

25 Dichotomous Hill, etc.). Among this set of models, the overall model fit and the fit in the region

26 of the BMR are evaluated to determine which models adequately represent the data. Finally, one

27 or more models are selected from the group of adequately fitting models to derive a POD for the

28 reference value. Regarding the selection of models to evaluate, the Benchmark Dose Technical

29 Guidance (see p. 26) states: "The initial selection of a group of models to fit to the data is

30 governed by the nature of the measurement that represents the endpoint of interest and the

31 experimental design used to generate the data. In addition, certain constraints on the models or

32 their parameter values sometimes need to be observed and may influence model selection." In

33 the Marysville data, a number of factors must be considered to determine an appropriate

34 modeling strategy: the nature of the data set, ability to estimate the effects of exposure and of

35 important covariate(s), the existence of a plateau or theoretical maximum response rate in a

36 population, and the ability to estimate a background rate of the outcome in a population. Each

37 factor is described below, and consideration of these factors in total resulted in a preference for

1   the Dichotomous Hill model, with a set of additional model forms suitable for evaluation of
2   sensitivity to model selection.
3

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

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

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

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

1   • Effect of exposure: Because the data set include estimates of individual exposure and
2   the goal is to derive an RfC, appropriate models need to include an independent
3   exposure variable. All the models listed above can estimate the effect of changes in
4   exposure on risk of the outcome, although the parameter that reflects the magnitude
5   of that effect changes across models. In models where exposure is included without
6   logarithmic transformation, the b parameter corresponding to exposure is interpreted
7   as a "slope" and represents the change in outcome per unit change in exposure. In
8   models where exposure is natural log transformed, the interpretation is somewhat
9   different; both the a and b parameters determine the shape of the exposure-response
10   relationship (e.g., $a + b \times \ln(x) = \ln(\exp(a) \times x^b)$). Thus, b is a power parameter and
11   behaves more like a shape parameter in this context, while $\exp(a)$ behaves like a

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traditional slope. This is an important distinction in interpreting models including
natural log transformation of the exposure (i.e., log-logistic, log-probit,
Michaelis-Menten, Dichotomous Hill).

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

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

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1   pleural plaques of 85.7% among Swedish shipyard workers with 50−54 years since
2   first exposure (Järvholm, 1992). Thus, a reasonable option would be to use the
3   Dichotomous Hill or Michaelis-Menten model and fix the plateau term at a value (i.e.,
4   85%) consistent with maximum observed prevalence rates in the asbestos literature.
5   EPA performed a sensitivity analysis (see Section 5.3.4) to evaluate the effect of
6   assumptions regarding the plateau on the POD.

7   •   Effect of covariates: As with the discussion for effect of exposure, a desirable model
8   attribute is the ability to estimate the effect of additional covariates. EPA evaluated a
9   variety of possible covariates and determined that in the primary analytic data set of
10   individuals evaluated in 2002−2005 and hired in 1972 or later, none showed evidence
11   of potential confounding of the LAA exposure-LPT relationship. Each of the models
12   listed above (logistic, probit, log-logistic, log-probit, Dichotomous Hill, and
13   Michaelis-Menten) allow for the inclusion of covariates. Specifically for modeling
14   LAA exposure and risk of LPT, one of the most important covariates to consider is
15   TSFE. As described above, the prevalence of pleural plaques (a subset of LPT) has
16   been shown to increase as TSFE increases, even in the absence of continued asbestos
17   exposure. Although the literature indicates TSFE is the most important time-related
18   factor, other factors may be important to consider, including age at examination, hire
19   year, job tenure (time elapsed from job start to job stop), and exposure duration
20   (taking into account gaps in exposure). There are also nontime-related factors which
21   may influence the association between LAA exposure and risk of LPT. These include
22   gender, smoking status, and BMI. Smoking is a particularly important variable to
23   consider when evaluating respiratory health outcomes. Each of these factors was
24   investigated in the primary data set. To be a potential confounder, the factor must be
25   associated with both LAA exposure and LPT, and must not be an intermediate in the
26   causal pathway between exposure and outcome. The association with natural
27   log-transformed LAA exposure in the subcohort was assessed using a linear
28   regression model, and the association with LPT was assessed using a logistic
29   regression model (see Table 5-6). While many of the time-related factors (with the
30   exception of age at x-ray examination) as well as male gender and former smoker
31   status were associated with each of the three exposure metrics, none were associated
32   with risk of LPT. Thus, none of the factors met the criteria of being associated with
33   both LAA exposure and LPT, and none were considered as potential confounders.
34   Further consideration of potential confounding and effect modification is addressed in
35   the uncertainty analyses described in Section 5.3.3.

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

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

[a]Association with exposure assessed using a linear regression model, where the outcome is natural log-transformed exposure and the predictor is the covariate of interest. Association with outcome assessed using a logistic model, where the outcome is LPT status and the predictor is the covariate of interest.
[b]Data on BMI were missing for 21 individuals. Thus, the AIC for this model cannot be compared with the AIC for other models in the table.

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

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

a) Models suitable for a dichotomous outcome

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

c) Ability to estimate effect of covariates

d) Ability to estimate or specify the plateau

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

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

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

1   The epidemiological models described above (logistic, probit, log-logistic, log-probit,
2   Dichotomous Hill, and Michaelis-Menten) are suited for dichotomous outcomes, and all allow
3   for the inclusion of covariates. However, the Michaelis-Menten model does not allow for
4   estimation of a separate shape parameter (*b* parameter is implicitly fixed at 1). The ability to
5   estimate both *a* and *b* (rather than imposing a preassumed shape) provides greater flexibility in
6   exposure-response modeling, and thus the Dichotomous Hill model is preferred over the
7   Michaelis-Menten model. The logistic and probit models do not include separate parameters for
8   either the background rate or a plateau. The three remaining models—log-logistic, log-probit,
9   Michaelis-Menten, and Dichotomous Hill—do allow for estimation of the effect of exposure and
10   the background rate, but only the Dichotomous Hill model includes a separate plateau parameter.
11   Therefore, the Dichotomous Hill model is considered to be the most flexible and potentially the
12   most suitable based on biological and epidemiologic properties in the absence of information on
13   actual model fit, which is also an important consideration in model selection. The
14   Michaelis-Menten, log-probit, and log-logistic models are also reasonable alternatives (note that
15   latter two models implicitly fix the plateau at 100%, above the maximum observed prevalence in
16   reported studies). These models are also evaluated for sensitivity to modeling properties and
17   assumptions. As described above, the plateau is an asymptotic parameter, and it may not be
18   possible to reliably estimate given the limitations of the data. The Marysville workers who
19   underwent health evaluations in 2002−2005 and whose job start date was on or after 1/1/1972
20   had relatively low levels of exposure and a narrow range of TSFE, and it is likely that estimation
21   of the maximum prevalence of LPT by radiograph is not well supported in these data. One
22   option to address this difficulty is to fix the plateau parameter at a value consistent with the
23   asbestos literature reviewed above. This assessment will use a plateau value of 85%, based on

1   the literature regarding maximum observed prevalence in populations reported to have had long

2   follow-up periods and significant exposure to asbestos, although the sensitivity of the model to

3   this assumption is examined in Section 5.3.4.

4

5   **5.2.2.6.2. *Considerations of exposure metric, statistical model fit and selection of***

6   ***exposure-response model.*** While the above description in Section 5.2.2.6.1 explains EPA's

7   preference to use the Dichotomous Hill model for exposure-response modeling in this data set

8   (along with a reasonable set of models to evaluate sensitivity to model form), the text below

9   explains EPA's evaluation of options for the specific exposure metrics to use, and the results of

10   the analysis of statistical fit among the considered models. As noted in Section 5.2.2.4, in the

11   absence of an MOA for pleural health effects, an understanding of the general biology and the

12   epidemiologic literature may help to inform the consideration of exposure metrics for

13   exposure-response modeling. For pleural effects, the timing of exposure, the intensity of

14   exposure, and the duration of exposure may all be important variables to predict the risk of LPT

15   and were considered in the regression modeling.

16   In the Marysville data, exposure information was collected for each individual based on

17   specific work location, season, and year. There are several ways in which these estimates of

18   exposure by person by year can be aggregated into a single measure. Exposure estimates can be

19   summed over each individual's work history to yield a cumulative exposure estimate for each

20   individual. The cumulative exposure may also be divided by duration of (occupational) exposure

21   to yield an average intensity of exposure (mean exposure). A third option for an exposure metric

22   is to weigh more heavily exposures occurring in the more distant past, using a RTW[22] exposure

23   metric for which each year is weighted by the number of years it occurs prior to the year in

24   which prevalence is evaluated. These three expressions of exposure can be used to derive a POD

25   with appropriate adjustment of the units to arrive at the RfC.

26   Table 5-8 shows the univariate model results for each of the model forms evaluated,

27   using each of the three different parameterizations of exposure. All models had adequate

28   goodness of fit (GOF), as indicated by the Hosmer-Lemeshow *p*-values (all had *p*-values ≥ 0.7,

29   substantially higher than the standard cutoff value of 0.10, below which a model is considered to

30   fit the data poorly), and were carried forward for further consideration. Because each of the

31   models shown in Table 5-8 was evaluated on the same data set (same number of observations,

32   and same response variable), it is appropriate to compare relative fit among them using the

33   Akaike's Information Criterion (AIC). The AIC for the models ranged from a low value of 73.8

---

[22]The RTW exposure value associated with a constant concentration (c), with 70-years duration and the evaluation of response at age 70 is the sum of $1 \times C + 2 \times C + \ldots 70 \times C$, which is equal to about $C \times 71 \times (70/2)$ or $C \times 2485$. This yields a concentration that is about eightfold lower than the concentration that would yield the same RTW exposure, and hence the same modeled risk, for a median experience in the cohort of 20-years duration starting about 30 years prior to exposure, which would yield a RTW exposure for a constant concentration of the sum of $11 \times C + 12 \times C + \ldots 30 \times C$, or $C \times 31 \times (20/2)$, or 310.

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1   (probit and Michaelis-Menten models using mean exposure) to a high of 79.3 (logistic model

2   using RTW exposure). Note that the Dichotomous Hill model with estimated plateau yielded

3   unrealistic parameter estimates when using either cumulative or RTW exposure (e.g., slope

4   estimates >100) and were considered less reliable. Within each model form, mean exposure

5   consistently provided a superior fit (as evidenced by lower AIC) compared to either cumulative

6   or RTW exposure.

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

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

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

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

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

---

[a]CE indicates cumulative exposure (fiber/cc-yr), Mean indicates mean exposure (fiber/cc), RTW indicates residence time weighted exposure (fiber/cc-yr^2), calculated using the midpoint of each work season.
[b]Shaded cell indicates the model did not yield a reasonable estimate for one or more parameters.

1   Each of the different candidate models shown in Table 5-8 is similar in general form, and
2 comparison of model fit informed by the biological and epidemiologic features of the models
3 does not strongly imply a preference for one model form over the others. For the mean exposure
4 model, the AIC values for the logistic, probit, log-logistic, log-probit, Dichotomous Hill model
5 with plateau fixed at 85%, and Michaelis-Menten model with plateau fixed at 85% ranged from
6 73.8 to 75.4, a difference of only 1.6 AIC units for the mean exposure model which indicates
7 essentially equivalent fits. Figure 5-3 shows a plot of the fit for the Dichotomous Hill model
8 with plateau fixed at 85% and the Michaelis Menten model with plateau fixed at 85%.
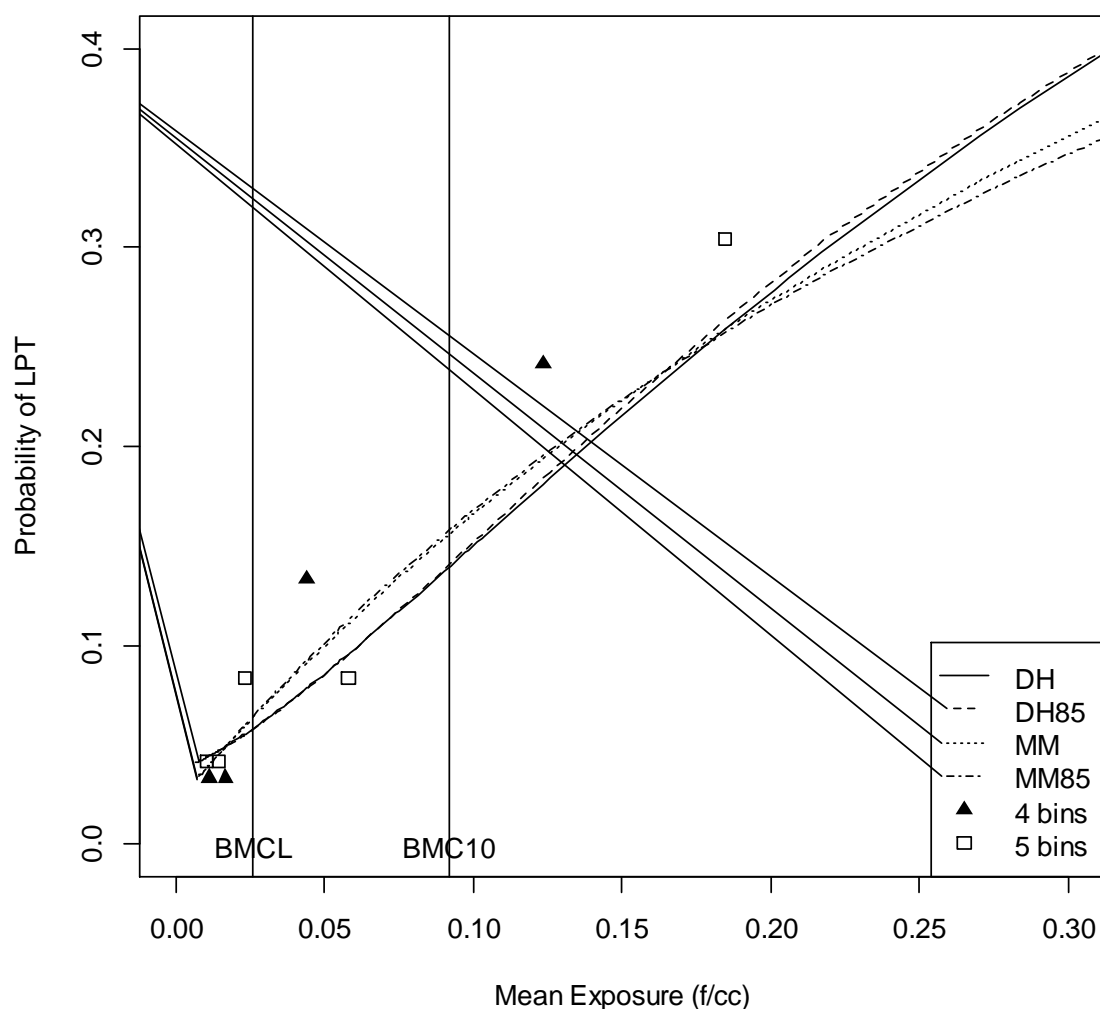
Figure 5-3: Plot of exposure-response models for probability of LPT as a function of mean concentration of occupational exposure in the subcohort. Based on the results in Table 5-8, the four lines show the predicted exposure-response shapes of the following models: Dichotomous-Hill model with estimated plateau (DH), Dichotomous-Hill model with plateau fixed at 85% (DH85), Michaelis-Menten model with estimated plateau (MM), and Michaelis-Menten model with plateau fixed at 85% (MM85). The Dichotomus-Hill with plateau fixed at 85% is the selected model and Michaelis-Menten with plateau fixed at 85% is the best fitted model according to AIC. The full range of observed exposure data extended to 0.77 fiber/cc; however, as interest in the fit is in the range of the BMC_{10}, the range of exposure values shown here is restricted to 0.3 fiber/cc. The two sets of unconnected symbols show the categorical probability estimates based on quartiles and quintiles of exposure plotted in the median concentration for each category. Data are aggregated in four bins based on quartiles (1,1,4,7 cases in each bin) and five bins based on quintiles (1,1,2,2,7 cases in each bin). Vertical lines at the BMC_{10} and BMCL are drawn at the corresponding estimates from Dichotomous-Hill model with plateau fixed at 85%. BMCs and BMCLs for other models are in Table 5-8.

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1   As described above, the Dichotomous Hill model with plateau fixed at 85% possesses
2   desirable biological/epidemiological properties and is the most flexible of the evaluated models.
3   This model had an AIC at the lower range of the models evaluated (75.4 when using mean
4   exposure or 76.8 when using cumulative or RTW exposure); the AIC for the model using mean
5   exposure was within two AIC units of the best-fitting models, a difference that is generally
6   considered indistinguishable with respect to relative model fit ([Burnham and Anderson, 2002]).
7   Because it was considered the most flexible model, the Dichotomous Hill model with plateau
8   fixed at 85% was selected as the primary model for RfC derivation. This model was carried
9   forward through the extensive sensitivity analyses (see Section 5.3) because it was considered to
10 be the model most likely to be able to detect sensitivity to covariates and alternative model
11 parameterization.
12   The RfC is "an estimate of an exposure (including sensitive subgroups) that is likely to be
13 without an appreciable risk of adverse health effects over a lifetime." ([U.S. EPA, 1994b]), where
14 a lifetime is commonly assumed to be 70 years. Thus, consideration of the effect of time
15 (specifically time elapsed from exposure to outcome evaluation) is an important aspect of
16 deriving an RfC. The literature on pleural abnormalities and asbestos generally supports a
17 conclusion that the amount of time elapsed between exposure and evaluation has a major impact
18 on observed response. The model form and/or the selection of an exposure metric should
19 incorporate considerations of time factors. As described above, in the primary data set (which
20 had a very limited range of TSFE values) neither TSFE nor any of the other covariates evaluated
21 were significantly associated with LPT. However, the epidemiologic literature is clear that the
22 timing of exposure is an important factor in evaluating risk over a lifetime, and it was considered
23 critical to address the time-course of exposure and LPT in deriving the RfC. Thus, one option
24 would be to incorporate TSFE through the choice of exposure metric. Neither mean nor
25 cumulative exposure takes into account the TSFE or the timing of subsequent exposures. The
26 RTW exposure metric does incorporate information for each year's exposure of the time between
27 that exposure and evaluation of the prevalence—exposure in a given time interval is weighted
28 according to time elapsed, with exposure occurring earlier given greater weight. This approach
29 might be preferable to a model including TSFE as a covariate along with mean or cumulative
30 exposure because the RTW metric weights each year of exposure according to the time elapsed
31 until health evaluation. However, while time prior to evaluation is "considered" when using the
32 RTW exposure metric, the subcohort with better exposure data is still limited in that the range of
33 TSFE in this group of workers is relatively narrow (from 23.14 to 32.63 years), which may
34 explain the lack of predictive value of TSFE in this group. Thus, utilizing this approach to
35 estimate a concentration yielding the same risk for a 70-year exposure is informed by a relatively
36 small range of TSFE values.
37   Therefore, EPA considered explicitly including TSFE as a covariate in exposure-response
38 modeling, along with either mean or cumulative exposure. As noted above, less variability is

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1   present in TSFE (and other time-related factors) for the subgroup of workers hired in 1972 or
2   later, compared to the larger study population of Marysville workers who underwent health
3   evaluations in 2002−2005 (regardless of hire date, $n = 252$). In this group, the median TSFE was
4   33.5 years (SD = 7.12 years) and the range was 23.1 to 47.3 years, considerably longer than the
5   subset of these workers whose job start date was on or after 1/1/1972. EPA selected the smaller
6   subgroup for primary exposure analysis because the exposure data after 1972 is of higher quality
7   even though the range in TSFE is more limited. However, it is possible to use a larger subset of
8   the Marysville workers with a wider range of time-related factors (but more uncertain exposure
9   information) to model the effect of TSFE, then include this effect as a fixed parameter when
10 modeling the exposure-response relationship among the primary analytic group of workers who
11 underwent health evaluations in 2002−2005 and were hired ≥1972. This hybrid model may be
12 used to calculate a BMCL for a scenario of lifetime exposure (70-years duration and 70-years
13 TSFE). This procedure could use either mean exposure or cumulative exposure. The use of
14 RTW may not be appropriate because RTW includes consideration of the timing of exposures
15 and thus a model using RTW in the exposure metric and TSFE as a covariate might have two
16 variables both reflecting the timing of exposure.
17
18 *Modeling procedure*
19   1) Fit the model (Dichotomous Hill with plateau fixed at 85%) in all the workers
20   evaluated in 2002−2005 (regardless of hire date) with TSFE and LAA exposure
21   (either represented as cumulative exposure [CE] or as mean exposure [C]) as
22   predictor variables.
23

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

25

26   2) Use the regression coefficient for TSFE calculated in (1), represented by "c", as a
27   fixed parameter in the model for workers who underwent health evaluations in
28   2002−2005, using data only on those hired in 1972 or later; fit the model to the data
29   on this subcohort using the individual data on both TSFE and LAA exposure as
30   independent variables—note that as in the larger cohort of all workers evaluated in
31   2002−2005, LAA exposure may be modeled as either mean exposure or cumulative
32   exposure.

33   3) Use some fixed value of TSFE to estimate the benchmark value and the lower limit
34   conditional upon that TSFE.
35

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

37

38   The bivariate modeling results for this hybrid model option are shown in Table 5-9. Both
39 mean and cumulative exposure metrics were evaluated on the basis of two measures of model fit.

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1   The AIC allows the comparison of the fit among two or more models of the same dependent

2   variable, and AIC results within approximately two units can be considered to be of equivalent

3   fit. The results in Table 5-9 show similar AIC values for the two hybrid models with exposure

4   characterized as mean concentration or as cumulative exposure. However, two studies in the

5   epidemiologic literature also compared mean concentration and cumulative exposure in relation

6   to the risk of pleural plaques and found that when also including TSFE as an explanatory

7   variable (as in the results shown in Table 5-9), mean exposure provided a significantly better

8   model fit (Paris et al., 2008). In addition, another study (Järvholm, 1992) proposed model

9   including TSFE and intensity of exposure and stated that this model is biologically interpretable;

10   statistical modeling of pleural thickening (18% diffuse) showed that duration of exposure does

11   not matter when TSFE is included in the model (Lilis et al., 1991).

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

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

[a]Note that the results in this table are from two different datat sets (Primary, $n = 119$ and Individuals with radiographs in 2002−2005, $n = 252$). The AICs for the models cannot be compared between the two data sets.

1   For the Marysville data, the model with cumulative exposure did not fit well on the other
2   measure of model fit. In the larger group of workers evaluated in 2002−2005 (regardless of hire
3   date), fit of cumulative exposure had a low *p*-value (i.e., <0.10) for the Hosmer-Lemeshow
4   goodness-of-fit statistic. Mean exposure did provide an adequate fit and was, therefore, carried
5   forward in the analysis as the primary basis of the derivation of the lifetime RfC in Section 5.2.3.
6   Although the model using cumulative exposure did not show an adequate fit based on the
7   Hosmer-Lemeshow goodness-of-fit test, the model fit as measured by the AIC was nearly
8   equivalent to the AIC for the mean exposure model, and the beta estimated for the effect of
9   TSFE was similar to that estimated in the model using mean exposure. Therefore, the derivation
10   of a chronic RfC based on the CE model is also shown in Section 5.2.3 for comparison.
11   In the model using mean exposure intensity in the larger data set of individuals evaluated
12   in 2002−2005, the beta coefficient for TSFE was 0.1075. This coefficient value was transported
13   to the equivalent model in the subset of workers hired in 1972 or later; at a TSFE of 28 years (the
14   median in this group of workers), the BMC and BMCL were 0.092 fiber/cc and 0.026 fiber/cc,
15   respectively. Ideally, the objective of the RfC derivation is to compute the BMCL for 70 years
16   (i.e., a lifetime) of exposure. However, the maximum observed TSFE in the primary cohort was
17   32.6 years, which while clearly a chronic exposure, cannot be expected to approximate a lifetime
18   exposure in this particular circumstance when TSFE is the most important predictive factor for
19   the prevalence of LPT. The BMCL values calculated at longer TSFEs were very low (e.g., a
20   BMCL of 2.7×10^{-6} at TSFE of 70 years) and the ratio of BMC to BMCL grows exponentially
21   such that these values at 70 years are considered to be unreliable (e.g., the BMC:BMCL ratio is
22   1,000 at TSFE of 70 years). This is likely because longer TSFE values are extrapolated well
23   outside of the range of the data, and attempting to extrapolate beyond ~30 years leads to greater
24   statistical uncertainty. Consequently, the BMC and BMCL values corresponding to 28 years
25   were selected as the primary modeling result, with the BMCL of 0.026 fiber/cc serving as the
26   POD for RfC derivation with some additional accommodation of the uncertainty in using less
27   than lifetime exposure data to estimate lifetime risks.
28   At the BMCL (2.6×10^{-2} fibers/cc), the final model leads to an estimated probability of
29   LPT of 0.06 at 28-years TSFE, and 0.61 at 70-years TSFE (see Figure 5-4). This 10-fold
30   increase in the probability of the critical effect going from the median TSFE in the cohort, to the
31   full lifetime, is used to derive a data-based subchronic to chronic uncertainty factor (UF) for RfC
32   derivation in the following section.

P(LPT) at the BMC and at the BMCL, estimated at TSFE=28 years
DH model with plateau=85%, mean exposure (f/cc)

PLOT   + + + P(LPT) for BMC of 0.0923 f/cc   * * * P(LPT) for BMCL of 2.6E-2 f/cc
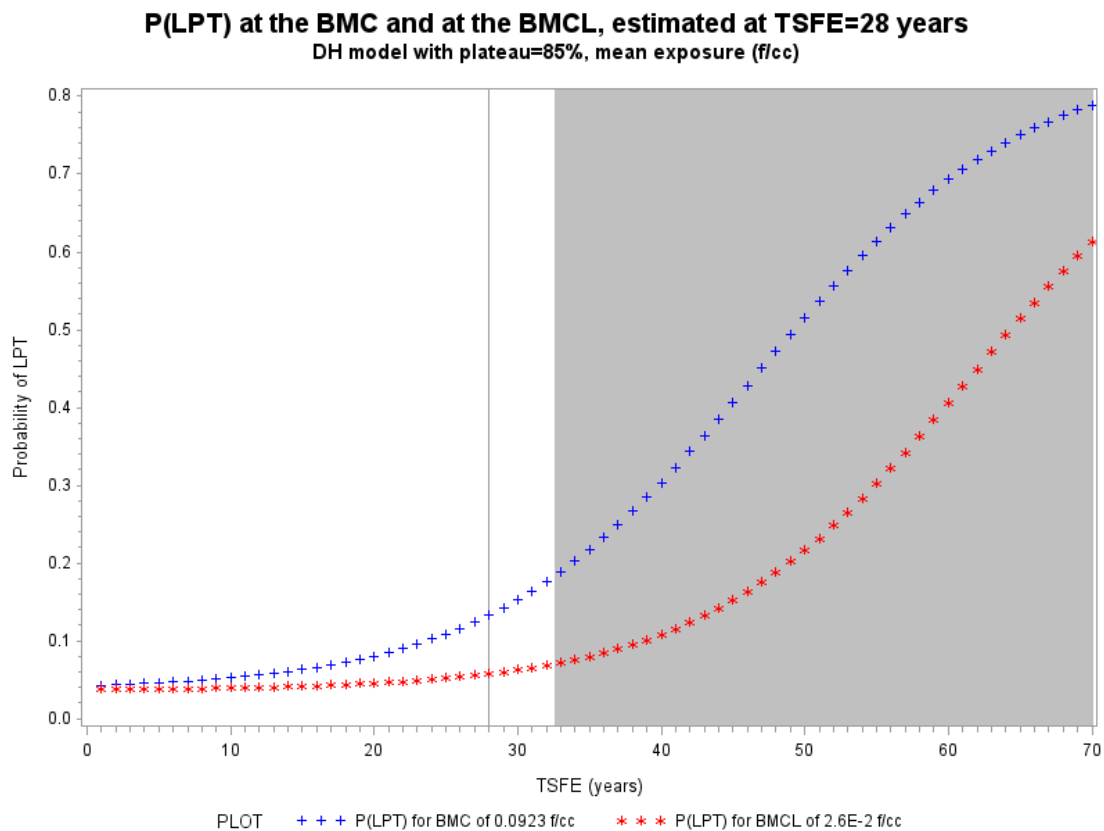
Figure 5-4. Predicted risk of localized pleural thickening (LPT) at the benchmark concentration (BMC) and the lower limit of the BMC (BMCL), using the hybrid Dichotomous Hill model with plateau fixed at 85%. The parameters for this were taken from Table 5-8. Note that the vertical reference line indicates TSFE = 28 years, used to calculate the BMC and BMCL. The shaded region indicates TSFE beyond that observed in the cohort of workers evaluated in 2002−2005.

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

Among the available studies that could provide exposure-response data for the relationship between LAA exposure and risk of LPT, consideration of study attributes led to the selection of a study of the Marysville, OH workers evaluated in 2002−2005 as the primary data set for RfC derivation (Rohs et al., 2008, see Section 5.2.1). An updated job-exposure matrix was available for this follow-up of the original study group, with a refined understanding of exposure to LAA throughout plant operation (see Section 5.2.3.1 and Appendix F). However, due to remaining uncertainties in exposures prior to 1972, EPA elected to focus on exposure-response modeling for the subgroup of plant employees hired in 1972 or later (see Section 5.2.3.2). The critical effect selected for derivation of the RfC is LPT, a persistent change to normal tissue structure associated with decreased pulmonary function.

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

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

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

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

- A subchronic-to-chronic uncertainty factor, UF_S, of 10 was applied because while the selected POD is from a study population including workers with chronic exposure defined as more than 10% of a lifetime (i.e., more than 7 years), for this particular health endpoint, even ~30 years of observation (Rohs et al., 2008) is insufficient to describe lifetime risks.

  Although data do exist to define an exposure-response relationship for radiographic abnormalities in the Marysville, OH worker cohort, these data are limited by the dates of the available radiographs. The data for the subcohort of workers exposed post-1972 allowed for assessing prevalence of LPT up to approximately 30 years after

1   first exposure. EPA used information from the larger group of all workers evaluated
2   in 2002−2005 to estimate the effect of TSFE because this group had greater
3   variability in TSFE (with a maximum TSFE of 47 years). However, the Marysville
4   data did not have information on effects after a full lifetime of exposure (i.e., 70-years
5   TSFE), and evidence indicates that the prevalence of pleural plaques is likely to
6   continue to increase over the life span (Paris et al., 2009; Paris et al., 2008; Jakobsson
7   et al., 1995; Hillerdal, 1994a; Järvholm, 1992; Lilis et al., 1991). As the RfC is
8   intended for a lifetime of exposure, and pleural thickening is known to progress
9   across the lifetime (even with less-than-lifetime exposures), the lack of health data
10   assessed at end of lifetime is a data gap. Using the model selected for derivation of
11   the RfC, the probability of LPT increases 10-fold between 28-years TSFE (the
12   median in the population of workers used for analysis) and 70-years TSFE. Thus, use
13   of a 10-fold UF for subchronic-to-chronic uncertainty should capture the uncertainty
14   due to increasing risk of LPT over the life course.

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

17   Although a large database exists for asbestos in general, only four study populations
18   exist for LAA specifically: the Minneapolis community study, the Marysville, OH
19   worker cohort, the Libby worker cohort, and the ATSDR community screening
20   (which includes some Libby worker cohort participants). Studies conducted in three
21   of these populations, the Libby worker cohort (Larson et al., 2012a), Minneapolis
22   community study (Alexander et al., 2012), and Marysville workers (Rohs et al.,
23   2008), have all demonstrated substantial numbers of LPT cases occurring at the
24   lowest exposure levels examined in each study (Christensen et al., 2013), lending
25   confidence to the use of LPT as a critical effect and (Rohs et al., 2008) as the
26   principal study for RfC derivation.

27   However, studies in the Libby population have also demonstrated an association
28   between exposure to LAA and autoimmune effects (i.e., self-reported autoimmune
29   disease and autoimmune markers in Libby residents (Marchand et al., 2012; Noonan
30   et al., 2006; Pfau et al., 2005). Because these studies did not provide
31   exposure-response information, it is unknown whether a lower POD or RfC would be
32   derived for these effects. For other (non-Libby) forms of amphibole asbestos, there is
33   evidence regarding autoimmune effects from a study of individuals in a community
34   exposed to tremolite. In this population, there were changes in immune parameters in
35   exposed individuals without pleural plaques, and additional immune markers
36   (including autoantibodies) were increased in individuals with pleural plaques (Zerva
37   et al., 1989). Also it has been hypothesized that shorter asbestos fibers reach the
38   pleura via passage through lymphatic channels (Peacock et al., 2000), although
39   experimental evidence is lacking for this or alternative potential mechanisms of fiber
40   migration. This uncertainty in the sequence of health effects (pleural or autoimmune)
41   is the basis for selecting a UF_D of 3.
42

43   The derivation of the RfC from the morbidity studies of the Marysville, OH worker
44 cohort (i.e., Rohs et al., 2008) was calculated from a POD, $BMCL_{10}$ for LPT of 0.026 fiber/cc,

1   and dividing by a composite UF of 300. As derived below, the chronic RfC is 8.67×10^{-5}

2   fibers/cc for LAA:

3

4   Chronic RfC for LPT = $BMCL_{10} \div UF$ (5-3)

5   = 0.026 fiber/cc $\div$ 300

6   = 8.67×10^{-5} fibers/cc, rounded to 9×10^{-5} fibers/cc

7

8   It should be noted that for the primary RfC and all the alternative RfCs, the fiber

9   concentrations are presented here as continuous lifetime exposure in fiber/cc where exposure

10   measurements are based on analysis of air filters by PCM. Current analytical instruments used

11   for PCM analysis have resulted in a standardization of minimum fiber width considered visible

12   by PCM between 0.2 and 0.25 μm. Historical PCM analysis (1960s and early 1970s) generally

13   had less resolution, and fibers with minimum widths of 0.4 or 0.44 μm were considered visible

14   by PCM (Amandus et al., 1987b; Rendall and Skikne, 1980). Methods are available to translate

15   exposure concentrations measured in other units into PCM units for comparison.

16

17   **5.2.3.1. *Derivation of a Reference Concentration (RfC) for the Alternative Endpoint of Any***
18   **   *Pleural Thickening (APT) in the Marysville Workers Who Underwent Health***
19   **   *Evaluations in 2002−2005 and Were Hired in 1972 or Later***

20   As shown in the uncertainty analyses in Section 5.3.5 (see Table 5-17), use of an

21   alternative critical effect of APT results in an almost identical $BMCL_{10}$ as derived for the

22   primary analysis using LPT as the critical effect. In the subcohort, the number of cases of APT

23   is identical to the number of cases of LPT, and in the larger group of workers evaluated in

24   2002−2005 used to estimate the effect of TSFE, the number of cases of APT is very similar to

25   the number of LPT cases (n = 69 cases of APT and n = 66 cases of LPT). In this larger group,

26   the regression coefficient for the effect of TSFE was very close when using either of these two

27   endpoints—values of 0.1108 for APT and 0.1075 for LPT. Thus, using the same uncertainty

28   factors as described above, the chronic RfC is 9.0×10^{-5} fibers/cc for LAA, using an alternative

29   endpoint of APT:

30

31   Chronic RfC for APT = $BMCL_{10} \div UF$ (5-4)

32   = 0.027 fiber/cc $\div$ 300

33   = 9.0×10^{-5} fibers/cc

34

35   This value is identical to the primary RfC derived using a critical effect of LPT, when

36   rounded to one significant digit. These results provide additional support to further substantiate

37   the primary RfC.

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1   **5.2.3.2.** *Derivation of a Reference Concentration (RfC) for the Alternative Endpoint of Any*
2   *Radiographic Change (ARC) in the Marysville Workers Who Underwent Health*
3   *Evaluations in 2002−2005 and Were Hired in 1972 or Later*

4   As shown in the uncertainty analyses in Section 5.3.5 (see Table 5-17), use of an
5   alternative critical effect of any radiographic change (ARC) results in an almost identical
6    $BMCL_{10}$ as derived for the primary analysis using LPT as the critical effect. In the subcohort,
7   the number of cases of ARC is identical to the number of cases of LPT, and in the larger group
8   of workers evaluated in 2002−2005 used to estimate the effect of TSFE, the number of cases of
9   APT is very similar to the number of LPT cases ($n = 71$ cases of ARC, and $n = 66$ cases of LPT).
10   In this larger group, the regression coefficient for the effect of TSFE was very close when using
11   either of these two endpoints—values of 0.1115 for ARC and 0.1075 for LPT. Thus, using the
12   same uncertainty factors as described above, the chronic RfC is 9.0×10^{-5} fibers/cc for LAA,
13   using an alternative endpoint of ARC:

14

15   Chronic RfC for ARC = $BMCL_{10} \div UF$ (5-5)
16   =   0.027 fiber/cc $\div$ 300
17   = 9.0×10^{-5} fibers/cc

18

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

22

23   **5.2.4. Derivation of a Reference Concentration (RfC) for Localized Pleural Thickening**
24   **(LPT) in the Marysville Workers Who Underwent Health Evaluations in 2002−2005**
25   **and Were Hired in 1972 or Later Based on the Cumulative Exposure Model**

26   As shown in the analyses in Section 5.2.2 (see Table 5-9), the model with TSFE and CE
27   yields a similar overall fit to the model based on TSFE and mean exposure as judged by AIC
28   values within 2 units (242.6 vs. 242.7). However, the CE model yielded an unacceptably low
29   value for the Hosmer-Lemeshow goodness-of-fit test ($p < 0.04 < 0.1$) when also including TSFE
30   in the model, and therefore, the mean exposure model was selected for the derivation of the RfC.
31   This same pattern was corroborated in the analysis of the combined cohort in Appendix E where
32   the same bivariate Dichotomous Hill model with plateau fixed at 85% passed the
33   Hosmer-Lemeshow goodness-of-fit test for the model with TSFE and mean exposure but yielded
34   an unacceptably low value for the model with TSFE and CE ($p = 0.006 < 0.1$; see Table E-4
35   Row: BV DH [CE, TSFE]).
36   However, as CE has been a traditional exposure metric of asbestos exposure, there may
37   be interest in an estimate of the RfC for such a model based on TSFE and CE. The use of an
38   alternative model based on the TSFE and CE data yields a $BMCL_{10}$ of 0.577 fiber/cc-yr using

1 LPT as the critical effect among individuals evaluated in 2002−2005 and hired in 1972 or later.

2 In order to adjust the POD to units of concentration (fiber/cc), this POD was divided by the mean

3 duration of occupational exposure (18.23 years) to yield an adjusted $BMCL_{10}$ of 0.0317 fiber/cc.

4 Using the same uncertainty factors as described above, the value of an RfC for LAA based on

5 TSFE and CE would be 1.0×10^{-4} fibers/cc:

6

7 Chronic RfC for LPT $=$ $BMCL_{10} \div UF$ (5-6)

8                         $=$ 0.0317 fiber/cc $\div$ 300

9                         $=$ 1.0×10^{-4} fibers/cc

10

11   This value is approximately 11% higher than the primary RfC derived using a critical

12 effect of LPT. As noted previously, this result is included for comparative purposes with the

13 primary RfC, but was not selected as the primary RfC as the model based on CE did not indicate

14 an adequate fit to the Marysville subcohort of workers evaluated in 2002−2005 and hired in 1972

15 or later when also including TSFE in the model.

16

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

20   EPA also conducted modeling of the full Marysville cohort to substantiate the derivation

21 of the RfC in the primary analytic subset of workers evaluated in 2002−2005 and hired in 1972

22 or later and considered in the previous sections. The "combined cohort" was assembled using all

23 individuals who participated in the health examination in 1980 (Lockey et al., 1984) and

24 2002−2005 (Rohs et al., 2008), and who were not exposed to asbestos from a source outside of

25 the Marysville facility (see Table 5-3 and Appendix E for details). Due to differences in the

26 1980 x-ray evaluations compared with the 2002−2005 x-ray evaluations, an alternative critical

27 effect of APT was used in the combined cohort modeling.

28   The modeling of the combined cohort is described in detail in Appendix E. A suite of

29 model forms (univariate and bivariate) and exposure metrics (mean exposure, cumulative

30 exposure, RTW exposure) were evaluated using the combined cohort of 434 individuals. Two

31 models (Cumulative Normal Dichotomous Hill and Cumulative Normal Michaelis Menten

32 models), which incorporated TSFE into the plateau term rather than as an independent predictor

33 alongside the exposure metric, were also evaluated as a supplement to the standard suite of

34 models.

35   The results for the BMC and BMCL for the three endpoints (LPT—defined as LPT

36 diagnosed in 2002−2005 and PT in 1980, APT, and ARC) are presented in Tables E-3, E-4, and

37 E-5. Any pleural thickening is selected as the preferred endpoint for the alternative derivation of

38 the reference concentration (RfC) for the combined cohort because the endpoint of APT is more

1 inclusive (it includes those with LPT and those with DPT in the absence of LPT) and eliminates
2 the uncertainty regarding the type of pleural thickening observed in the 1980 study (Lockey et
3 al., 1984) using the 1971 ILO guidance. The two models selected for derivation of an RfC were
4 (1) the same bivariate Dichotomous Hill model with fixed plateau used in the primary analysis
5 based on TSFE and mean concentration and (2) the cumulative normal Dichotomous Hill model
6 with fixed background rate of APT based on TSFE and CE. Additionally, in keeping with the
7 primary analysis of the subcohort hired in 1972 or later, an analogous hybrid analysis of the
8 subcohort based on the combined cohort was also conducted based on the two selected models.
9 All of these results are presented at a value of TSFE = 70 years for those models that were able
10 to reasonably extrapolate the TSFE value outside the observed range (47 years maximum) and
11 for the median value of TSFE in the combine cohort (25 years) for models where the
12 extrapolation to 70 years was not reasonable.
13   Following EPA practices and guidance (U.S. EPA, 2002, 1994b) as discussed in
14 Section 5.2.3, a composite uncertainty factor (UF) of 300 is used when deriving the RfC from the
15 POD calculated at the median TSFE (25 years). This includes an uncertainty factor of 10 to
16 account for intraspecies variability ($UF_H = 10$), a factor of three to account for database
17 uncertainty ($UF_D = 3$) and an extra factor (UF_S) of 10 to account for the lack of information on
18 people at risk for a complete lifetime ($UF_S = 10$). When using the POD based on the BMCL
19 calculated at TSFE = 70 years, the additional adjustment factor of 10 is not necessary and a
20 composite UF of 30 is used ($UF_H = 10$ and $UF_D = 3$). The calculations of the RfC for the
21 combined cohort and the Rohs subcohort using both options are shown in Table 5-10. The RfCs
22 are rounded to one significant digit.
23

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

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

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

1 For comparison, the above values all fall within approximately threefold when compared
2 to the primary RfC for LPT of 9×10^{-5} fibers/cc derived in Section 5.2.3 from the Marysville
3 workers who underwent health evaluations in 2002−2005 and were hired in 1972 or later. These
4 results provide additional support to further substantiate the primary RfC.
5
6 **5.2.6. Summary of Reference Concentration Values (RfCs) for the Different Health**
7 **Endpoints and Different Sets of Workers in the Marysville Cohort**

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

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

Location	Study population	Health endpoint	Occupational LAA exposure	Residential LAA exposure	Occupational TSFE	Residential TSFE	Model	Exposure metrics	RfC	Section
Cohorts										
Libby, MT	Workers	LPT	Measured	Unknown	Measured	Unknown	---	---	---	5.2.1
Minneapolis, MN	Residents	LPT	---	Modeled	---	Unclear	---	---	---	5.2.1
Marysville, OH	Workers	LPT, APT, ARC	Measured ≥1972	---	Measured	---	**---**	**---**	**---**	5.2.1
RfC estimates										
Marysville, OH	**Hired ≥1972**	**LPT**	**Measured**	**None**	**Measured**	**---**	**Hybrid Rohs DH$_{85}$; TSFE = 28 yr**	**TSFE and C**	**9E-5**	**5.2.3**
Marysville, OH	Hired ≥1972	APT	Measured	None	Measured	---	Hybrid Rohs DH$_{85}$; TSFE = 28 yr	TSFE and C	9E-5	5.2.3.1
Marysville, OH	Hired ≥1972	ARC	Measured	None	Measured	---	Hybrid Rohs DH$_{85}$; TSFE = 28 yr	TSFE and C	9E-5	5.2.3.2
Marysville, OH	Hired ≥1972	LPT	Measured	None	Measured	---	Hybrid Rohs DH$_{85}$; TSFE = 28 yr	TSFE and CE	1E-4	5.2.4
Marysville, OH	All hires	APT	Measured ≥1972	None	Measured	---	Combined cohort CN DH; TSFE = 25 yr	TSFE and CE	1E-4	5.2.5 App. E
Marysville, OH	All hires	APT	Measured ≥1972	None	Measured	---	Combined cohort CN DH; TSFE = 25 yr	TSFE and C	2E-4	5.2.5 App. E
Marysville, OH	All hires	APT	Measured ≥1972	None	Measured	---	Hybrid combined cohort DH$_{85}$; TSFE = 25 yr	TSFE and CE	1E-4	5.2.5 App. E
Marysville, OH	All hires	APT	Measured ≥1972	None	Measured	---	Combined cohort CN DH; TSFE = 70 yr	TSFE and CE	3E-5	5.2.5 App. E
Marysville, OH	All hires	APT	Measured ≥1972	None	Measured	---	Hybrid combined cohort DH$_{85}$; TSFE = 70 yr	TSFE and CE	3E-5	5.2.5 App. E

Abbreviations: Health endpoint (LPT = localized pleural thickening, APT = any pleural thickening, ARC = any radiographic change).

Models (hybrid Rohs = 2-step model fit to full Rohs cohort then Rohs subcohort, hybrid combined cohort = 2-step model fit to combined cohort then to the Rohs subcohort, DH$_{85}$ = Dichotomous Hill with plateau fixed at 85%, CN DH = cumulative normal Dichotomous Hill).

Exposure metrics (TSFE = time since first exposure, C = mean concentration, CE = cumulative exposure).

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5.3. UNCERTAINTIES IN THE INHALATION REFERENCE CONCENTRATION (RFC)

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

5.3.1. Uncertainty in the Exposure Reconstruction

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

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

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

1   1980. The exposure distribution in Marysville workers is summarized in Table 5-12, which

2   shows the mean, cumulative, and RTW exposure metrics for the full cohort of workers, the

3   subset of those evaluated in 2002−2005, and the primary analytic group of workers evaluated in

4   2002−2005 and hired in 1972 or later. To evaluate the potential impact of assumptions regarding

5   exposure after 1980 when the use of Libby vermiculite ores was considered to have ceased, EPA

6   conducted a sensitivity analysis using the hybrid Dichotomous Hill model with plateau fixed at

7   85%, but truncating exposures at 12/31/1980 (see Table 5-13). Note that except where stated

8   otherwise, this model (hybrid Dichotomous Hill model with plateau fixed at 85%) was used for

9   all sensitivity analyses. Using the truncated exposures, the POD increased from

10   2.6×10^{-2} fibers/cc, to 3.9×10^{-2} fibers/cc. However, note that for the model with truncated

11   exposures, the modeling in the larger group of workers evaluated in 2002−2005 showed a poor

12   fit (Hosmer-Lemeshow GOF p-value < 0.10). These results are included for comparative

13   purposes but should be interpreted with caution.

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

Exposure metrics, based on arithmetic mean	All individuals evaluated in 1980 and/or in 2002−2005[a]		Individuals evaluated in 2002−2005		Individuals evaluated in 2002−2005, hired in 1972 or later	
	Mean (SD)	Median (25th–75th percentiles)	Mean (SD)	Median (25th–75th percentiles)	Mean (SD)	Median (25th–75th percentiles)
Cumulative exposure, all yr (fiber/cc-yr)						
Arithmetic mean	7.9232 (17.9598) Range: 0.003−96.91	1.1252 (0.3414−3.7684)	8.75 (19.12) Range: 0.005−96.91	1.26 (0.51−5.20)	1.439 (2.5479) Range: 0.005−17.33	0.5048 (0.2188−1.5519)
Geometric mean	2.9258 (7.0248) Range: 0.001−37.73	0.2132 (0.1004−1.2635)	3.24 (7.48) Range: 0.002−37.73	0.29 (0.14−1.78)	0.4756 (0.8734) Range: 0.002−6.05	0.1785 (0.087−0.4632)
Mean exposure, all yr (fiber/cc)						
Arithmetic mean	0.3733 (0.7942) Range: 0.007−4.34	0.0566 (0.0267−0.2364)	0.31 (0.65) Range: 0.007−4.10	0.05 (0.02−0.20)	0.0716 (0.1239) Range: 0.007−0.77	0.0234 (0.0133−0.074)
Geometric mean	0.1366 (0.3101) Range: 0.003−1.70	0.0111 (0.0068−0.0719)	0.11 (0.25) Range: 0.003−1.59	0.01 (0.006−0.07)	0.0236 (0.0422) Range: 0.003−0.26	0.0085 (0.0062−0.0222)
Residence time-weighted exposure, all yr (fiber/cc-yr), calculated using midpoint of season dates						
Arithmetic mean	193.3093 (519.3874) Range: 0.0007−3500.66	19.4767 (4.2550−78.0944)	294.38 (687.95) Range: 0.12−3500.66	34.31 (11.07−154.36)	33.7415 (69.2231) Range: 0.12−474.01	10.2075 (3.9055−29.1246)
Geometric mean	72.2260 (204.1052) Range: 0.0003−1373.22	4.1835 (0.9229−25.2179)	110.14 (270.86) Range: 0.05−1373.22	6.24 (3.06−49.81)	11.1415 (24.2783) Range: 0.05−168.17	3.3526 (1.6814−8.5014)
Cumulative exposure, through 1980 (fiber/cc-yr)						
Arithmetic mean	7.6544 (17.8658) Range: 0.003−95.09	0.9708 (0.2120−3.3925)	8.27 (18.95) Range: 0.005−95.09	0.97 (0.22−4.65)	0.9638 (2.2774) Range: 0.005−15.37	0.212 (0.0564−0.5849)
Geometric mean	2.8324 (7.0007) Range: 0.001−37.20	0.1277 (0.0502−1.0805)	3.08 (7.43) Range: 0.002−37.20	0.13 (0.05−1.55)	0.3119 (0.8027) Range: 0.002−5.48	0.0478 (0.0244−0.1279)
Mean exposure, through 1980 (fiber/cc)						
Arithmetic mean	0.4863 (0.9568) Range: 0.008−4.34	0.0766 (0.0375−0.2950)	0.51 (0.98) Range: 0.008−4.33	0.07 (0.04−0.40)	0.1422 (0.2911) Range: 0.008−1.84	0.0352 (0.0193−0.1027)

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

	All individuals evaluated in 1980 and/or in 2002−2005[a]		Individuals evaluated in 2002−2005		Individuals evaluated in 2002−2005, hired in 1972 or later	
Geometric mean	0.1767 (0.3732) Range: 0.003−1.70	0.0110 (0.0074−0.0968)	0.19 (0.38) Range: 0.003−1.68	0.01 (0.007−0.11)	0.0452 (0.1013) Range: 0.003−0.66	0.0102 (0.0063−0.0261)
Residence time-weighted exposure, through 1980 (fiber/cc-yr), calculated using midpoint of season dates						
Arithmetic mean	189.5463 (517.2418) Range: 0.0007−3475.17	16.0931 (2.7315−69.9986)	287.78 (685.61) Range: 0.12−3475.17	30.08 (6.07−137.64)	27.2008 (65.8222) Range: 0.12−448.51	5.9930 (1.4107−16.0968)
Geometric mean	70.9061 (203.4978) Range: 0.0003−1365.69	2.4223 (0.6805−23.5698)	107.84 (270.24) Range: 0.05−1365.69	4.05 (1.34−43.96)	8.8655 (23.3699) Range: 0.05−160.64	1.3228 (0.6124−3.6592)

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

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

	Exposures based on arithmetic mean—Primary Analysis		Exposures based on arithmetic mean, truncated at 1980	
	Primary	**Individuals with radiographs in 2002−2005 (to get beta for TSFE)**	**Primary**	**Individuals with radiographs in 2002−2005 (to get beta for TSFE)**
Hosmer-Lemeshow GOF *p*-value	0.73626	0.34206	0.63257	0.00790
Model AIC	75.5	242.7	78.0	244.6
Alpha (intercept)	−1.9798 (SE = 1.2270)	−3.4130 (SE = 1.1368)	−3.4612 (SE = 0.9790)	−4.14881 (SE = 1.4937)
Bkg (background)	0.03682 (SE = 0.04037)	0 (--)	0.0594 (SE = 0.0360)	0.0079 (SE = 0.0491)
Beta for TSFE	0.1075 (fixed)	0.1075 (SE = 0.0281), *p* = 0.0002	0.1167 (fixed)	0.1167 (SE = 0.0379), *p* = 0.0023
Beta for ln (mean exposure)	1.2750 (SE = 0.7159), *p* = 0.0775	0.4819 (SE = 0.1390), *p* = 0.0006	1.4054 (SE = 1.3328), *p* = 0.2938	0.4223 (SE = 0.1517), *p* = 0.0058
BMC and BMCL at 28 yr (f/cc)	0.0923 and 2.6×10^{-2}		0.2761 and 3.9×10^{-2}	

	Exposures based on geometric mean		Exposures based on geometric mean, truncated at 1980	
	Primary	**Individuals with radiographs in 2002−2005 (to get beta for TSFE)**	**Primary**	**Individuals with radiographs in 2002−2005 (to get beta for TSFE)**
Hosmer-Lemeshow GOF *p*-value	0.23188	0.07022	0.68399	0.02812
Model AIC	75.7	244.1	78.1	245.6
Alpha (intercept)	−1.0630 (SE = 1.9499)	−3.6638 (SE = 1.1191)	−2.4799 (SE = 1.9039)	−4.1735 (SE = 1.0727)
Bkg (background)	0.0367 (SE = 0.0461)	0 (--)	0.0578 (SE = 0.0401)	0 (--)
Beta for TSFE	0.1234 (fixed)	0.1234 (SE = 0.0276), *p* < 0.0001	0.1266 (fixed)	0.1266 (SE = 0.0276), *p* < 0.0001
Beta for ln (mean exposure)	1.2527 (SE = 0.7173), *p* = 0.0833	0.4012 (SE = 0.1213), *p* = 0.0011	1.2118 (SE = 1.0841), *p* = 0.2659	0.3256 (SE = 0.1015), *p* = 0.0015
BMC and BMCL at 28 yr (f/cc)	0.0298 and 9.1×10^{-3}		0.0796 and 9.9×10^{-3}	

1   Another potential source of uncertainty in the exposure reconstruction is the method used
2   to average multiple fiber measurements for a given location (within the Marysville facility) and
3   time period. The arithmetic mean of multiple measurements was used here, but an alternative
4   approach would be to use the geometric mean, which has the effect of "dampening" outliers or
5   extreme values. EPA conducted a sensitivity analysis for exposures estimated using the
6   geometric mean of multiple fiber measurements and found that the PODs were lower than those
7   estimated for the primary analysis (9.1×10^{-3} fibers/cc considering all years of exposure, and
8   9.9×10^{-3} fibers/cc if exposures were truncated after 1980) (see Table 5-13). The lower PODs
9   are a result of the approximately threefold lower exposures estimated for each individual worker
10   when using the geometric mean; in the Marysville workers evaluated in 2002−2005 and hired in
11   1972 or later, the median of each individual's mean exposure intensity estimated using the
12   arithmetic versus the geometric mean of multiple fiber measurements in the plant were
13   0.0234 fiber/cc and 0.0085 fiber/cc, respectively. Note that for both models utilizing geometric
14   mean exposures, the modeling in the larger group of workers evaluated in 2002−2005 showed
15   poor fit (Hosmer-Lemeshow GOF p-value < 0.10). These results are included for comparative
16   purposes but should be interpreted with caution.
17   Potential coexposure to other chemicals was present in the Marysville facility (see
18   Section 4.1.2.2.2). These other chemicals were used after expansion of vermiculite ore in
19   another area of the facility. Industrial hygiene data showed very low levels of fibers in the areas
20   where the additional chemicals were added to the expanded vermiculite. In addition, none of
21   these chemicals are volatile. The most likely route of exposure to these chemicals is through
22   dermal contact. It is unlikely that any coexposure to these particular chemicals would alter the
23   exposure-response relationship of LAA in the respiratory system (see Section 4.1.2.2.2).
24   The University of Cincinnati research team assumed no exposure to LAA occurred
25   outside of the workplace for the Marysville workers. 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 clothes before leaving the workplace was standard
28   practice at the end of the shift, and approximately 64% of the workers showered before leaving
29   the workplace. For these workers, it is likely that additional exposure outside the workplace was
30   minimal. However, for the remainder of the workers, it is reasonable to assume that additional
31   exposure could have occurred at home. Additional data collected by the University of Cincinnati
32   research team document that no increased prevalence of pleural or parenchymal change
33   consistent with asbestos exposure was observed in household contacts of the workers from the
34   Marysville facility (Hilbert et al., 2013).
35
36   **5.3.2. Uncertainty in the Radiographic Assessment of Localized Pleural Thickening (LPT)**
37   The use of conventional radiographs to diagnose pleural thickening has several
38   limitations. The localized thickening must be of sufficient size and thickness to be viewed on the

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1   x-ray, and small lesions may exist but not reported. More severe and larger lesions are more
2   reliably detected on radiographs. There are also potential interferences. Fat pads may be
3   mistaken for pleural plaques because they generally occur against the ribcage in a similar
4   location (Gilmartin, 1979); this is one source of potential disagreement among x-ray readers.
5   Often signs of trauma (e.g., fractured ribs) and radiographic signs of past tuberculosis infection
6   can be seen and are noted by the reader. In these cases, LPT would not be diagnosed. There is a
7   certain amount of subjectivity when viewing the x-rays in determining which features are
8   representative of pleural thickening and whether signs of alternative etiology can be noted; thus,
9   multiple certified readers are generally consulted, and a consensus of opinions determines the
10   diagnosis. Regardless, the potential for outcome misclassification still exists. However,
11   uncertainty in the presence or absence of localized pleural thickening in each individual is
12   decreased by the use of three highly qualified chest radiologists evaluating the radiographic films
13   and the use of the majority vote of the readers for the diagnosis.
14   BMI was investigated as a potential explanatory variable because fat pads can sometimes
15   be misdiagnosed as pleural thickening. The effect of such outcome misclassification would be to
16   attenuate the observed association between exposure and outcome. In the Marysville data, BMI
17   was not measured in the 1980 examination but was available for most participants of the 2000s
18   examination (available for most of those in the data sets used to derive the RfC). To address
19   whether fat deposits may affect outcome classification, EPA considered the effect of adding BMI
20   as a covariate in the model. However, BMI did not display an association with odds of localized
21   pleural thickening in this population ($p = 0.6933$).
22

5.3.3. Uncertainty Due to Potential Confounding

24   Along with the effect of BMI, other covariates were also evaluated for potential
25   confounding of the association between LAA exposure and LPT in the Marysville workers (see
26   Section 5.2.2.6.1). Covariates included both demographic characteristics (gender, smoking
27   status, BMI) as well as potentially exposure-related factors (hire year, job tenure, exposure
28   duration, and age at x-ray).
29   Smoking is a particularly important variable to consider when evaluating respiratory
30   health outcomes. Although data are mixed, a few studies suggest smoking may affect the risk of
31   developing asbestos-related pleural thickening or timing of such pleural thickening development.
32   However, no studies were identified that assessed the relationship between LPT specifically and
33   any measure of smoking status. Plaques as defined in earlier ILO classification systems have not
34   been associated with smoking in asbestos-exposed workers (Mastrangelo et al., 2009; Paris et al.,
35   2009; Koskinen et al., 1998).
36   Some evidence indicates that small interstitial opacities (asbestosis) and asbestos-related
37   DPT may be associated with smoking. Studies among populations exposed to other general
38   types of asbestos have reported mixed effects on the impact of smoking on risk of radiographic

1   abnormalities; two studies reported a significant association between risk of all pleural

2   thickening, including both pleural plaques and diffuse pleural thickening (McMillan et al., 1980),

3   or any pleural abnormality (Welch et al., 2007) and smoking after controlling for some measure

4   of asbestos exposure. A larger number of studies reported borderline associations when

5   examining risk of pleural changes (Adgate et al., 2011; Paris et al., 2008; Dement et al., 2003;

6   Zitting et al., 1996; Yano et al., 1993; Lilis et al., 1991; Baker et al., 1985) or no association with

7   smoking (Soulat et al., 1999; Neri et al., 1996; Ehrlich et al., 1992; Delclos et al., 1990;

8   Rosenstock et al., 1988). Possible reasons for the different findings include varying quality of

9   smoking information (some used categories of ever/never or former/current/never, while others

10   used pack-years) and differences in the specific outcome studied.

11   As the current classification of LPT includes cases that would have been classified as

12   diffuse pleural thickening without costophrenic angle involvement in previous ILO guidelines,

13   investigation of the potential for smoking to modify the risk of LPT is warranted. In the Libby

14   workers cohort, McDonald et al. (1986b) assessed pleural thickening of the chest wall (both

15   discrete and diffuse regardless of CPA involvement) and found smoking status (current, former,

16   or never smoker) was of borderline statistical significance ($p = 0.10$) in a regression model,

17   controlling for LAA exposure and age. This result is consistent with the broader asbestos

18   literature, addressing all pleural thickening or all pleural abnormalities. Amandus et al. (1987a)

19   evaluated radiographic abnormalities consistent with the current LPT designation; the authors

20   took a different analytic approach to assess smoking effects, constructing separate models for the

21   full cohort and restricting to current and former smokers. The parameter estimates were not

22   statistically significant for the two models, although the coefficients corresponding to LAA

23   exposure were slightly higher for the full cohort model. In the Marysville workers cohort,

24   smoking was characterized using pack-years in the original study (Lockey et al., 1984) and as

25   ever or never smoking in the follow-up study (Rohs et al., 2008). Lockey et al. (1984) reported

26   that the pack-years variable was statistically significantly associated with risk of all radiographic

27   changes using discriminate analysis (any pleural thickening, small interstitial opacities, and

28   blunting of the CPA) but did not present results for effect of smoking controlling for LAA

29   exposure. Rohs et al. (2008) did not find a difference in smoking prevalence among those with

30   and without any radiographic changes but also did not report results controlling for LAA

31   exposure, or for LPT specifically.

32   None of the potential confounding factors examined were significantly associated with

33   LPT after controlling for LAA exposure in the primary data set of workers evaluated in

34   2002−2005 and hired in 1972 or later. However, the effect of each covariate was reexamined in

35   the primary (hybrid) model which utilized information from the larger set of workers evaluated

36   in 2002−2005, regardless of hire date (see Table 5-14). Each covariate was included (one at a

37   time) in the primary model, and the statistical significance and effect on the model parameters

38   evaluated. None were statistically significantly related to risk of LPT, with p-values for the

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1   corresponding beta coefficients ranging from 0.1533 (gender) to 0.9858 (hire year). Note that

2   because these main effects were not statistically significantly associated with LPT, they would

3   not be expected to modify the association between LAA exposure (controlling for TSFE) and

4   LPT. It is unlikely that there would be opposing effects for exposure and the covariates

5   examined that would "cancel each other out" and mask true effect measure modification. Thus,

6   effect modification was not considered to be an issue in these analyses. It is not surprising that

7   the time-related factors were not statistically significant (and had little effect on the estimated

8   beta coefficient for exposure) because these factors were highly correlated with TSFE (which

9   was already included in the primary model). The effect of exposure was higher when including

10   gender and smoking status (current, ex- or never smoker) and lower when including ever-smoker

11   status and BMI. Although the effect of gender was not significant, there were relatively few

12   women in the Marysville workers population ($n = 16$ in the workers evaluated in 2002−2005,

13   and $n = 13$ in the subgroup hired in 1972 or later). In the primary analytic group, the prevalence

14   of LPT was not very different by gender, but the comparison is limited by sample size—there

15   was 1 woman among the total of 13 with LPT (prevalence of 7.7%), while the other 12 cases

16   (including the individual with LPT and DPT) were among the 106 men (prevalence of 11.3%).

17   However, women also tended to have lower LAA exposure in this study population―for

18   example, median cumulative exposure was 0.17 (interquartile range: 0.05, 0.26) fiber/cc-yr

19   among women, compared with 0.56 (interquartile range: 0.23, 1.78) fibers/cc-yr among

20   men―which could explain the lower prevalence. Larson et al. (2012a) found that among Libby

21   workers (93.2% of whom were male), the prevalence of LPT was 37% among men and 9%

22   among the 23 women included in the study, but exposure levels by gender were not provided in

23   the published report. In the Minneapolis community study, the prevalence of all pleural

24   abnormalities was 16.5% among men, compared to 4.6% among women (adjusted odds ratio and

25   95% confidence interval of 3.8 [1.6, 8.9]; Alexander et al., 2012), but again, exposure levels by

26   gender were not reported. Thus, the potential for different effects by gender merits further

27   investigation.

28   In the Marysville workers, the variables representing smoking history (either current

29   versus ex- versus never smoker, or ever smoker versus never smoker) were not statistically

30   significant. However, the limited sample size (only three cases were never smokers) and limited

31   nature of the smoking information precluded further analysis of smoking; thus, further research

32   is needed on the effect of smoking in relation to LPT risk among asbestos-exposed populations.

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

	Primary analysis	Including gender	Including ever smoker status	Including smoking status (compared to never smoker)	Including BMI
Hosmer-Lemeshow GOF *p*-value	0.73625	0.72137	0.43468	0.88918	0.95082
Model AIC	75.5	75.0	76.1	78.5	60.7†
Alpha (intercept)	−1.9798 (SE = 1.2270)	4.8281 (SE = 5.1146)	−2.8954 (SE = 1.2344)	1.2111 (SE = 4.0064)	−3.0224 (SE = 2.1693)
Bkg (background)	0.03682 (SE = 0.04037)	0.0603 (SE = 0.0258)	0.0212 (SE = 0.0246)	0.0677 (SE = 0.0262)	0 (--)
Beta for TSFE	0.1075 (fixed)	0.1075 (fixed)	0.1075 (fixed)	0.1075 (fixed)	0.1075 (fixed)
Beta for ln (mean exposure)	1.2750 (SE = 0.7159), *p* = 0.0775	2.8080 (SE = 1.5440), *p* = 0.0715	1.1182 (SE = 0.4558), *p* = 0.0156	3.6756 (SE = 2.6246), *p* = 0.1640	0.9723 (SE = 0.3583), *p* = 0.0079
Beta for covariate	--	−5.0804 (SE = 3.5349), *p* = 0.1533	1.1701 (SE = 0.9993), *p* = 0.2440	Ex-smoker: −2.2659 (SE = 2.9748), *p* = 0.4477 Current smoker: 2.2180 (SE = 2.7013), *p* = 0.4132	0.0238 (SE = 0.0600), *p* = 0.6933

		Including hire yr	Including job tenure (yr)	Including exposure duration (yr)	Including age at x-ray (yr)
Hosmer-Lemeshow GOF *p*-value		0.73619	0.46477	0.70317	0.41903
Model AIC		77.5	77.2	77.4	77.3
Alpha (intercept)		−2.0004 (SE = 0.0006)	−1.2689 (SE = 1.9188)	−1.5075 (SE = 1.9288)	0.4511 (SE = 8.4602)
Bkg (background)		0.0368 (SE = 0.0404)	0.0350 (SE = 0.0426)	0.0368 (SE = 0.0421)	0.0437 (SE = 0.0558)
Beta for TSFE		0.1075 (fixed)	0.1075 (fixed)	0.1075 (fixed)	0.1075 (fixed)
Beta for ln (mean exposure)		1.2757 (SE = 0.7175), *p* = 0.0779	1.2498 (SE = 0.6919), *p* = 0.0734	1.2747 (SE = 0.7179), *p* = 0.0784	1.4362 (SE = 1.2550), *p* = 0.2548
Beta for covariate		0.00001 (SE = 0.0006), *p* = 0.9858	−0.0358 (SE = 0.0665), *p* = 0.5914	−0.0234 (SE = 0.0681), *p* = 0.7321	−0.0422 (SE = 0.1391), *p* = 0.7621

1   **5.3.4. Uncertainty Due to Time Since First Exposure (TSFE)**

2   Some uncertainty is associated with the length of follow-up of the Marysville cohort.
3   There was relatively little variation in TSFE among the workers evaluated in 2002−2005 and
4   hired in 1972 or later. It is anticipated that the prevalence of localized pleural thickening in the
5   study population will likely continue to increase with passage of time. However, EPA took that
6   into account both in modeling and in its application of uncertainty factors. EPA utilized
7   information from the broader group of workers evaluated in 2002−2005 (i.e., regardless of hire
8   date) and with a wider range of TSFE, to estimate the effect of time. However, because even this
9   larger group lacked information on full lifetime exposure (maximum TSFE of 47 years), the
10   modeling approach may not accurately reflect the exposure-response relationship that would be
11   seen with a longer follow-up time. As one approach to gauge the sensitivity of the model, the
12   plateau parameter―representing theoretical maximum prevalence of LPT when both exposure
13   and TSFE are very large―was investigated further (see Table 5-15). As described above, the
14   plateau parameter for the primary modeling was fixed at a literature-derived value of 85%
15   (Järvholm, 1992; Lilis et al., 1991). The sensitivity of the POD to this assumption was
16   investigated by looking at two alternative fixed values, 70 and 100% (i.e., the log-logistic
17   model), as well as estimating the plateau parameter from the data. The value of 70% was
18   selected for sensitivity analysis because in a cross-sectional study of Libby workers and residents
19   seen at a clinic in Libby, Winters et al. (2012) observed a prevalence of 72% for pleural
20   thickening, although the maximum TSFE was not known. Note that for the model with
21   estimated rather than fixed plateau, the modeling in the larger group of workers evaluated in
22   2002−2005 showed poor fit (Hosmer-Lemeshow GOF p-value < 0.10); these results are included
23   for comparative purposes but should be interpreted with caution.

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

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

1   The effects on the POD resulting from different assumptions regarding the plateau were
2   small. When assuming different fixed values (70, 85, and 100%) the POD only ranged from
3   2.6×10^{-2} to 2.7×10^{-2} fibers/cc. Estimating the plateau from the data led to a slightly higher
4   POD of 3.0×10^{-2} fibers/cc. These results lend confidence that assumptions regarding maximum
5   prevalence of LPT in the population do not have a substantial impact on the estimated POD.
6   As described in Section 5.2.2.6.1, one option to incorporate TSFE would be to utilize the
7   RTW exposure metric, which incorporates aspects of both exposure duration and TSFE. This
8   option was not selected for RfC derivation due to the narrow range of TSFE among the primary
9   analytic group of Marysville workers who underwent health evaluations in 2002−2005 and
10   whose job start date was on or after 1/1/1972. However, this approach was used as a sensitivity
11   analysis, estimating the concentration that, if experienced over 70 years, would yield the BMR.
12   The model with RTW as the metric derives as its POD a "benchmark residence time-weighted"
13   quantity in units of fibers/cc-yr^2 and its associated confidence interval. In order to convert the
14   benchmark quantity in units of fibers/cc-yr^2 and its associated lower limit into a 70-year
15   exposure concentration (in units of fiber/cc), the constant 70-year concentration yielding that
16   RTW should be determined where 70 years is both the duration and the time elapsed between the
17   first year of exposure and the health evaluation. That concentration is equal to the benchmark
18   RTW (or its lower limit) divided by the residence time-weighted value for exposures across
19   70 years: $1+….+70 = [(70 \times 71 \text{ years})/2]$, as sum of first N natural numbers is equal to
20   $(N \times (N + 1))/2$. The results of using RTW exposure with the preferred model (Dichotomous
21   Hill with plateau fixed at 85%) are shown in Table 5-16. For comparison, results also using the
22   RTW exposure metric but using alternate model forms are also shown; the model fits and results
23   are very similar for the Dichotomous Hill, log-logistic, and log-probit models, with the PODs all
24   ~0.003 fiber/cc for a scenario of 70-years exposure duration and 70-years TSFE. The
25   Michaelis-Menten model provided a lower AIC (2 units lower than the Dichotomous Hill
26   model), and the POD was slightly higher (0.0057 versus 0.0034 fiber/cc).

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

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

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

1   Advantages of this approach using the RTW exposure metric in the subcohort are that it
2 relies solely on the individuals with higher quality exposure information and consistent
3 radiograph evaluation, and uses an exposure metric that weights more heavily exposure
4 occurring in the more distant past. However, the modeling still relies solely on the subgroup of
5 workers with little variation in TSFE, and whose TSFE values are for less than a full lifetime.
6 This lack of variability in TSFE limits the ability to explore how risk of LPT varies across the
7 life span. However, it does provide an important comparison for the primary RfC; the BMCLs
8 estimated using this approach range from 0.018 to 0.035 fiber/cc, similar to the BMCL estimated
9 in the primary analysis (0.026 fiber/cc).
10   Another source of information regarding TSFE comes from the study by Larson et al.
11 (2010a) which examined serial radiographs conducted on a group of Libby vermiculite workers

1   with pleural or parenchymal changes. The mean follow-up time was 21.6 years, with a

2   maximum of 44.9 years. They found that among those workers with localized pleural

3   thickening, all cases were identified within 30 years, and that the median time from hire to the

4   first detection of localized pleural thickening was 8.6 years. Although the retrospective

5   evaluation of radiographs is a different and more sensitive procedure, these findings indicate that

6   the range of follow-up time in the Marysville subcohort is likely sufficient to support the

7   exposure-response modeling developed in this current assessment. Note that the likelihood that

8   prevalence of localized pleural thickening is expected to increase over the life span is a principal

9   rationale cited for the selection of a subchronic-to-chronic UF of 10 in this current assessment.

10

11   **5.3.5. Uncertainty in the Endpoint Definition**

12   The critical effect selected for RfC derivation is localized pleural thickening. As a

13   sensitivity analysis, an alternative critical effect of any radiographic change was also investigated

14   and found to yield an essentially identical POD (i.e., a BMCL of 2.7×10^{-2}, compared with

15   2.6×10^{-2} in the primary analysis), as that using the same modeling approach in the primary

16   analysis. Almost no information existed on radiographic changes other than LPT in the primary

17   analytic group of workers (evaluated in 2002−2005, hired in 1972 or later) because only one case

18   of DPT was reported and that individual also had LPT. No individuals had interstitial changes.

19   However, some individuals had DPT and/or interstitial changes (with and without LPT) in the

20   larger group of workers evaluated in 2002−2005, which allowed investigation of the effect of

21   TSFE considering alternative endpoint definitions.

22   The primary analysis contrasted individuals with LPT (with or without other radiographic

23   endpoints) to those without any radiographic changes. In the group of workers evaluated in

24   2002−2005, this had the effect of excluding five individuals with DPT and/or interstitial changes,

25   but without LPT. In the subgroup of workers hired in 1972 or later, this distinction had no effect

26   because the single case of DPT also had LPT (and thus was included as a case), and no

27   individuals showed interstitial changes. As a sensitivity analysis, the modeling procedure was

28   repeated, using three alternative endpoint definitions (see Table 5-17). The first contrasts all

29   those with LPT (with or without other endpoints) to those without LPT. Thus, the comparison

30   group could include those with DPT and/or interstitial changes but without LPT. The second

31   model used an endpoint of "any radiographic change." The third sensitivity model contrasted

32   those with LPT only to those with no radiographic abnormalities. Note that for two of the

33   alternative models (those contrasting LPT with no LPT, and any radiographic change with no

34   radiographic change) the modeling in the larger group of workers evaluated in 2002−2005

35   showed poor fits (Hosmer-Lemeshow GOF p-values < 0.10); these results are included for

36   comparative purposes, but should be interpreted with caution.

Table 5-17. Effect of using different case/noncase definitions

	LPT vs. no radiographic abnormalities—primary analysis		LPT vs. no LPT		Any radiographic abnormality vs. no radiographic abnormalities		LPT alone vs. no radiographic abnormalities		Any pleural thickening vs. no radiographic abnormalities	
	All individuals with radiographs in 2002−2005 ($n = 247$)	PRIMARY (hired ≥1972, $n = 119$)	All individuals with radiographs in 2002−2005 ($n = 252$)	PRIMARY (hired ≥1972, $n = 119$)	All individuals with radiographs in 2002−2005 ($n = 252$)	PRIMARY (hired ≥1972, $n = 119$)	All individuals with radiographs in 2002−2005 ($n = 237$)	PRIMARY (hired ≥1972, $n = 118$)	All individuals with radiographs in 2002−2005 ($n = 237$)	PRIMARY (hired ≥1972, $n = 118$)
Hosmer-Lemeshow GOF p-value	0.34206	0.73626	0.05378	0.73640	0.09052	0.73552	0.18854	0.73497	0.10716	0.73565
AIC	242.7	75.5	249.9	75.5	250.0	75.5	230.9	74.1	247.0	75.5
Alpha (intercept)	−3.4130 (SE = 1.1368)	−1.9798 (SE = 1.2270)	−3.4421 (SE = 1.1192)	−1.8537 (SE = 1.2275)	−3.4126 (SE = 1.1376)	−2.1027 (SE = 1.2268)	−3.7837 (SE = 1.1633)	−2.2944 (SE = 1.1804)	−3.4334 (SE = 1.1347)	−2.0812 (SE = 1.2268)
Bkg (background)	0 (--)	0.03682 (SE = 0.04037)	0 (--)	0.03669 (SE = 0.04038)	0 (--)	0.03697 (SE = 0.04037)	0 (--)	0.0341 (SE = 0.0409)	0 (--)	0.03694 (SE = 0.04037)
Beta for TSFE	0.1075 (SE = 0.0281), $p = 0.0002$	0.1075 (fixed)	0.1034 (SE = 0.0275), $p = 0.0002$	0. 1034 (fixed)	0.1115 (SE = 0.0282), $p = 0.0001$	0. 1115 (fixed)	0.1056 (SE = 0.0282), $p = 0.0002$	0.1056 (fixed)	0.1108 (SE = 0.0282), $p = 0.0001$	0.1108 (fixed)
Beta for ln(mean exposure)	0.4819 (SE = 0.1390), $p = 0.0006$	1.2750 (SE = 0.7159), $p = 0.0775$	0.4342 (SE = 0.1324), $p = 0.0012$	1.2764 (SE = 0.7161), $p = 0.0772$	0.5125 (SE = 0.1415), $p = 0.0004$	1. 2739 (SE = 0.7160), $p = 0.0778$	0.3507 (SE = 0.1404), $p = 0.0132$	1.1247 (SE = 0.6467), $p = 0.0846$	0.5042 (SE = 0.1409), $p = 0.0004$	1.2741 (SE = 0.7160), $p = 0.0777$
BMC/BMCL at 28 yr (f/cc)	--	0.0923/ 2.6×10^{-2} (Ratio = 3.5)	--	0.0918/ 2.6×10^{-2} (Ratio = 3.5)	--	0.0929/ 2.7×10^{-2} (Ratio = 3.5)	--	0.0931/ 2.5×10^{-2} (Ratio = 3.8)	--	0.0928/ 2.7×10^{-2} (Ratio = 3.4)

1   The effect of TSFE in these sensitivity analyses using different endpoint definitions was very

2   similar to that in the primary model and led to nearly identical PODs (2.5 to 2.7×10^{-2} fibers/cc).

3   These results lend confidence to the primary analysis.

4   Additionally, EPA conducted a sensitivity analysis using a multinomial model to incorporate

5   information from all outcome groups. The multinomial logistic model is similar to the logistic

6   model and compares each outcome group to the referent group (i.e., no radiographic change) and

7   estimates separate model parameters (intercepts and beta coefficients) for each comparison.

8   With only two outcome groups, the logistic and multinomial models are equivalent. As

9   described earlier, there were noticeable differences when contrasting individuals who had LPT

10   alone, with those who had LPT along with DPT and/or interstitial changes. Thus, two different

11   multinomial models were considered. In the first, the outcome groups were (1) no radiographic

12   change (referent), (2) any LPT (with or without other radiographic changes), and (3) DPT and/or

13   interstitial changes (without LPT) (see Table 5-18). In the second model, the outcome groups

14   were defined as (1) no radiographic change (referent), (2) LPT alone, (3) LPT along with other

15   radiographic changes, and (4) DPT and/or interstitial changes (without LPT). Each of these was

16   contrasted to a logistic model, which is equivalent except that those with DPT and/or interstitial

17   changes without LPT are excluded (i.e., as was done for the primary analysis).

Table 5-18. Exposure-response modeling for any localized pleural thickening (LPT) in the Marysville workers who underwent health evaluations in 2002−2005 (*n* = 252), comparing the multinomial model and logistic model with different outcome group definitions[a]

	Logistic	Multinomial Model 1	Multinomial Model 2
Pearson GOF *p*-value	0.5170	0.9653	0.9999
AIC[b]	249.6	299.3	348.5
Alpha$_1$ (intercept)	−5.1351 (SE = 0.8638)	−5.1980 (SE = 0.8695)	−5.3174 (SE = 0.8946)
Alpha$_2$ (intercept)	--	−8.4598 (SE = 2.9194)	−7.4075 (SE = 2.4490)
Alpha$_3$ (intercept)	--	--	−8.3324 (SE = 2.9481)
Beta$_1$ for mean exposure	0.5878 (SE = 0.2596), $p = 0.0236$	0.5914 (SE = 0.2595), $p = 0.0225$	0.3208 (SE = 0.2957), $p = 0.2779$
Beta$_2$ for mean exposure	--	0.9443 (SE = 0.4625), $p = 0.0412$	1.5242 (SE = 0.4097), $p = 0.0002$
Beta$_3$ for mean exposure	--	--	1.0483 (SE = 0.4988), $p = 0.0356$
Beta$_1$ for TSFE	0.1103 (SE = 0.0237), $p < 0.0001$	0.1120 (SE = 0.0239), $p < 0.0001$	0.1144 (SE = 0.0245), $p < 0.0001$
Beta$_2$ for TSFE—DPT/interstitial changes vs. no change	--	0.1221 (SE = 0.0753), $p = 0.1050$	0.0958 (SE = 0.0651), $p = 0.1413$
Beta$_3$ for TSFE	--	--	0.1173 (SE = 0.0768), $p = 0.1266$

[a]The multinomial model is a generalized form of the logistic regression for >2 outcome categories (not ordered). The model is of the form

$$p_i(x, t) = 1 1 + \exp[-a_i - b_i \times x - c_i \times t]$$

Where p_i is the probability of being in the ith outcome group, and separate intercepts (*a*) and beta coefficients (*b*, *c*) are estimated for effect of predictors on probability of being in each group. Multinomial Model 1 contrasts no radiographic change (referent, Group 0) to those with any LPT (Group 1) and to those with DPT and/or interstitial changes but without LPT (Group 2). Multinomial Model 2 contrasts no radiographic change (referent, Group 0) to those with LPT alone (Group 1), to those with LPT along with DPT and/or interstitial changes (Group 2), and to those with DPT and/or interstitial changes but without LPT (Group 3).

[b]AIC not comparable between multinomial model and logistic model because the number of individuals is different (multinomial, *n* = 252 compared to logistic, *n* = 247).

1   The effect of TSFE was very similar across all the models and outcome groups, with the
2 corresponding beta coefficent ranging from 0.0958 to 0.1221 (compared to 0.1075 in the primary
3 analysis). The effect of mean exposure was much more variable, and the corresponding beta
4 coefficients were notably higher for those with DPT and/or interstitial changes (either alone or
5 along with LPT) compared to those for LPT alone. These results are in accordance with the
6 descriptive statistics shown in Table 5-4, which highlighted that while exposure patterns were

1 different among outcome groups, there was relatively less variation in TSFE. These results lend
2 confidence to the effect of TSFE used in the primary analysis.
3
4 **5.3.6. Summary of Sensitivity Analyses**
5   EPA conducted numerous sensitivity analyses for comparison with the primary analysis
6 used to derive the RfC.[23] These included analyses to explore the effect of exposure assessment
7 decisions (e.g., use of the cumulative exposure metric, truncation of exposures post-1980, and
8 use of arithmetic versus the geometric mean for exposure reconstruction); potential confounding
9 factors (time-related and nontime-related); the effect of TSFE (e.g., assumptions regarding the
10 plateau and use of the RTW exposure metric); and the definition of cases and noncases (e.g.,
11 varying case/noncase groups, use of the multinomial model). The results of other sensitivity
12 analyses are summarized in Table 5-19. In each case, the estimated BMCL was within an order
13 of magnitude of the POD . The biggest impacts came from using cumulative exposure (rather
14 than mean exposure), truncating exposures after 1980, and using the geometric mean versus the
15 arithmetic mean for exposure reconstruction (differences of −68 to +50% from the POD).
16 Assumptions regarding the plateau parameter (or estimating the plateau rather than fixing its
17 value) had a very small effect on the BMCL (differences of 0 to +5% from the POD). Similarly,
18 small differences in case and noncase definition led to small changes in the BMCL (differences
19 of −3.9 to +3.9%). Finally, the use of RTW exposure alone (rather than mean exposure and
20 TSFE) as the predictor in the subset of workers evaluated in 2002−2005 and hired in 1972 or
21 later, led to a difference of −19.2% in the BMCL.

---

[23]The primary analysis used a hybrid Dichotomous Hill model with plateau fixed at 85%, with mean exposure as the
exposure metric. The effect of TSFE was estimated in the set of Marysville workers evaluated in 2002−2005, and
carried over to the modeling performed in the subset of these workers who were hired in 1972 or later. The BMCL
was estimated for a TSFE of 28 years, which served as the POD for RfC derivation. A composite UF of 300 was
applied to account for various sources of uncertainty, leading to an RfC of 9×10^{-5} fibers/cc.

Table 5-19. Summary of sensitivity analyses. Exposure-response modeling performed using mean exposure in the hybrid Dichotomous Hill model with plateau fixed at 85%, Marysville workers who underwent health evaluations in 2002−2005 and whose job start date was on or after 1/1/1972 ($n = 119$). Effect of TSFE estimated in workers evaluated in 2002−2005 regardless of hire date.

Sensitivity analysis	BMC/BMCL at 28 yr (fiber/cc)	Percentage difference in BMCL from primary analysis[a] [(sensitivity analysis-primary)/primary] × 100
Primary modeling	$0.0923/2.6 \times 10^{-2}$	--
Use of cumulative exposure rather than mean exposure	$0.0266/8.2 \times 10^{-3*}$	−68.46
Exposures based on arithmetic mean, truncated at 1980	$0.2761/3.9 \times 10^{-2}$	+50.00
Exposures based on geometric mean	$0.0298/9.1 \times 10^{-3}$	−65.00
Exposures based on geometric mean, truncated at 1980	$0.0796/9.9 \times 10^{-3}$	−61.92
Plateau fixed at 70%	$0.0920/2.7 \times 10^{-2}$	+3.85
Plateau fixed at 100%	$0.0924/2.6 \times 10^{-2}$	0.00
Plateau estimated	$0.1022/3.0 \times 10^{-2}$	+15.38
Contrast any LPT vs. no LPT	$0.0918/2.6 \times 10^{-2}$	0.00
Contrast any radiographic change vs. no radiographic change	$0.0929/2.7 \times 10^{-2}$	+3.85
Contrast LPT only vs. no radiographic change	$0.0931/2.5 \times 10^{-2}$	−3.85
Alternative modeling using RTW exposure in the subgroup of workers evaluated in 2002−2005, hired in 1972 or later	$0.0844/2.1 \times 10^{-2}$	−19.23

[a]The BMC and BMCL are 1.8622 and 0.5770 fibers/cc-yr, respectively. These values were divided by 70 yr to obtain the BMC and BMCL in terms of fiber/cc.

1   Multiple statistical model forms applied to different sets and subsets of the principal study
2   population all yield results within less than an order of magnitude around the BMCL. Each of
3   these sensitivity analyses further substantiates the BMCL used to derive the RfC.
4
5   **5.4. CANCER EXPOSURE-RESPONSE ASSESSMENT**
6   **5.4.1. Overview of Methodological Approach**
7   The inhalation unit risk (IUR) is defined as an upper-bound excess lifetime cancer risk
8   estimated to result from continuous exposure to an agent at a concentration of 1 µg/L in water, or
9   1 µg/m^3 in air. However, current health standards for asbestos are based on health effects
10   observed in occupational cohorts and are given in fiber/cc of air as counted by PCM (OSHA,

1 [1994](); [U.S. EPA, 1988a](). Thus, when examining the available health effects data on cancer for
2 LAA, the best available studies at this time report exposure concentration in terms of fiber/cc
3 counted by PCM (see Section 4.1.4). The cancer effects identified in populations with exposure
4 to LAA (see Section 4.1.4) are cancer mortality from mesothelioma and lung cancer (see
5 Section 5.4.2.2 for other cancers identified in populations exposed to asbestos in general).
6 Therefore, the IUR represents the upper-bound excess lifetime risk of mortality from either
7 mesothelioma or lung cancer in the general U.S. population from chronic inhalation exposure to
8 LAA at a concentration of 1 fiber/cc of air.
9   IURs are based on human data when appropriate epidemiologic studies are available.
10 The general approach to developing an IUR from human epidemiologic data is to first
11 quantitatively evaluate the exposure-response relationship (slope) for that agent in the studied
12 population. For the current assessment, the first step was to identify the most appropriate data
13 set available to quantitatively estimate the effects of LAA exposure on cancer mortality. Once
14 the relevant data describing a well-defined group of individuals along with their exposures and
15 health outcomes were selected (see Section 5.4.2), an appropriate statistical model form (i.e.,
16 Poisson or Cox) was selected that adequately fit the specific nature of the data, and then each
17 person's individual-level exposures were modeled using a variety of possible exposure metrics
18 informed by the epidemiologic literature . Exposure-response modeling was conducted for each
19 cancer mortality endpoint individually (see Section 5.4.3). In some cases, the statistical model
20 forms and the specific metrics of exposure used for each cancer endpoint may have been
21 different. For example, the 1988 EPA general asbestos assessment found different model
22 forms/metrics for mesothelioma and lung cancer. Appropriate covariates, which may be
23 important predictors of cancer mortality, were included in the statistical models. These models
24 were then evaluated to assess how the different exposure metric representing estimated
25 occupational exposures fit the observed epidemiologic data. The empirical model fits were
26 compared against those models suggested by the epidemiologic literature before selecting one
27 model for mesothelioma mortality and one for lung cancer mortality.
28   The selected cancer exposure-response relationships (slopes) for mesothelioma (KM) and
29 lung cancer (KL), which were estimated from the epidemiologic data on the Libby workers
30 cohort, were then applied to the general U.S. population in a life-table analysis using age-specific
31 mortality statistics to determine the exposure level that would be expected to result in a specified
32 level of response over a lifetime of continuous exposure. EPA typically selects a response level
33 of 1% extra risk because this response level is generally near the low end of the observable range
34 for such data. Extra risk is defined as equaling $(R_x - R_o) \div (1 - R_o)$, where R_x here is the lifetime
35 cancer mortality risk in the exposed population and R_o is the lifetime cancer mortality risk in an
36 unexposed population (i.e., the background risk). In the case of lung cancer, the expected
37 lifetime risk of lung cancer mortality in the unexposed general U.S. population is approximately
38 5%; thus, this human health assessment seeks to estimate the level of exposure to LAA that

1   would be expected to result in a 1% extra lifetime risk of lung cancer mortality equivalent to a
2   lifetime risk of lung cancer mortality of 5.95%: $[(0.0595 − 0.05) ÷ (1 − 0.05) = 0.01]$. This
3   corresponds to a relative risk (R_x/R_o) of about 1.2, which is near the low end of the observable
4   range for most epidemiologic studies of cancer. For mesothelioma mortality, an absolute risk
5   was considered, rather than extra risk, for two reasons: (1) mesothelioma is very rare in the
6   general population and (2) mesothelioma is almost exclusively caused by exposure to asbestos
7   and other mineral fibers, including LAA. Because the background rate of mesothelioma is
8   negligible, absolute risk models of exposure-response were considered more appropriate than
9   relative risk models, thereby justifying the definition of the target response rate in absolute terms
10 rather than in relative terms.
11   A life-table analysis (see Appendix G for details) was used to compute the 95% lower
12 bound on the level of LAA at which a lifetime exposure corresponds to a 1% extra risk of lung
13 cancer mortality (1% absolute risk for mesothelioma) in the general U.S. population using
14 age-specific mortality statistics and the exposure-response relationships for each cancer endpoint
15 as estimated in the Libby worker cohort. This lower bound on the level of exposure serves as the
16 POD for extrapolation to lower exposures and for deriving the unit risk. Details of this analysis
17 are presented in Section 5.4.5. Cancer-specific unit risk estimates were obtained by dividing the
18 extra risk (1%) by the POD. The cancer-specific unit risk estimates for mortality from either
19 mesothelioma or lung cancer were then statistically combined to derive the final IUR (see
20 Section 5.4.5.3). Uncertainties in this cancer assessment are described in detail in Section 5.4.6.
21

22 **5.4.2. Choice of Study/Data—with Rationale and Justification**
23   This human health assessment is specific to LAA. The current assessment does not seek
24 to evaluate quantitative exposure-response data on cancer risks from studies of asbestos that did
25 not originate in Libby, MT. However, this assessment does draw upon the exposure-response
26 models developed for other kinds of amphibole asbestos, as described in the epidemiologic
27 literature, to address uncertainty in model selection.
28   The available sources of cancer data include the cohort of workers employed at the
29 vermiculite mining and milling operation in and around Libby, MT. This cohort has been the
30 subject of several epidemiologic analyses of cancer risks, described in detail in Section 4.1.4
31 (Larson et al., 2010b; Moolgavkar et al., 2010; Sullivan, 2007; Amandus and Wheeler, 1987;
32 McDonald et al., 1986a). There have also been published reports on cases of mesothelioma in
33 the Libby, MT area (Whitehouse et al., 2008) and mortality data published by the ATSDR
34 (2000). However, published mortality data on Libby, MT residents (Whitehouse et al., 2008;
35 ATSDR, 2000) could not be used in exposure-response modeling due to lack of quantitative
36 exposure data.
37   The most appropriate available data set with quantitative exposure data for deriving
38 quantitative cancer mortality risk estimates based on LAA exposure in humans is the cohort of

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1 workers employed at the vermiculite mining and milling operation in and around Libby, MT

2 (hereafter referred to as the Libby worker cohort). These data are considered the most

3 appropriate to inform this human health assessment for several reasons: (1) these workers were

4 directly exposed to LAA, (2) detailed work histories and job-specific exposure estimates are

5 available to reconstruct estimates of each individual's occupational exposure experience, (3) the

6 cohort is sufficiently large and has been followed for a sufficiently long period of time for cancer

7 to develop (i.e., cancer incidence) and cause mortality, and (4) the broad range of exposure

8 experiences in this cohort provided an information-rich data set, which allowed evaluation of

9 several different metrics, or mathematical expressions, of exposure. Uncertainties in these data

10 are discussed in Section 5.4.6.

11   The only other available cohort exposed to LAA was the cohort of workers from a

12 Marysville, Ohio vermiculite processing plant (see Section 4.1.1.2; Rohs et al., 2008; Lockey et

13 al., 1984). The study of pleural changes in this population was the basis of the noncancer

14 exposure-response analyses (see Section 5.3). Regarding mortality among the Marysville

15 workers, Dunning et al. (2012) reported 2 mesothelioma deaths and 16 lung cancer deaths. The

16 Libby worker cohort was a more suitable candidate for cancer exposure-response modeling than

17 the Marysville worker cohort due to the larger number of cases (see Table 5-3 compared to

18 Tables 5-20 and 5-22).

19

20 **5.4.2.1.** *Description of the Libby Worker Cohort*

21   Cancer mortality in the Libby worker cohort has been extensively studied (see

22 Section 4.1.4). McDonald et al. (2004, 2002; 1986a) published three studies on a subset of the

23 cohort. Scientists from NIOSH conducted two epidemiologic investigations, resulting in several

24 published reports on different subsets of the cohort (Sullivan, 2007; Amandus et al., 1988;

25 Amandus and Wheeler, 1987). Berman and Crump (2008) and Moolgavkar et al. (2010)

26 reanalyzed the Sullivan (2007) data with mortality follow-up through 2001. Larson et al.

27 (2010b) analyzed an ATSDR reconstruction of the Libby worker cohort from company records

28 with exposure estimates obtained from NIOSH with mortality follow-up through 2006.

29   According to Sullivan (2007), nearly all of these study subjects were workers on-site at

30 the Libby, MT vermiculite mine, mill, or processing plant. Although the mine and other

31 facilities were several miles from downtown Libby, MT, some of the study subjects worked at

32 vermiculite ore expansion plants, at the Export Plant, or at offices in the town (see

33 Section 4.1.1.2). Workers may have also been assigned jobs as truck drivers or jobs working in

34 the screening plant, railroad loading dock, expansion plants, or an office. Individuals'

35 demographic and work history data were abstracted from company personnel and pay records. A

36 database created by NIOSH in the 1980s contained demographic data and work history starting

37 from September 1935 and vital status at the end of 1981 for 1,881 workers. NIOSH compared

38 these data with company records on microfilm, and work history data were reabstracted to ensure

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1   data quality. One person was removed from the cohort because company records stated that he

2   was hired but never worked (Sullivan, 2007). Nine workers with Social Security numbers listed

3   in company records were excluded because demographic and work history data were not

4   available, leaving 1,871 workers in the cohort available for epidemiologic analysis. Table 5-20

5   shows the demographic, mortality, and exposure characteristics of this cohort.

6

Table 5-20. Demographic, mortality, and exposure characteristics of the Libby worker cohort

Characteristic	All workers
Number of workers	1,871
Number of deaths from all causes	1,009
Number of deaths from mesothelioma	18
Number of deaths from lung cancer	111
Number of deaths from laryngeal cancer	2
Number of deaths from ovarian cancer	0
Number of deaths from intestinal or colorectal cancer	15
Number of deaths from chronic obstructive pulmonary disease	71
Mean yr of birth	1929
Mean yr of hire	1959
Mean age at hire (yr)	30.2
Mean person-yr of follow-up (no lag)	35.9
Total person-yr of follow-up (no lag)	67,101
Mean employment duration (yr)	2.6
Mean cumulative exposure (fiber/cc-yr)	96.0
Median cumulative exposure (fiber/cc-yr)	9.8
Range of cumulative exposures (no lag) (fiber/cc-yr)[a]	0−1,722

[a]According to the work histories and JEM, there were 26 workers who had zero exposure. These individuals (7 men and 19 women) all worked at the office downtown.

1   NIOSH updated the cohort vital status through 2006 using the National Death Index
2   NDI-Plus; Bilgrad (1999), and these data were used for this analysis. Workers known to be alive
3   on or after January 1, 1979 (the date NDI began tracking deaths nationwide), but not found in the
4   NDI search, were assumed to have been alive on December 31, 2006 (Sullivan, 2007). Nearly
5   54% of workers in the cohort (*n* = 1,009) had died by December 31, 2006. NIOSH researchers
6   obtained death certificates from across the United States (while exposure occurred in and around
7   Libby, deaths could have occurred elsewhere) for deaths prior to 1979, and the causes of death
8   were coded to the ICD revision that was in effect at the time of death by a single National Center
9   for Health Statistics-trained nosologist. After 1979, ICD codes were obtained from the
10   NDI-Plus. For workers known to be deceased, the underlying cause of death was determined
11   from death certificates and coded to the ICD codes using the rubrics of the ICD revision in effect
12   at the time of death (ICD-5 (WHO, 1938), ICD-6 (WHO, 1948), ICD-7 (WHO, 1957), ICD-8
13   (WHO, 1967), ICD-9 (WHO, 1977), or ICD-10 (WHO, 1992).
14   Basic demographic information on the occupational cohort members was largely
15   complete. However, when data were missing, they were statistically imputed (i.e., assigned) by
16   NIOSH based on several reasonable assumptions regarding gender, race, and date of birth. For
17   example, seven workers with unknown gender were assumed to be male because 96% of the
18   workforce was male, and NIOSH's review of names did not challenge that assumption (Sullivan,
19   2007). Workers of unknown race (*n* = 935) were assumed to be white because workers at this
20   facility were known to be primarily white, and U.S. Census Bureau data from 2004 indicate that
21   90−95% of the local population identify themselves as white (Sullivan, 2007). Date of birth was
22   estimated for four workers with unknown birth dates by subtracting the cohort's mean age at hire
23   from the worker's hire date. The impact of this imputation procedure on the analytic results can
24   reasonably be expected to be minimal.
25
26   **5.4.2.2. *Description of Cancer Endpoints***
27   The cancer exposure-response assessment focuses on two cancer endpoints,
28   mesothelioma and lung cancer, although there is evidence that other cancer endpoints may also
29   be associated with exposure to asbestos in general. The IARC has concluded that sufficient
30   evidence in humans is present that other types of asbestos (chrysotile, crocidolite, amosite,
31   tremolite, actinolite, and anthophyllite) are causally associated with mesothelioma and lung
32   cancer, as well as cancer of the larynx and the ovary (Straif et al., 2009). Among the entire
33   Libby worker cohort, only two deaths were found to be due to laryngeal cancer, and no deaths
34   from ovarian cancer occurred among the 84 female workers. Therefore, EPA did not evaluate
35   these other outcomes as part of this current assessment. The limited number of female workers
36   in this cohort is discussed later as a source of uncertainty in the derived estimates (see
37   Section 5.4.6).

The endpoint for both mesothelioma and lung cancer was mortality, not incidence. Incidence data are not available for the Libby worker cohort. Nevertheless, mortality rates approximate incidence rates for cancers such as lung cancer and mesothelioma because the survival time between cancer incidence and cancer mortality is short. According to data from the National Cancer Institute's Surveillance Epidemiology and End Results (SEER) data on cancer incidence, mortality, and survival (Howlader et al., 2013), the median length of survival with mesothelioma is less than 1 year, with 2-year survival for males about 20%, and 5-year survival for males about 6%. For lung cancer, the median length of survival is less than 1 year, with 2-year survival for males about 25% and 5-year survival for males about 17%. Therefore, while the absolute rates of cancer mortality at follow-up may underestimate the rates of cancer incidence, it is considered to be unlikely that such discrepancies would be of significant magnitude. The use of mortality statistics instead of incidence statistics as a source of uncertainty in the derived estimates is further discussed in Section 5.4.6.

It is well established in the literature that mortality rates calculated from death certificates are lower than true mortality rates due to both lung cancer and, to a larger degree, mesothelioma. These discrepancies are due mainly to misdiagnoses and imperfect sensitivity of the coding system. Lung cancer sensitivity[24] ranges from 86% in an asbestos-exposed cohort (Selikoff and Seidman, 1992), to 95% in the general population (Percy et al., 1981); mesothelioma sensitivity ranges from 40% for ICD-9 (Selikoff and Seidman, 1992) to about 80% for ICD-10 (Camidge et al., 2006; Pinheiro et al., 2004). This underestimation of the true mortality rate results in a lower estimated risk compared with that which would be estimated based on the true rate. EPA modeled the risk of mesothelioma mortality using an absolute risk model, while the risk of lung cancer mortality is modeled using a relative risk model. The underestimation of risk is much more pronounced for the absolute risk model (mesothelioma) than for the relative risk model (lung cancer). For lung cancer risks, misdiagnosis rates would need to be different with respect to exposure levels, and this is unlikely among the Libby workers that were included in the lung cancer analysis because nosologists are blinded to exposure levels when coding lung cancer as a cause of death. Therefore, EPA considered use of a procedure to adjust risks for mesothelioma underascertainment (see Section 5.4.5.1.1)—but not for lung cancer.

Mesothelioma did not have a distinct ICD code prior to introduction of the 10th revision (ICD-10), which although released in 1992, was not implemented in United States until 1999. Death certificates from 1940 to 1978 were reviewed by the NIOSH principal investigator (Sullivan, 2007) to identify any mention of mesothelioma on the death certificate, as is the standard procedure for assessing mesothelioma mortality and has been used in other analyses of Libby worker cohort mesothelioma mortality (Larson et al., 2010b; McDonald et al., 2004). For deaths in the Libby worker cohort occurring from 1979 to 1998, death certificates were obtained

---

[24]Sensitivity is measured by the percentage of actual lung cancer deaths that are detected.

1   if the NDI identified the cause of death as one of the possible mesothelioma codes identified by
2   Marsh et al. (2001), as respiratory cancer, nonmalignant respiratory disease, digestive cancer, or
3   unspecified cancer. For deaths in the Libby worker cohort that occurred after 1998, the ICD-10
4   code for mesothelioma was used. In total, 18 mesothelioma deaths were identified by NIOSH
5   using the methods of Sullivan (2007), which serve as the basis for this current assessment;
6   19 mesothelioma deaths were identified by Larson et al. (2010b) for the same cohort from all
7   death certificates rather than from death certificates with one of the specifically targeted set of
8   causes of death identified above in Sullivan (2007).
9   Whitehouse et al. (2008) identified four mesothelioma cases among workers that, as the
10 authors suggested, were not included in the Sullivan (2007) study with mortality follow-up
11 through 2001; no other information was provided. Three mesothelioma cases from these four
12 were most likely accounted for during the update of the NIOSH cohort from 2001 to 2006, which
13 serves as the basis for this current assessment. Whitehouse et al. (2008) also provided detailed
14 information on 11 residential cases, but this information could not be used in exposure-response
15 analyses for this current assessment because there is no quantitative exposure information for
16 these cases and no information defining or enumerating the population from which these cases
17 arose.
18   Lung cancer mortality was based on the underlying cause of death identified by the ICD
19 code on death certificates according to the ICD version in use at the time of death. Based on
20 these different ICD codes, lung cancer mortality included malignant neoplasms of the trachea,
21 bronchus, and lung, and was identified by the following codes: ICD-5 code "047" (excluding
22 "47c, Cancer of unspecified respiratory organs"), ICD-6 codes "162" or "163," ICD-7 codes
23 "162" or "163" (excluding "162.2, Cancer of the pleura"), ICD-8 and ICD-9 code "162," and
24 ICD-10 codes "C33" or "C34." In all, there were 111 deaths with an underlying cause attributed
25 to lung cancer. All deaths after 1960 were coded as bronchus or lung because the ICD versions
26 in use at that time distinguished malignant neoplasms of the trachea as distinct from neoplasms
27 of the bronchus and lung. Other investigators of this cohort have used slightly different
28 definitions of lung cancer or used different follow-up periods, as described in Section 4.1.1.1
29 (Studies of Libby, MT Vermiculite Mining and Milling Operations Workers).
30
31 **5.4.2.3.** *Description of Libby Worker Cohort Work Histories*
32   NIOSH staff abstracted demographic data and work history data from company personnel
33 and payroll records. An individual's work history was determined from job change slips, which
34 recorded any new job assignment, date of change, and change in hourly pay rate (which differed
35 by the job assignment). Work history records span the time period from September 1935 to May
36 1982. Dates of termination were unknown for 58 of 640 workers (9%) who left employment
37 before September 1953. EPA adopted the assumption used by NIOSH (Sullivan, 2007) that
38 these people worked for 384 days, based on the mean duration of employment among all workers

1   with known termination dates before September 1953. The majority of workers in this cohort as

2   a whole and those hired on or after January 1, 1960 worked at multiple jobs; many of the

3   workers switched jobs repeatedly, and the changes in exposures associated with changes in job is

4   accounted for through the use of the job- and time-specific JEM described in the following

5   section.

6

7   **5.4.2.4. *Description of Libby Amphibole Asbestos Exposures***

8   The operations at the mine and in and around Libby, the conditions of exposure, and the

9   job-specific estimates of exposure intensity have been thoroughly described in Section 4.1

10 (Sullivan, 2007; Amandus et al., 1987b; McDonald et al., 1986a). Briefly, miners extracted

11 vermiculite ore from an open-pit mine that operated on Zonolite Mountain outside the town of

12 Libby, MT. The ore was processed locally in a dry mill (1935−1974) and/or two wet mills

13 (1950−1974 and 1974–1990). The resulting concentrate was transported by railroad to

14 processing plants around the United States where the vermiculite was expanded for use in

15 loose-fill attic insulation, gardening, and other products (see Section 2.1). EPA adopted the JEM

16 developed and used by Sullivan (2007), which was in turn based on that used in the earlier

17 NIOSH study for jobs through 1982 (Amandus et al., 1987b; Amandus and Wheeler, 1987). As

18 discussed in more detail in Section 4.1, Amandus et al. (1987b) defined 25 location operations in

19 the Libby facilities to which they assigned exposure intensity based on available information (see

20 Table 5-21). A job category may have involved more than one location operation, and the

21 8-hour time-weighted average (TWA) exposure (8-hour TWA) for each job category in the JEM

22 was calculated from the exposure intensity and time spent at each location operation (Amandus

23 et al., 1987b).

24

Table 5-21. Exposure intensity (fiber/cc) for each location operation from the beginning of operations through 1982 Amandus et al. (1987b); Table VII

Location operation	Yr									
	<1950	1950−59	1960−63	1964−67	1968−70	1971	1972−74	1975−76	1977−79	1980−82
Downtown office building	0	0	0	0	0	0	0	0	0	0
Bus ride	1.2	1.2	1.2	1.2	1.2	1.2	1.2	0	0	0
Mine office	1.0	1.0	1.0	1.0	1.0	1.0	1.0	0.5	0.5	0.5
Mine misc.	1.6	1.6	1.6	1.6	1.6	1.6	1.6	0.8	0.8	0.8
Mine—nondrilling	2.6	2.6	2.6	2.6	2.6	2.6	2.6	0.6	0.6	0.6
Transfer point	2.2	2.2	2.2	2.2	2.2	2.2	2.2	0.6	0.6	0.6
Quality control lab	13.1	13.1	13.1	2.6	2.6	2.6	2.6	0.6	0.6	0.6
Service area by mill	1.9	1.9	1.9	3.8	1.9	1.9	1.9	0.2	0.2	0.2
Dry mill	168.4	168.4	168.4	33.2	33.2	33.2	16.6	--	--	--
Dry mill sweeping	182.1	182.1	182.1	35.9	35.9	35.9	19	--	--	--
Old and new wet mill—millwright	--	7.0	7.0	7.0	7.0	7.0	7.0	0.6	0.6	0.6
Old wet mill—nonmillwright	--	3.7	3.7	3.7	3.7	3.7	3.7	--	--	--
New wet mill—nonmillwright	--	--	--	--	--	--	3.2	2.0	0.8	0.8
Skip area	88.3	88.3	88.3	17.4	17.4	17.4	4.8	0.6	0.6	0.6
Concentrate hauling	5.5	5.5	5.5	5.5	5.5	5.5	5.5	0.4	0.4	0.4
River station binside	21.2	21.2	21.2	21.2	21.2	21.2	21.2	0.7	0.7	0.7
River conveyor tunnel	112.5	112.5	112.5	112.5	112.5	112.5	112.5	0.3	0.3	0.3
River office binside	10.6	10.6	10.6	10.6	10.6	10.6	10.6	0.2	0.2	0.2
Verxite plant	22.6	22.6	2.8	2.8	2.8	--	--	--	--	--

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Table 5-21. Exposure intensity (fiber/cc) for each location operation from the beginning of operations through 1982 Amandus et al. (1987b); Table VII (continued)

Location operation		<1950	1950−59	1960−63	1964−67	1968−70	1971	1972−74	1975−76	1977−79	1980−82
							Yr				
Tails belt		7.3	7.3	7.3	7.3	7.3	7.3	7.3	0.7	0.7	0.7
Screen plant		--	--	--	--	--	--	--	0.5	0.5	0.5
Drilling	High	23	23	23	23	9.2	9.2	9.2	0.6	0.6	0.6
	Low	6.7	6.7	6.7	6.7	6.7	9.2	9.2	0.6	0.6	0.6
Ore loading	High	82.5	27.7	10.7	10.7	3.2	3.2	3.2	0.2	0.2	0.2
	Low	24	15	9	9	3.2	3.2	3.2	0.2	0.2	0.2
River dock	High	116.9	42.5	17	17	17	5.1	5.1	0.5	0.5	0.5
	Low	38	19	6.4	6.4	5.1	5.1	5.1	0.5	0.5	0.5
Bagging plant	High	12.9	12.9	12.9	12.9	12.9	12.9	4.3	1.2	1.2	1.2
	Low	4.6	4.6	4.6	4.6	4.6	4.6	4.3	1.2	1.2	1.2

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1   For the later data in Table 5-21 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. Therefore, the JEM for 1967−1982 is based on direct analytic measurements in air
4   for each location operation (Amandus et al., 1987b). With the exception of two location
5   operations in the dry mill, no air samples were available for other location operations at the mine
6   and processing facilities before 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 25 pre-1967 location
10   operations was extrapolated from post-1967 measurements based on reasoned assumptions for
11   each location operation (Amandus et al., 1987b).

12   In contrast to the exposure information available for 1967 through 1982, the amount and
13   quality of measurement data in the facility in earlier years were much more limited (Amandus et
14   al., 1987b). A total of 40 dust samples were taken, exclusively in the dry mill, over the years
15   1950−1964. Using these measurements, higher exposures were inferred to occur before 1964
16   than in later years.

17   Air samples collected by the State of Montana were available for the dry mill
18   from 1956−1969, but these were analyzed for total dust, not asbestos fibers. Total dust samples
19   (collected by a midget impinger) were examined by light microscopy, but no distinction was
20   made among mineral dusts, debris, and asbestos fibers. All objects were counted and reported in
21   the units of million particles per cubic foot (mppcf). Amandus et al. (1987b) developed a range
22   of conversion ratios between total dust and asbestos fiber counts based on the comparison of
23   contemporaneous air sampling in the dry mill (see Section 4.1.1.2) and selected a conversion
24   ratio of 4.0 fibers/cc per mppcf to estimate exposure intensity for two location operations in the
25   dry mill for the years prior to 1967. Uncertainties in the selection of this conversion ratio are
26   described in detail in Section 5.4.6.1.2.1.

27   The exposure intensity (fiber/cc) for each of the location operations (see Table 5-21) was
28   used to calculate an estimate of daily occupational exposure for each job category in the JEM.
29   For each job, the time spent at each location operation and the exposure intensity for each
30   location operation was averaged to derive an estimate of the 8-hour TWA. The resulting JEM
31   available for this current assessment and previous epidemiologic studies of the Libby worker
32   cohort is based on the air concentration of fibers as enumerated by PCM, which measures fibers
33   longer than 5 μm with an aspect ratio >3:1 (i.e., the fiber size regulated under the Occupational
34   Safety & Health Administration [OSHA] standard (OSHA, 2006)). Additionally, only fibers that
35   are wide enough to be viewed on PCM can be detected with this method. Amandus et al.
36   (1987b) considered fibers >0.44 μm in diameter to be visible by PCM in the historical filter
37   analysis. More recent techniques have refined the PCM method, and fibers greater than 0.25 μm

1   in diameter are now considered PCM fibers (IPCS, 1986). Uncertainties related to difference in

2   defining PCM fibers are discussed in Section 5.4.6.1.2.1.

3   Amandus et al. (1987b) recognized the uncertainty in the pre-1968 exposures assigned to

4   the cohort. Although there is some uncertainty in the dust-to-fiber conversion, this conversion

5   (4.0 fibers/cc per mppcf) was based on dust and fiber data contemporaneously collected in the

6   dry mill and only applied to the dry mill environment. Amandus et al. (1987b) considered a

7   range of possible conversion factors (1.2−11.5 fibers/cc per mppcf). Greater uncertainty may lie

8   with the reasoned assumptions used to extrapolate exposures to the early decades for all location

9   operations considered. For example, there were four location operations for which Amandus et

10   al. (1987b) estimated a range of possible exposure intensities―drilling, ore loading, the river

11   dock, and the bagging plant, where intensity of exposure may vary as much as threefold between

12   the low and high estimates (see Table 5-21). Finally, some workers were employed after 1982

13   and up until 1993, when demolition of the facilities was completed (Larson et al., 2010b). These

14   exposures were not evaluated by Sullivan (2007) and were not included in the NIOSH JEM.

15   Because exposure concentrations in 1982 (see Table 5-21) were generally at or below

16   1.2 fibers/cc, it is unlikely that the overall cumulative exposures of this limited set of workers

17   were significantly underestimated by not including exposures during this time. Uncertainties in

18   all aspects of the JEM and the associated exposure assessment are described in Section 5.4.6.1.2.

19   There was one important limitation of the NIOSH work history data in assigning

20   exposure levels for each job. In the earlier study (Amandus and Wheeler, 1987), workers with

21   "common laborer" job assignments and some workers with unknown job assignments hired

22   between 1935 and 1959 were all assigned the same, relatively low exposure levels estimated for

23   the mill yard (Sullivan, 2007). In addition, reabstracting work histories for the more recent study

24   (Sullivan, 2007) identified several job assignments not mentioned in the earlier publications.

25   Sullivan (2007) estimated exposure for the additional job and calendar time period-specific

26   combinations based on professional experience and review of exposure records from earlier

27   studies of the Libby worker cohort (Amandus et al., 1987b; Amandus and Wheeler, 1987;

28   McDonald et al., 1986a). EPA found that of the 991 workers hired before 1960, 811 workers

29   (82%) had at least one job with an unknown job assignment, with 706 (71%) listing neither job

30   department nor job assignment. In the more recent study by Sullivan (2007), these same workers

31   were all assigned the same, relatively high TWA exposure intensity estimated for all jobs during

32   that time period (66.5 fibers/cc). The lack of information on specific job assignments for such a

33   large portion of these early workers, during the time period when exposures were higher, resulted

34   in significant exposure misclassification and effectively yielded exposure estimates that were

35   differentiated only by the duration of each worker's employment. Because of the lack of more

36   specific measured fiber exposure data during this early period, EPA experienced difficulties in

37   identifying an adequate exposure-response model fit for the complete cohort including all hires.

38   These difficulties are described in detail in Section 5.4.3.4. As a result, the IUR analyses were

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1   based on the subset of workers hired after 1959 (i.e., on or after January 1, 1960), totaling

2   880 workers (i.e., full cohort [$n = 1,871$] minus those hired before 1960 [$n = 991$]). Of these

3   880 workers hired after 1959, 28 workers had at least one job with an unknown job assignment

4   with nine having all job and department assignments between 1960−1963 listed as unknown. As

5   described in Sullivan (2007), NIOSH assigned these workers a TWA estimated exposure

6   intensity of 66.5 fibers/cc. Uncertainties in the exposure assessment for this subcohort are

7   described in Section 5.4.6.1.2.4. While the Sullivan (2007) study was limited to the white male

8   workers, EPA's analysis includes all workers regardless of race or gender. Table 5-22 shows the

9   demographic, mortality, and exposure characteristics of the subcohort hired after 1959.

Table 5-22. Demographic, mortality, and exposure characteristics of the subset of the Libby worker subcohort hired after 1959

Characteristic	Subcohort hired after 1959
Number of workers	880
Number of deaths from all causes	230
Number of deaths from mesothelioma	7
Number of deaths from lung cancer	32
Number of deaths from laryngeal cancer	2
Number of deaths from ovarian cancer	0
Number of deaths from colorectal cancer	5
Number of deaths from chronic obstructive pulmonary disease	18
Mean yr of birth	1942
Mean yr of hire	1971
Mean age at hire (yr)	28.6
Mean person-yr of follow-up (no lag)	32.2
Total person-yr of follow-up (no lag)	28,354
Mean employment duration (yr)	2.4
Mean cumulative exposure (fiber/cc-yr)	19.2
Median cumulative exposure (fiber/cc-yr)	3.4
Range of cumulative exposures (no lag) (fiber/cc-yr)[a]	0−462

[a]According to the work histories and JEM, there were 21 subcohort workers who had zero cumulative exposure. These 21 individuals all worked at the office downtown.

1   Figure 5-5 shows a three-dimensional representation of the JEM used by <u>Sullivan (2007)</u>

2   and in this cancer exposure-response assessment (note that the figure does not include all jobs

3   and is meant to be illustrative rather than comprehensive). The three axes show the intensity of

4   fiber exposure as an 8-hour TWA (fiber/cc, vertical axis) for selected job categories over time

5   (horizontal axes). For several jobs, the estimated 8-hour TWA was greater than 100 fibers/cc for

6   the decades prior to 1963.
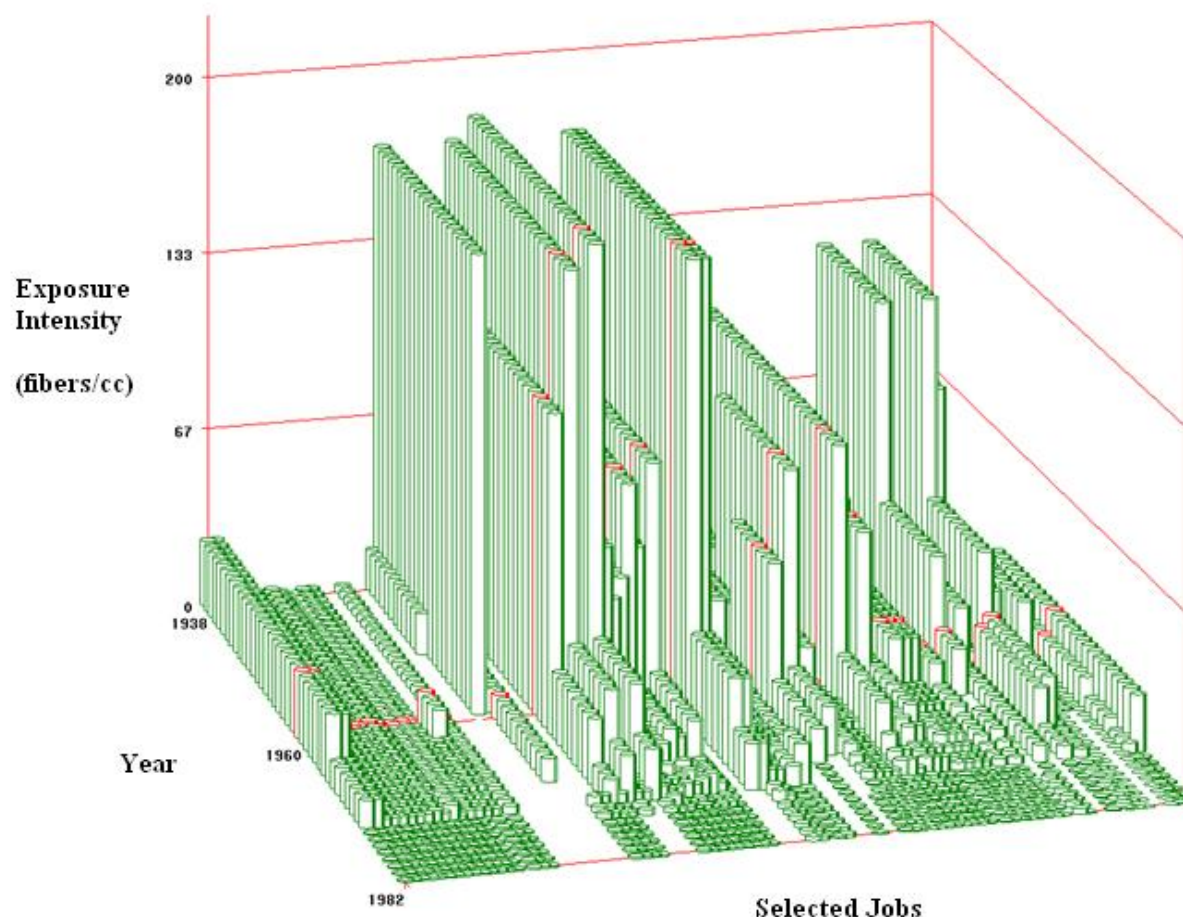
Figure 5-5. **Plot of the National Institute for Occupational Safety and Health (NIOSH) job-exposure matrix for different job categories over time.** The height of each bar represents the intensity of exposure as an 8-hour TWA (fiber/cc) for a job in a particular year. Each row for "Selected Jobs" represents a specific job category. The line at 1960 marks the beginning of jobs included in the subcohort of Libby workers used to derive the inhalation unit risk.

1 **5.4.2.5. *Estimated Exposures Based on Job-Exposure Matrix (JEM) and Work Histories***

2   Exposure-response modeling of epidemiologic data is based on several considerations as

3 summarized by Finkelstein (1985):

4

5   After identification of an occupational hazard one of the goals of occupational

6   epidemiology is to quantify the risks by determining the dose-response relations

7   for the toxic agent. In many circumstances little is known about the dose received

8   by target tissues; the data available usually pertain only to exposure to various

9   concentrations of the toxic material in the workplace. The calculation of dose

10   requires additional physiological and chemical information relating to absorption,

11   distribution, biochemical reactions, retention, and clearance.

12   In asbestos epidemiology the usual measure of exposure is the product of the

13   concentration of asbestos dust in the air (fibers or particles per mL) and the

14   duration of exposure to each concentration summed over the entire duration of

15   exposure (years).

16

17   Cumulative exposure (CE) has been the traditional method of measuring exposure in

18 epidemiologic analyses of many different occupational and environmental exposures and was the

19 exposure metric applied to the risk of lung cancer mortality in the IRIS assessment for general

20 asbestos (U.S. EPA, 1988a). That said, different health outcomes may be best described using

21 different exposure metrics. The risk of mesothelioma mortality in the IRIS assessment for

22 general asbestos (U.S. EPA, 1988a) used a different exposure metric based on a linear function

23 of concentration added to a function of TSFE and duration of exposure. Additional exposure

24 metrics were also assessed for both mesothelioma and lung cancer mortality risks.

25   Two alternative approaches to developing exposure metrics to describe the effects of

26 concentrations of asbestos dust in the air on the risks of mortality have also been proposed. The

27 first alternative was proposed by Jahr (1974), who studied silica-induced pneumoconiosis and

28 suggested that exposures to occupational dusts could be weighted by the time since exposure.

29 This yields an exposure metric that gives greater weight to earlier exposures. The second

30 alternative was proposed by Berry et al. (1979) who subsequently suggested the application of

31 exposure metrics that allowed for the clearance of dust or fibers by using a decay term on

32 exposures.

33   For the evaluation of mortality risk from mesothelioma for general asbestos, U.S. EPA

34 (1988a) used a different exposure metric than was used for lung cancer mortality, which factored

35 in the TSFE. As observed in U.S. EPA (1988a), it is important to note that different

36 characterizations of estimated occupational exposures may be reasonably expected to be

37 associated with different endpoints.

38   Many studies have been limited in the availability of detailed exposure data—especially

39 at the individual level. In the Libby worker cohort, detailed work histories were matched with

40 job-specific exposure estimates, allowing for the reconstruction of each individual's estimated

1   occupational exposure over time. From this information-rich, individual-level data set from
2   NIOSH, EPA constructed a suite of the different metrics of occupational exposure which had
3   been proposed in the asbestos literature or used in the IRIS asbestos assessment (U.S. EPA,
4   1988a). This suite of metrics was defined a priori to encompass a reasonable set of proposed
5   exposure metrics to allow sufficient flexibility in model fit to these data. The types of exposure
6   metrics evaluated were intended to allow for more or less weight to be placed on earlier or later
7   exposures. These simulated exposure metrics were derived mathematically to approximate
8   underlying processes that are not well understood (see Section 5.4.6). Thus, the empirical fit of
9   various exposure metrics to the observed epidemiologic data is evaluated statistically, and the
10   exposure metrics have epidemiological interpretation but do not necessarily have direct
11   biological interpretations.
12   The first exposure metric—CE—is a simple addition of each day's exposure across time
13   (see eq 5-7). CE has been widely used in modeling risk of cancer in occupational epidemiology
14   and has been used for modeling lung cancer (Larson et al., 2010b; Moolgavkar et al., 2010;
15   Berman and Crump, 2008; Sullivan, 2007; McDonald et al., 2004) and mesothelioma (McDonald
16   et al., 2004) in the Libby worker cohort. When using this exposure metric in the risk model, all
17   exposures (other than for years removed from consideration based on a lag assumption) have
18   equal weight regardless of when they occurred and lead to the same estimated cancer risk
19   whether exposure happened early or later in life.
20   EPA calculated each individual's occupational CE to LAA over time from their date of
21   hire until the date they ceased to be employed in the Libby operations or until the date NIOSH
22   collected the work history data for those still employed in May 1982. Workers were assumed to
23   remain at their CE on the last day of work until death or the end of the follow-up period on
24   December 31, 2006. Each worker's CE at any time point (daily increment) since their date of
25   hire was computed as the sum of their exposure intensity (fiber/cc) on each specific occupational
26   day (x_t) from Day 1 through Day k. Mathematically, this was defined as

27
28   $$\text{CE at time } t_k = \sum_{j=1}^{k} x_{t_j}$$ (5-7)
29
30   Where
31
32   x_{t_j} = the estimated job-specific exposure intensity for the day t_j, and
33   t_k = the day on which the exposure is estimated.
34
35   A second exposure metric—RTW exposure—gives additional weight to early exposures.
36   By doing so, the RTW exposure metric allows the possibility that early exposures are more
37   influential on cancer mortality predictions in the model. Unlike many chemicals that are rapidly

1   metabolized in the body and excreted, asbestos fibers are durable, and some remain in the body
2   for years. Fibers that remain in the lung may continue to damage lung cells and tissue unless
3   they are removed or cleared (see Section 3.2). Similarly, fibers that translocate to the pleura may
4   damage cells as long as they remain in this tissue. Therefore, a fiber exposure may not only
5   damage tissue during the initial exposure, but fibers may remain in these tissues, with tissue fiber
6   concentration as well as cellular and tissue damage accumulating over time. While this
7   represents a biological point of view, in an epidemiologic context in which the exposure is
8   ambient fiber concentration and the event of interest is simply a cause of death (rather than
9   survival time), it is uncertain what metrics of exposure might fit the observed data and could be
10   considered most appropriate.

11   The RTW exposure metric in this current assessment is sometimes called the cumulative
12   burden, or the area under the curve. A type of RTW metric was proposed for modeling of
13   mesothelioma mortality by Newhouse and Berry (1976) based on a general understanding of the
14   relationship between tumor incidence rate and time to cancer (Cook et al., 1969) as well as
15   animal models of mesothelioma (Berry and Wagner, 1969).

16   A similar type of RTW metric was proposed in Peto (1978) and was subsequently applied
17   by Peto et al. (1982), discussed by Finkelstein (1985), and applied in the derivation of the IUR in
18   the 1988 IRIS assessment for asbestos (U.S. EPA, 1988a). McDonald et al. (2004) and
19   Moolgavkar et al. (2010) used RTW-type metrics for modeling mesothelioma in the Libby
20   worker cohort, and McDonald et al. (2004) applied an RTW metric for modeling lung cancer
21   mortality in the Libby worker cohort.

22   In calculating RTW, each day's exposure is multiplied by the time since exposure
23   occurred up to the time t_k when RTW is estimated (see eq 5-8). The intent of RTW CE is to
24   allow for earlier exposures to contribute greater weight.

25

26    $$\text{RTW CE at time } \underline{t_k} = \sum_{j=1}^{k} x_{t_j} \times (t_k - t_j) \qquad\qquad (5\text{-}8)$$

27

28   Where

29

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

31   t_k = the day k on which the exposure is estimated.

32

33   The CE and RTW exposure metrics result in increasing or sustained metrics of exposure
34   across time. However, some cellular and genetic damage can be repaired over time after
35   exposure, decreasing the cancer risk from exposure over time. Additionally, asbestos fibers are
36   cleared (removed) from the lung through natural processes and translocated to other tissues (see

Section 3.2.1.1). Therefore, when considering lung cancer, it is possible that removal of asbestos fibers from the lung could reduce lung cancer risk over time. Although less is known about removal of asbestos from the pleura, clearance mechanisms may be operative in that tissue as well (see Section 3.2.1.2). As noted earlier, Berry et al. (1979) proposed the use of exposure metrics which addressed the issue of clearance through a mathematical decay term that modified estimated occupational exposures. For mesothelioma, modeling a decay term on exposure has been proposed by Berry (1999). Based on this proposal, several studies applied a decay term to modeling mesothelioma mortality (Berry et al., 2009; Reid et al., 2009; Barone-Adesi et al., 2008; Gasparrini et al., 2008; Clements et al., 2007; Hodgson et al., 2005; Berry et al., 2004). Similarly, publications indicate that the relative risk of lung cancer due to asbestos exposure declines 15−20 years after the cessation of exposure to asbestos (Magnani et al., 2008; Hauptmann et al., 2002).

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

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

$$\text{CE with half-life at time } t_k = \sum_{j=1}^{k} \left\{ x_{t_j} \times \exp\left[\frac{\ln(0.5) \times (t_k - t_j)}{T_{1/2}} \right] \right\} \qquad (5\text{-}9)$$

Where

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

t_k = the day k on which the exposure is estimated, and

$T_{1/2}$ = half-life of 5, 10, 15 or 20 years.

$$\text{RTW with half-life at time } t_k = \sum_{j=1}^{k} \left\{ x_{t_j} \times (t_k - t_j) \times \exp\left[\frac{\ln(0.5) \times (t_k - t_j)}{T_{1/2}} \right] \right\} \qquad (5\text{-}10)$$

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1   In addition to the considerations described above for selecting metrics to represent

2 estimated ambient exposure to LAA for use in predicting the risk of mortality, there is the

3 important issue of potentially modifying the exposure metrics to account for cancer latency.

4 Without knowledge of the specific timing of etiologically relevant exposure that may initiate and

5 promote cancers that ultimately result in mortality, any exposure metric may include exposures

6 during some time period that do not have bearing on the risk of mortality. In the absence of such

7 information on the specific cancer latency associated with a specific exposure, Rothman (1981)

8 suggested that the most relevant exposure period could be identified by comparing the fit of

9 exposure metrics across multiple lag periods to allow for the identification of the optimal latency

10 period as an expression of a lag time between exposure and mortality. This has since become a

11 standard practice in occupational and environmental epidemiology. Accordingly, exposure

12 estimates for all exposure metrics were adjusted to account for the time period between the onset

13 of cancer and mortality. The lag period defines an interval before death, or end of follow-up,

14 during which any exposure is excluded from the calculation of the exposure metric. Cohort

15 members who died or were lost within the initial years of follow-up were assigned lagged

16 exposure values of zero if they had not been followed for longer than the lag time. The various

17 exposure metrics were lagged at 10, 15, and 20 years to account for different potential cancer

18 latencies within the limitations of the available data. Metrics without a lag were fit for

19 comparison purposes but were not considered to be biologically reasonable, given that the

20 outcome under analysis is cancer mortality (specifically, mesothelioma and lung cancer), for

21 which latency periods of 10 years or more have been suggested for asbestos (U.S. EPA, 1988a).

22 Consequently, metrics that were not adjusted by lagging exposure in the final years before

23 mortality (or the end of follow-up) were not considered further in the development of an IUR for

24 LAA.

25   In addition to the exposure metrics used in the lung cancer mortality analysis, modeling

26 of mesothelioma mortality (see Section 5.4.3.1) included additional exposure models. The Peto

27 model (Peto et al., 1982; Peto, 1979) uses a cubic power function of TSFE and a linear function

28 of exposure concentration. The model developed by Peto was then adapted in the IRIS (U.S.

29 EPA, 1988a) asbestos assessment. The linear function of concentration was developed based on

30 estimated average workplace concentrations over several asbestos cohorts exposed to chrysotile,

31 amphiboles, and mixed fibers. The two amphibole-exposed cohorts were U.S workers exposed

32 to amosite and Australian workers exposed to crocidolite; for both cohorts there was little

33 exposure information at the time these reports were published. As Health Effects

34 Institute-Asbestos Research (HEI, 1991) noted "No extensive measurements of historical

35 exposure levels are available for the cohorts exposed predominantly to crocidolite or amosite."

36 The only other mesothelioma models proposed in the literature for amphibole asbestos were

37 developed by Berry (1991) for crocidolite. Berry et al. (2012) found that models that allow for

38 clearance (mathematically, multiplicative $\exp[-\lambda \times T]$) better match the actual mortality

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1   experience of the Wittenoom, Australia crocidolite cohort with more than 50 years follow-up,

2   compared with Peto-type models. In particular, they found that models with a higher power of

3   TSFE of 5.4 (compared to power = 3 for Peto) and a decay rate of 15%/year (half-life of

4   approximately 5 years) fits the observed data best, followed by models with a power of TSFE of

5   3.9 and a decay rate of 6.8%/year (half-life of approximately 10 years). However, the exposure

6   data calculated for the Berry analysis was based on just one study of airborne levels.

7   Nevertheless, cumulative exposures calculated from these have been shown to be internally valid

8   based on association with fiber lung burden (Berry et al., 2012).

9   Peto's model (also used in the 1988 IRIS assessment for asbestos (U.S. EPA, 1988a) is

10

11 $$Im = C \times Q_k \times KM \qquad\qquad (5\text{-}11)$$

12   where

13

14   Im = the observed deaths from mesothelioma/person-years (i.e., the mesothelioma
15   mortality rate),

16   C = the average concentration of asbestos in the air,

17   KM = an estimated slope describing the relationship between LAA exposure and
18   mesothelioma mortality, and

19   Q_k = the function of the TSFE (t) and the duration of exposure (d):

20   For $t \leq 10$, Q_k = 0

21   For $10 < t \leq d + 10$, Q_k = $(t - 10)^k$

22   For $t > d + 10$, Q_k = $(t - 10)^k - (t - 10 - d)^k$.

23   Alternatively, $Im = C \times Q_k \times KM \times \exp(-\lambda \times t)$ defines the Peto model with clearance.

24   Possible values of λ and k suggested in the literature (Berry et al., 2012) are $\lambda = 0.068$ or 0.15 and

25    $k = 3.9$ or 5.4. As the Peto model and the Peto model with clearance were both proposed in the

26   amphibole asbestos literature, these models were carried forward in the analysis below.

27

28   **5.4.3. Exposure-Response Modeling**

29   As discussed above, consideration of biology and previous epidemiologic studies

30   informed the range of models considered. There is not sufficient information to select models

31   for the epidemiology data on the basis of the biological mechanism of action for lung cancer or

32   mesothelioma (see Section 3). In this situation, EPA's practice is to investigate several modeling

33   options to determine how to best empirically model the exposure-response relationship in the

34   range of the observed data as well as consider exposure-response models suggested in the

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1   epidemiologic literature. For LAA, possible exposure metrics were explored for model fit to the

2   chosen modelforms. The exposure metric options were selected to provide a range of shapes that

3   was sufficiently flexible to allow for a variety of ways that time and duration might relate to

4   cancer risk in the data being modeled.

5   The following sections provide information about modeling of the full cohort first, the

6   difficulties in identifying adequately fitting models to these data, and the decision to base the

7   analysis on a subcohort of workers that allowed for identifying adequately fitting models.

8

9   **5.4.3.1. *Modeling of Mesothelioma Exposure Response in the Libby Worker Cohort***

10   The background incidence of mesothelioma is extremely low (Hillerdal, 1983). The

11 evaluated exposure-response models examine the relationship of the absolute risk of

12 mesothelioma mortality attributable to LAA exposure, because it is not clear that a background

13 risk of mesothelioma mortality exists among people who were truly unexposed to asbestos (as

14 opposed to the relative risk model, which is used for lung cancer mortality; see Section 5.4.3.3).

15 EPA does not have a specific technical guidance for model selection based on human cancer

16 data, but as a general consideration, EPA's BMD Technical Guidance (U.S. EPA, 2012) states

17 that "The initial selection of a group of models to fit to the data is governed by the nature of the

18 measurement that represents the endpoint of interest and the experimental design used to

19 generate the data." Here, the most prominent feature of the data is the rarity of mesothelioma

20 deaths. Correspondingly, Poisson models are employed to estimate the absolute risk of

21 mesothelioma, as the Poisson distribution is an appropriate model for use with data that are

22 counts of a relatively rare outcome, such as observed mesothelioma deaths in the Libby worker

23 cohort. Other parametric survival models, such as the Weibull model have been used for

24 absolute risk calculation, but they are not generally used for data with rare outcomes.

25 Consequently, there are no examples in the literature of the Weibull or other parametric survival

26 model ever being used for modeling mesothelioma mortality. Previous analyses of

27 mesothelioma mortality in the Libby worker cohort also used the Poisson model (Moolgavkar et

28 al., 2010; McDonald et al., 2004). Mathematically, the Poisson distribution specifies the

29 probability of *k* events occurring as

30

$$P(k) = \frac{\lambda^k e^{-\lambda}}{k!}$$

31   (5-12)

32

33 where λ is parameterized with the exposure metric (defined in Section 5.4.2.5). Then, life-table

34 analysis is used to estimate risks in the general U.S. population for the derivation of the unit risk

35 of mesothelioma mortality (see Section 5.4.5.1). In the standard Poisson distribution, the

36 assumption is that the mean is equal to the variance. However, actual count data often exhibit

1   overdispersion, a statistical consideration when the variance is larger than the mean; thus, EPA

2   evaluated potential for overdispersion.

3   Estimation of the exposure-response relationship for mesothelioma mortality was

4   performed using a Monte Carlo Markov Chain (MCMC) Bayesian approach with an

5   uninformative or diffuse (almost flat) prior (WinBUGS Version 1.4 Spiegelhalter et al., 2003).

6   Use of diffuse priors is a standard procedure in Bayesian analysis, in situations like this one,

7   when there is no prior knowledge about the toxicity of LAA under a particular model. Because

8   this analysis focuses only on the Libby worker cohort and does not try to factor in data from

9   other sources in estimating potency, use of a diffuse prior is considered appropriate for this

10   analysis.

11   The benefit of using the WinBUGS software is its computational ease and that it provides

12   a posterior distribution of the mesothelioma coeficient (KM) rather than just a point estimate. A

13   diffuse (high variance) Gaussian distribution, truncated to exclude negative parameter values, is

14   used as a diffuse prior. With such a prior, results of MCMC analysis are expected to be similar

15   to maximum likelihood estimation in a non-Bayesian analysis. Standard practices of MCMC

16   (Spiegelhalter et al., 2003) analysis were followed for verifying convergence and sensitivity to

17   the choice of initial values. The posterior distribution is based on three chains with a burn-in of

18   10,000 (i.e., the first 10,000 simulations are dropped so that remaining samples are drawn from a

19   distribution close enough to the true stationary distribution to be usable for estimation and

20   inference) and thinning rate of 10 (i.e., only each 10th simulation is used—thus reducing

21   autocorrelation), such that 3,000 total simulations constitute the posterior distribution of KM.

22   The mean of the posterior distribution served as a central estimate, and the 90% credible

23   interval[25] defined the 5th percentile and the 95th percentile of the distribution, which served as

24   bounds for the 95th lower and upper one-sided confidence intervals, respectively.

25   The fit of multiple metrics of exposure, the Peto model and the Peto model with clearance

26   (see Section 5.4.2.5), as well as exposure intensity, duration of exposure, age at death or loss to

27   follow-up, and TSFE were compared using the Deviance Information Criterion (DIC). The DIC

28   (Spiegelhalter et al., 2002) is used in Bayesian analysis and is an analogue of the AIC, with

29   smaller values indicating a better statistical fit to the data. Use of the DIC and AIC is standard

30   practice in comparing the fit of nonnested models to the same data set with the same dependent

31   outcome variable but different independent covariates. According to Burnham and Anderson

32   (2002), "These methods allow the data-based selection of a 'best' fitting model and a ranking

33   and weighting of the remaining models in a predefined set." Because of the small number of

34   deaths from mesothelioma in absolute terms, only uni- and bivariate models (with age or TSFE

35   as the second covariate) were considered. Gender and race were not used as covariates because

---

[25]A credible interval is the Bayesian analogue of a confidence interval.

1   all mesothelioma deaths were observed in men assumed to be white ([Sullivan, 2007](#)). Each

2   exposure metric was lagged by 0, 10, 15, or 20 years, where appropriate.

3

4   **5.4.3.2. *Results of the Analysis of Mesothelioma Mortality in the Full Libby Worker Cohort***

5   While the final analytic exposure-response modeling for mesothelioma is based on the

6   subcohort of workers hired after 1959 when exposure data were considered to be superior (see

7   Section 5.4.3.5), it is important to understand how different metrics of exposure in the

8   epidemiologic literature are related to risk in the full cohort as these age- and time-related

9   variables are well characterized in the full cohort. A parallel set of tables is provided for the

10   subcohort of workers hired after 1959 in Section 5.4.3.5.

11   Tables 5-23 to 5-25 show rates of mesothelioma mortality in the full cohort by duration

12   of exposure, age of first exposure, and TSFE. Mesothelioma rates look to be independent of the

13   age of first exposure, but duration of exposure and TSFE both show relationships with

14   mesothelioma mortality rate. EPA also evaluated the potential for overdispersion of the counts

15   of mesothelioma deaths. In the Libby worker cohort, mean and variance of exposure are nearly

16   identical at 9.62×10^{-3} and 9.53×10^{-3}, respectively, making overdispersion very unlikely.

17

Table 5-23. Mesothelioma mortality rate shown by duration of exposure (yr) in the full Libby worker cohort including all hires ($n = 1,871$)

	Duration				
	0−1 yr	**1−2 yr**	**2−3 yr**	**3−5 yr**	**5+ yr**
Deaths/PY	3/40,417	1/7,493	3/4,429	2/4,984	9/9,778
Rate $\times 10^{-4}$	0.7	1.3	6.8	4.0	9.2

PY = Person-yr

Table 5-24. Mesothelioma mortality rate shown by age at first exposure in the full Libby worker cohort including all hires ($n = 1,871$)

	Age		
	15−25 yr old	**25−35 yr old**	**35+ yr old**
Deaths/PY	5/30,872	11/22,447	2/13,782
Rate $\times 10^{-4}$	1.6	4.9	1.5

Table 5-25. Mesothelioma mortality rate shown by time since first exposure (TSFE) in the full Libby worker cohort including all hires ($n = 1,871$)

	Time since first exposure					
	<15 yr	**15−25 yr**	**25−35 yr**	**35−45 yr**	**45−55 yr**	**55−68.1 yr**
Deaths/PY	0/27,186	2/16,553	5/12,775	8/6,818	2/3,025	1/744
Rate $\times$ 10^{-4}	0	1.2	3.9	11.7	6.6	13.4

1   For the full Libby worker cohort ($n = 1,871$), in the continuous analysis examining one
2   explanatory variable at a time (see Table 5-26), the duration of exposure provided a considerably
3   better model fit than the other possible exposure metrics, indicating that this exposure metric was
4   the best single predictor of mesothelioma mortality in the full Libby worker cohort. A model,
5   which included duration of exposure and age at death or censoring, provided the overall best fit
6   (DIC = 196). Counterintuitively, the inclusion of information on the concentration of exposure
7   in addition to the duration of exposure (as expressed by CE, which is the product of duration and
8   concentration) resulted in a degradation in model fit compared to the model with just the
9   duration of exposure (see Table 5-26). From the models proposed in the amphibole asbestos
10   literature, the Peto model (see eq 5-11) had a much higher DIC of 233.7 in the analysis of the full
11   cohort. For the Peto model, KM was estimated to be 1.85×10^{-9} and its 95th upper bound was
12   2.59×10^{-9}. The Peto model with power terms on time-since-first-exposure $k = 3.9$ and 5.4 and
13   clearance terms of 6.8 and 15% per year, respectively, did not improve fit over the standard Peto
14   model.

Table 5-26. Comparison of model fit of various univariate exposure metrics for mesothelioma mortality in the full Libby worker cohort including all hires ($n = 1,871$).[a] Only models with DIC within 10 units of the DIC of the model with the lowest DIC are shown.[b]

Variable	DIC
Duration of exposure	202.9
Age at death or censoring	209.2
CE lagged 15 yr	209.5
CE lagged 10 yr	209.9
RTW lagged 10 yr with 5-yr half-life	210.4
CE lagged 10 yr with 20-yr half-life	210.6
RTW with 5-yr half-life	210.7
RTW with 10-yr half-life	211.0
CE	211.4
Time since first exposure	211.4

[a]Because one of the mesothelioma deaths occurred less than 20 yr from start of the exposure, lag 20 metrics assigned no exposure to this case, which resulted in the very poor fit of exposure metrics lagged 20 yr.
[b]Lower DIC values represent better fits.

1   It is likely that the poorer fit seen when using information on exposure concentration is
2 the result of the fact that duration of exposure is measured with comparatively little error, while
3 derivation of specific exposure concentrations may be subject to a sizable measurement error.
4 Moreover, as described in Section 5.4.2.3, for 706 of 991 (71%) workers hired from 1935 to
5 1959, only the duration of exposure was known, but not the job category or department code.
6 Thus, the same time-weighted average estimated exposure intensity for that time period had been
7 assigned to 653 of these workers[26] (Sullivan, 2007). Particularly large exposure measurement
8 error, among more than two-thirds of the workers hired prior to 1960 who were assigned the
9 same exposure intensity, resulted in the duration of exposure being the best predictor of
10 mesothelioma mortality. Additionally, estimates of exposure intensity prior to 1968 have greater
11 uncertainty associated with them than more recent exposure measurements, which are based on
12 fiber counts in air samples analyzed by PCM. For the majority of job locations (23 of 25), no
13 exposure measurements were available before 1968, and exposures were estimated based on
14 employee interviews (in 1982) and what was known about major changes in operations between
15 1935 and 1967. For two exposure locations, the dust-to-fiber conversion ratio is based on
16 measurements taken in the late 1960s, so extrapolations from the mid 1960s to the early 1960s is

---

[26]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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1 likely to be more certain than extrapolation further back in time. The metric using only duration
2 of exposure fit best and the additional incorporation of exposure intensity information, as
3 expressed as the CE, only worsened the fit. Therefore, it is unlikely that IUR estimates can be
4 developed using the full cohort data because the early exposure values (which were
5 predominantly inferred from later data and based on missing job information) were not
6 predictive of mesothelioma mortality.
7

8 **5.4.3.3.** *Modeling and Results of Lung Cancer Exposure Response in the Full Libby Worker*
9 *Cohort*

10 As noted in the previous section, while the final analytic exposure-response modeling is
11 based in the subcohort of workers hires after 1959, it is important to understand how different
12 metrics of exposure that appear in the epidemiologic literature are related to risk in the full
13 cohort. A parallel set of tables is provided for the subcohort of workers hired after 1959 in
14 Section 5.4.3.6.
15 Tables 5-27 to 5-29 show the mortality rates of lung cancer mortality by duration of
16 exposure, age of first exposure, and TSFE for the full Libby worker cohort ($n = 1,871$). Lung
17 cancer rates in the Libby worker cohort are substantially higher than mesothelioma rates (see
18 Section 5.4.3.2). Basic stratified models of lung cancer rates and standardized mortality ratios
19 (SMRs) in this population show increased rate with increases in duration of exposure greater
20 than 5 years, age at first exposure and TSFE.

Table 5-27. Lung cancer mortality rate shown by duration of exposure (yr) in the full Libby worker cohort including all hires ($n = 1,871$)

	Duration				
	0−1 yr	**1−2 yr**	**2−3 yr**	**3−5 yr**	**5+ yr**
Deaths/PY	60/40,417	9/7,493	6/4,429	5/4,984	31/9,778
Rate × 10^{-4}	14.8	12.0	13.5	10.0	31.7
White male deaths/white male PY	57/37,761	9/7,030	6/4,168	5/4,767	31/9,610
White male rate × 10^{-4}	15.1	12.8	14.4	10.5	32.3
White male $SMR_{Montana}$	2.3	2.0	2.2	1.6	5.0
White male $SMR_{U.S.}$	2.0	1.7	1.9	1.4	4.2

SMR standardized to white male lung cancer mortality rates obtained from NCI (2012).

Table 5-28. Lung cancer mortality rate shown by age at first exposure in the full Libby worker cohort including all hires ($n = 1,871$)

	Age		
	15−25 yr old	**25−35 yr old**	**35+ yr old**
Deaths/PY	28/30,872	42/22,447	41/13,872
Rate × 10^{-4}	9.1	18.7	29.7

SMR not computed due to lack of comparable rates.

Table 5-29. Lung cancer mortality rate shown by time since first exposure (TSFE) in the full Libby worker cohort including all hires ($n = 1,871$)

	Time since first exposure (yr)					
	<15	**15−25**	**25−35**	**35−45**	**45−55**	**55−68.1**
Deaths/PY	12/27,186	19/16,553	35/12,775	21/6,818	21/3,025	3/744
Rate × 10^{-4}	4.4	11.5	27.4	30.8	69.4	40.3
White male deaths/white male PY	11/25,651	19/15,569	33/12,112	21/6,482	21/2,843	3/680
White male rate × 10^{-4}	4.3	12.2	27.2	32.4	73.9	44.1
White male $SMR_{Montana}$	0.7	1.9	4.2	5.0	11.5	6.9
White male $SMR_{U.S.}$	0.6	1.6	3.5	4.2	9.6	5.7

SMR standardized to white male lung cancer mortality rates obtained from NCI (2012).

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1   EPA does not currently have specific technical guidance for model selection based on
2 human cancer data. However, below we explain the process and criteria used in the assessment.
3 Standard models from similar exposure-response analyses available in the epidemiologic
4 literature may be candidate models for exposure-response analyses when they are appropriate to
5 the epidemiologic data at hand.
6   As noted above for mesothelioma, models are selected and evaluated based on the nature
7 of the data set, which for lung cancer, warrants the ability to use the time-dependent data. The
8 mesothelioma mortality data were modeled using the Poisson model within a Bayesian
9 framework to estimate the absolute risk, because mesothelioma is very rare in the general
10 population (Hillerdal, 1983). While the Poisson model is appropriate for modeling very rare
11 events, the standard form does not allow for inclusion of the time-varying nature of exposure.
12 Lung cancer is more common than mesothelioma and does have a known background risk.
13 Thus, modeling of lung cancer mortality is based on the relative risk rather than the absolute risk
14 and was conducted in a frequentist framework, which is the standard methodology for
15 epidemiologic analyses. A frequentist framework is an alternative method of inference, drawing
16 conclusions from sample data with the emphasis on the observed frequencies of the data.
17   Standard epidemiologic models for relative risk include Poisson, logistic, conditional
18 logistic, and Cox models. Multistage clonal expansions models are also available. However,
19 only the Cox models and clonal expansion models can accommodate the analysis of
20 time-varying covariates as in the case of the Libby worker cohort. While different researchers
21 have used two-stage clonal expansion models to model asbestos-related health endpoints from an
22 occupational cohort of asbestos textile workers in South Carolina (Zeka et al., 2011; Richardson,
23 2009), divergent model results raise questions about the resilience of this method when applied
24 to epidemiologic cohorts. Specifically, the two-stage clonal expansion analysis by Richardson
25 (2009) fit the data well and was complementary and consistent with his accompanying Cox
26 regression analysis, while the two-stage clonal expansion analysis by Zeka et al. (2011) on the
27 same cohort population, but with a different length of mortality follow-up, did not completely
28 converge, indicating poor model fit. One issue is that epidemiologic cohorts may be less regular
29 in nature than toxicological studies in the sense that epidemiologic cohorts can be dynamic, with
30 people joining at different times, possibly leaving and then rejoining. By comparison, in animal
31 studies, it is more typical for all the subjects to undergo the identical exposure protocol.
32 Additionally, the degree to which the results of two-stage clonal expansion models depends upon
33 multiple additional assumptions is not yet well understood and EPA does not have reliable
34 information available on which to make the required assumptions for the Libby worker cohort
35 (e.g., the number of cells at risk, constraints on the spontaneous rates of first and second
36 mutations, allowing for a fixed lag between malignant transformation of a cell and death from
37 cancer, etc.). Therefore, in addition to the basic stratified models of lung cancer risk by duration
38 of exposure, by age at first exposure, and by TSFE, EPA selected the Cox model as the most

1 appropriate model for exposure-response modeling based on the suitability of this model to the
2 nature of the data set (i.e., time-dependent exposure information), the long history of usage in
3 analyses of occupational cohorts, and the commonality of usage in other epidemiologic analyses
4 of the Libby workers cohort.

5 No other standard epidemiological model formulations allow for the analysis of
6 time-varying exposures in the manner achieved by the Cox proportional hazards model. The
7 exposure-response relationship (proportional hazards ratio) determined in this model intrinsically
8 takes into account the effects of other causes of mortality that are unrelated to exposure (i.e.,
9 independent censoring). Further, all comparisons are made within the cohort by comparing the
10 mortality experience of people with different exposures within the same cohort population.
11 Nonetheless, the issue of competing risks that are dependent on exposure (e.g., asbestosis or
12 nonmalignant respiratory disease) is an acknowledged uncertainty for this and other types of
13 analyses (see Section 5.4.6).

14 The Cox proportional hazards model (Cox, 1972) is one of the most commonly used
15 statistical models for the epidemiologic analysis of survival and mortality in cohort studies with
16 extensive follow-up, including studies of the Libby worker cohort (Larson et al., 2010b;
17 Moolgavkar et al., 2010). In the Cox proportional hazards model, the conditional hazard
18 function, given the covariate array Z, is assumed to have the form

19

20
$$\lambda(t \mid Z) = \lambda_0(t) \exp(\beta^T Z)$$
(5-13)

21

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

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

36 Other methods common to occupational epidemiology, such as the use of standardized
37 mortality ratios (results shown above in Tables 5-27 through 5-29) typically rely upon

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1   comparisons of the mortality experience in an exposed population group compared to that in the

2   general population. However, the comparison population may not always be appropriate due to

3   differences in general health status (e.g., the healthy worker effect) and differences in exposure

4   to other risk factors for a specific disease (e.g., smoking history). The lack of comparability

5   between the study population and the comparison population can lead to confounding by other

6   measured or unmeasured characteristics that may be statistically associated with both the

7   exposure of interest and the endpoint. The Cox proportional hazards model controls for such

8   potentially confounding characteristics by using a comparison group from within the study

9   population (i.e., internal controls). Internal controls are a statistically appropriate comparison

10   group because they are expected to be more similar in potentially confounding characteristics to

11   the remainder of the cohort, thereby controlling for both measured and unmeasured confounding

12   and helping ensure that comparisons are more statistically valid.

13

14   **5.4.3.3.1. *Lung cancer mortality analysis in the Libby worker cohort.*** As described in the

15   previous section, quantitative exposure-response relationships for lung cancer mortality were

16   evaluated using the Cox proportional hazards model. Cox proportional hazards models of this

17   type require the specification of a timescale. Age is typically the time-related variable with the

18   strongest relationship to cancer mortality and was used as the timescale in these analyses. Use of

19   age as the timescale in a time-varying Cox proportional hazards model controls for age as a risk

20   factor by design rather than by parametric modeling and effectively rules out age as a potential

21   confounder. Individual covariates available to EPA in the complete analytic data set compiled

22   from the NIOSH data were evaluated for their ability to explain lung cancer mortality. These

23   included gender, race, birth year, age at hire, and various exposure-related variables including

24   TWA workplace intensity of exposure in fiber/cc, job type, and the start and stop date of each

25   different job. These data allowed for the computation of cumulative exposure, cumulative

26   exposure with application of a half-life, and RTW cumulative exposure, with and without

27   application of a half-life (see Section 5.4.2.5). Each exposure metric was also lagged by 0, 10,

28   15, or 20 years. The use of a lag period aims to account for the latency period between the onset

29   of lung cancer (which occurs some time before clinical diagnosis) and lung cancer mortality.

30   All lung cancer mortality analyses were conducted using SAS software version 9.1 (SAS,

31   Cary, NC). EPA fit the extended Cox proportional hazards model (Tableman and Kim, 2004;

32   Kleinbaum and Klein, 1996), which included both time-independent factors such as gender, race,

33   and date of birth, as well as time-dependent measures of LAA exposure over the entire time

34   course of each individual's lifetime from his or her date of hire until death or loss to follow-up.

35   The inclusion of date of birth in these analyses controls for potential birth cohort effect.

36   EPA's analyses of time-dependent exposure data included goodness-of-fit testing of the

37   proportionality assumption for the Libby worker cohort. Because Cox proportional hazard

38   models rely on the assumption that the hazard rate among the exposed is proportional to the

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1 hazard rate among the unexposed, it is important to evaluate the model against this assumption.

2 Therefore, analyses of extended Cox proportional hazards models tested this assumption using a

3 Wald test on the model interaction term between the LAA exposure metric and the timescale

4 (i.e., age). As a general rule, a nonzero slope that is either increasing or decreasing indicates a

5 violation of the proportional hazards assumption. Wald tests for the complete cohort consistently

6 showed that the interaction term was a statistically significant predictor of lung cancer mortality

7 ($p < 0.05$) and was interpreted as evidence that the hazards did not remain proportional over

8 time. The cause of the lack of proportionality is unknown, but several likely explanations are

9 discussed in Section 5.4.3.4 below and in the discussion of uncertainties in Section 5.4.6.1.

10

11 **5.4.3.4. *Rationale for Analyzing the Subcohort of Libby Workers After 1959***

12 Several possible explanations exist for the finding that duration of exposure was the best

13 fitting exposure metric for mesothelioma mortality, as well as the finding of the lack of

14 proportionality of hazards in the lung cancer mortality modeling.

15

16 • Duration of exposure, but not department code or job category, was known for 706 of
17 991 (71%) workers hired from 1935 to 1959. Without knowledge of the job category, the
18 same exposure concentration had been assigned to almost all of these workers, likely
19 resulting in a particularly large measurement error for exposure in approximately
20 one-third of the total cohort of 1,871 workers. Assigning the same exposure
21 concentration to so many of the workers hired before 1960, regardless of job, likely
22 resulted in significant exposure misclassification and may explain the superior fit for
23 duration of exposure in modeling of mesothelioma mortality relative to the other
24 exposure metrics based on measured exposures.

25 • Even where the job category was identified, few exposure data exist prior to 1968. For
26 the majority of job locations (23 of 25), no exposure measurements were available prior
27 to 1967, and so exposures were estimated based on employee interviews (conducted in
28 1982) to determine what was known about major changes in operations between 1935
29 and 1967. For two job locations, dust-to-PCM extrapolations are based on measurements
30 taken in the late 1960s; thus, extrapolating from the mid 1960s to the early 1960s is likely
31 to be more certain than extrapolating further back in time. Random error in these
32 exposure measurements would also generally attenuate the strength of association
33 between exposure and observed effect during the earlier years of mine operation, and
34 thus, a greater degree of measurement error in the earlier years could have resulted in the
35 lack in proportionality of the hazard ratios for lung cancer over time. A greater degree of
36 measurement error in the earlier years could also provide an explanation for the worse fit
37 of the mesothelioma models that incorporated these exposure measures.

38 • Another explanation for the lack of proportional hazards in modeling lung cancer
39 mortality may be that this cohort has an anomalous age structure due to the hiring of
40 much older individuals during the time of the Second World War. Among those workers
41 in the cohort hired prior to 1960, 9% were older than 50 years at the time of hire, and
42 22% were older than 40 years. Among those workers hired in 1960 or afterwards, only
43 4% were older than 50 years, and 14% were older than 40 years. Older workers differ

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1   from younger workers in several potentially important ways that could alter their
2   response to exposures. Older workers were born in a different era, with different
3   nutritional and public health standards, which may influence mortality patterns.

4   • The lack of proportional hazards in modeling lung cancer mortality may also be a
5   reflection of confounding or effect modification, which can change in magnitude over
6   time. The most likely candidate for confounding or effect modification is smoking.
7   NIOSH records show that of the 1,871 workers in the full Libby workers cohort,
8   1,121 workers (60%) were missing smoking status data, while 750 (40%) had data with
9   values "*S*" (Smoker), "*Q*" (Former Smoker), or "*N*" (Nonsmoker). Given this high
10   percentage of missing values, EPA did not consider these smoking data to be adequate
11   for use in the evaluation of confounding or effect modification. Effect modification by
12   age is another possibility and may also explain the lack of proportionality in the modeling
13   of lung cancer mortality as has been noted by Richardson (2009) in a two-stage clonal
14   expansion model of lung cancer risk in a cohort of asbestos exposed workers; however,
15   similar two-stage clonal expansion modeling of lung cancer risk in the same cohort of
16   workers was unable to replicate that finding, which may be due to the reliance of this
17   methodology on additional assumptions which EPA does not have a basis for making
18   (see discussion of two-stage modeling in Section 5.4.3.3).

19   • Smoking rates and patterns among the subcohort of workers hired after 1959 are likely to
20   have been more similar because smoking rates change more slowly over shorter periods
21   of time than over longer ones. This restriction in time period of hiring would also result
22   in less variation by birth year cohort, which is strongly related to smoking patterns as
23   people of different generations develop different smoking rates. Thus, this restriction in
24   the time period of hiring may make the cohort members more similar to each other,
25   thereby possibly reducing the potential impact of any smoking-related confounding.
26   Further discussion of the relevance of smoking can be found in the section on
27   uncertainties (see Section 5.4.6).
28

29   When the assumption of proportionality is not met, the potential influence of
30 confounding factors in the full-cohort analysis of lung cancer mortality is of concern.
31 Additionally, the lack of job category information for 71% of the workers hired prior to 1960 and
32 greater measurement error in early exposures may result in significant random exposure
33 measurement error, which may bias the observed exposure-response relationships towards the
34 null.
35   Although duration of exposure was the best exposure metric for modeling mesothelioma
36 mortality in the full cohort, it does not allow quantitatively estimating an exposure-response
37 relationship to support IUR. In addition, violation of the underlying statistical assumptions
38 adversely affected modeling of lung cancer mortality in the full cohort. Therefore, EPA chose to
39 undertake a subcohort analysis of workers hires after 1959.
40   While it is generally true that the use of more data is an advantage in statistical analyses
41 because it allows for the computation of more statistically precise effect estimates, this advantage
42 could not be realized, because of the difficulty in deriving risks from the full cohort analysis (see

1   next section on uncertainties remaining in the subcohort). The reasons stated in Section 5.4.2 for

2   choice of Libby worker cohort data over other study populations are still valid for the subcohort.

3   In particular, (1) these workers were directly exposed to LAA, (2) detailed work histories and

4   job-specific exposure estimates are available to reconstruct estimates of each individual's

5   occupational exposure experience with only nine workers completely missing job and

6   department codes during the period when relatively high average time-weighted estimated

7   exposure intensity was assigned, (3) the subcohort is still sufficiently large and has been

8   followed for a sufficiently long period of time for cancer to develop (i.e., cancer incidence)

9   resulting in mortality, and (4) the broad range of exposure experiences in the subcohort provided

10   an information-rich data set.

11   EPA initially examined the fit of these models using several exposure metrics to predict

12   mortality from mesothelioma and found that in this subcohort, the exposure metrics that included

13   information on exposure concentration provided superior statistical fits to the exposure metrics

14   based only on employment duration. In this same subcohort, the assumptions of the Cox

15   proportional hazards model for analysis of lung cancer were also satisfied for the modeling of

16   time-varying exposure.

17   On the other hand, there are quantitative uncertainties related to the choice of the

18   subcohort. First of all, the numbers of cases of both lung cancer and mesothelioma are lower

19   than in the whole cohort. Second, the follow-up of subcohort, while in excess of 40 years, may

20   not be sufficiently long to encompass all potential lung cancer, especially, mesothelioma

21   mortality related to LAA exposures. Third, the subcohort is younger and overall mortality is

22   lower than in the full cohort. However, the choice of the subcohort is appropriate because of the

23   superior exposure information based on a higher percentage of assigned exposure from actual

24   measurements as opposed to inferred exposure values. The higher percentage of actual

25   measurements allows a more accurate dose-response evaluation (see the discussion in Lenters et

26   al., 2012; Lenters et al., 2011) on the impact the quality of the exposure information has on

27   estimates of dose-response relationships (see Bateson and Kopylev, 2014).

28

29   **5.4.3.5.** *Results of the Analysis of Mesothelioma Mortality in the Subcohort*

30   Of the 880 workers hired after 1959, 230 (26%) had died by December 31, 2006. The

31   number of mesothelioma deaths in the subcohort is seven (two deaths coded in ICD-10 and five

32   deaths coded in ICD-9). The mesothelioma death rate of 2.47 per 10,000 person-years for the

33   subcohort is similar to the mesothelioma death rate of 2.68 per 10,000 person-years for the full

34   cohort (18 mesothelioma deaths), with a difference of less than 10%.

35   Tables 5-30 to 5-32 show the mesothelioma mortality rate by duration of exposure, age of

36   first exposure, and TSFE. As in the full cohort, both duration of exposure and TSFE show a

37   relationship with mesothelioma mortality rate. However, unlike the full cohort, where there was

38   no relationship with age at first exposure, in the subcohort, ages greater than 25 may be

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1 associated with higher risk than those below 25. EPA again evaluated the potential for
2 overdispersion of the counts of mesothelioma deaths. In the subcohort, mean and variance of
3 exposure are 7.95×10^{-3} and 7.90×10^{-3}, respectively. Therefore, as in the full cohort,
4 overdispersion is very unlikely.
5

**Table 5-30. Mesothelioma mortality rate in the subcohort of employees
hired after 1959 shown by duration of exposure (yr)**

	Duration			
	0−1 yr	**1−2 yr**	**2−5 yr**	**5+ yr**
Deaths/PY	1/14,942	0/4,129	1/4,614	5/4,669
Rate $\times$ 10^{-4}	0.7	0	2.2	10.7

**Table 5-31. Mesothelioma mortality rate in the subcohort of employees
hired after 1959 shown by age at first exposure**

	Age		
	15−25 yr old	**25−35 yr old**	**35+ yr old**
Deaths/PY	1/14,104	4/9,029	2/5,222
Rate $\times$ 10^{-4}	0.7	4.4	3.8

**Table 5-32. Mesothelioma mortality rate in the subcohort of employees
hired after 1959 shown by time since first exposure (TSFE)**

	Time since first exposure			
	<15 yr	**15−25 yr**	**25−35 yr**	**35+ yr**
Deaths/PY	0/12,954	2/8,155	3/5,731	2/1,514
Rate $\times$ 10^{-4}	0	2.5	5.2	13.2

6   It is important to note that these marginal analyses, as well as the marginal analyses in the
7 full cohort (see Section 5.4.3.2), do not specifically include the quantitative effects of the
8 exposure—only the timing of exposure. Therefore, these marginal analyses provide an
9 incomplete understanding of the quantitative exposure-response relationship. To more fully
10 understand the effect of the timing of exposure, the quantitative effect of exposure must be
11 modeled. Unlike the full cohort where personal exposure information is mostly missing,
12 subcohort personal exposure information is available. Therefore, EPA next investigated the
13 overall fit of different exposure models and then tabulated and represented graphically the
14 mesothelioma mortality rate as predicted by several models that include personal exposure
15 information.

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1   Table 5-33 shows the relative fit of various exposure metrics for mesothelioma mortality
2   in the subcohort hired after 1959, including only those exposure metrics with information
3   weights greater than 0.01. Information weights are computed from the DICs (Burnham and
4   Anderson, 2002), and commonly used in Bayesian analyses. Information weights are computed
5   by first assessing the differences between the best DIC and each of the others ($\Delta\ DIC_i$) (see
6   eq 5-14).
7

$$DIC\ w_i = \exp\left(-\frac{1}{2}\Delta\ DIC_i\right)\Big/\sum_{r=1}^{R}\exp\left(-\frac{1}{2}\Delta\ DIC_i\right)$$

8   (5-14)
9   where
10
11   R is the number of models and
12       $DIC\ w_i$ is information weight of the ith model.

Table 5-33. Comparison of model fit of exposure metrics for mesothelioma mortality in the subcohort hired after 1959.[a] Only the model fits with information weights greater than 0.010 are shown.[b]

Exposure metric	Lag(yr)	DIC	Information weight
CE with 5-yr half-life	15	70.6	0.428
CE with 5-yr half-life	10	72.8	0.143
CE with 10-yr half-life	10	73.9	0.082
CE with 10-yr half-life	15	74.0	0.078
CE with 10-yr half-life	0	74.5	0.061
CE with 5-yr half-life	0	75.0	0.047
CE with 15-yr half-life	10	75.7	0.033
CE with 15-yr half-life	0	76.0	0.029
CE with 15-yr half-life	15	76.1	0.028
CE with 20-yr half-life	10	76.7	0.020
CE with 20-yr half-life	0	77.0	0.017
CE with 20-yr half-life	15	77.2	0.016

[a]Because one of mesothelioma deaths occurred in less than 20 yr from start of the exposure, lag 20 metrics assigned no exposure to this case, and the very poor fit of lag 20 metrics is a result.
[b]As discussed in Section 5.4.2.4, models with lag 0 were not considered further in derivation of unit risks.

1   Metrics with higher DICs and lower information weights indicate a poorer model fit and
2   are not included in Table 5-33. The other exposure metrics that were evaluated included those
3   metrics used in the full cohort analysis (duration of exposure, TSFE, age at death or censoring,
4   RTW metrics, and CE with lag metrics), but none of these metrics fit as well as the metrics in
5   Table 5-33.

6   The two metrics with cumulative exposure lagged 15 and 10 years, both with 5-year
7   half-life, provided the two best fits as indicated by their lower DIC values and higher information
8   weights (see Table 5-33). Cumulative exposures lagged 10 or 15 years, both with 10-year
9   half-life, provided the next two best fits according to DIC values, but models including each of
10   these metrics exhibited noticeably lower information weights than the best metric. All metrics in
11   Table 5-33 contain a decay term and have the same number of parameters in their corresponding
12   model, allowing for a direct comparison of the DIC values and information weights.

13   For models from the amphibole asbestos literature, in the subcohort hired after 1959, the
14   DIC value for mesothelioma using the Peto metric (see eq 5-11) is substantially higher
15   (DIC = 98.4) than for any of the metrics in Table 5-33. This indicates that the metric of exposure
16   used in the previous IRIS IUR (U.S. EPA, 1988a) does not provide as good a fit for the LAA
17   worker cohort as the other metrics of exposure in Table 5-33. Setting the power term on time
18   since first exposure (k in eq 5-11) in the IRIS IUR (U.S. EPA, 1988a) metric to the values of 2
19   and 4, as suggested by U.S. EPA (1986a), continues to yield substantially higher DIC values
20   compared to the fit values of the exposure metrics in Table 5-33 (DIC = 89.2 and 107.9,
21   respectively). For the Peto model with clearance, increasing the power term in the Peto model
22   with clearance to $k = 3.9$ with decay $\lambda = 0.068$ and $k = 5.4$ with decay $\lambda = 0.015$ decreased DIC
23   slightly from the standard Peto model itself (DIC = 95.4 and 95.3, respectively). Using CE
24   instead of C in decay models, as discussed in Berry et al. (2012), made the fit much worse, as
25   measured by DIC. The fit also degraded when using the Berry et al. (2012) models of the form
26   $(C \text{ or } CE) \times (T - 5)^k$.

27   Next, EPA considered which covariates should be added to the model with the exposure
28   metric that provided the best fit. The addition of covariates "age at death or censoring" and
29   "TSFE" did not improve the fit, as measured by DIC (results not shown).

30   As discussed above, EPA tabulated the mesothelioma rates for the two best fitting metrics
31   in Table 5-33 and for alternative models proposed in the amphibole asbestos literature (i.e., Peto
32   model and Peto model with clearance) in Tables 5-34 to 5-38. These tables show information by
33   quintiles for each metric of exposure.

34   The first two tables (see Tables 5-34, 5-35) show a dose-response relationship between
35   mesothelioma deaths and values of each exposure metric—while the mesothelioma data are
36   sparse, higher values of metric correspond to higher rate of mesothelioma. Tables 5-36 to 5-38
37   show a somewhat less clear dose-response relationship for the Peto model and the Peto model
38   with clearance, as the relationship between metric and rate appears to be somewhat parabolic.

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Table 5-34. Mesothelioma mortality rate in the subcohort of employees hired after 1959 for the cumulative exposure (CE) with 15-year lag and 5-year half-life

	CE with 15-yr lag and 5-yr half-life				
	0−0.024	**0.024−0.094**	**0.094−0.27**	**0.27−0.97**	**0.97+**
Deaths/PY	1/4,858	0/5,975	0/5,827	0/5,494	6/5,751
Rate × 10^{-4}	2.1	0	0	0	10.4

Table 5-35. Mesothelioma mortality rate in the subcohort of employees hired after 1959 for the cumulative exposure (CE) with 10-year lag and 5-year half-life

	CE with 10-yr lag and 5-yr half-life				
	0−0.015	**0.015−0.05**	**0.05−0.15**	**0.15−0.55**	**0.55+**
Deaths/PY	1/5,315	0/5,626	0/5,953	1/5,995	5/5,465
Rate × 10^{-4}	1.9	0	0	1.7	9.1

Table 5-36. Mesothelioma mortality rate in the subcohort of employees hired after 1959 for the Peto model

	Peto metric				
	0−130	**130−760**	**760−3,530**	**3,530−18,070**	**18,070+**
Deaths/PY	1/4,585	0/5,460	0/5,639	4/5,943	2/6,727
Rate × 10^{-4}	2.2	0	0	6.7	3.0

Table 5-37. Mesothelioma mortality rate in the subcohort of employees hired after 1959 for the Peto model with power $k = 3.9$ and decay $\lambda = 6.8\%$/yr

	Peto metric with power $k = 3.9$ and decay $\lambda = 6.8\%$/yr				
	0−311	**311−1,837**	**1,837−7,400**	**7,400−35,330**	**35,330+**
Deaths/PY	1/4,515	0/5,531	0/5,718	4/5,988	2/6,603
Rate × 10^{-4}	2.4	0	0	6.7	3.0

Table 5-38. Mesothelioma mortality rate in the subcohort of employees hired after 1959 for the Peto model with power $k = 5.4$ and decay $\lambda = 15\%/yr$

	Peto metric with power $k = 5.4$ and decay $\lambda = 15\%/yr$				
	0−2,883	**2,883−17,029**	**17,029−67,762**	**67,762−287,614**	**287,614+**
Deaths/PY	1/4,492	0/5,588	0/5,710	4/5,941	2/6,624
Rate $\times$ 10^{-4}	2.2	0	0	6.7	3.0

1   To further illustrate the fit of the Peto model to the Libby mesothelioma data, the
2   frequency of the values of exposure computed using the Peto method and two best-fitting
3   exposure metrics, which were CE with 5-year half-life and 10- or 15-year lag, were plotted and
4   the mesothelioma cases were noted (see Figures 5-6 to 5-8). These figures provide more
5   information than Tables 5-34 through 5-36. The histograms show in a relative scale the
6   frequency of occurrence of each value of the specific exposure metric, thereby revealing the
7   complete distribution and showing where exposure values of the cases were. In these figures, the
8   exposure metric has been transformed to the natural log scale which yields a more normalized
9   distribution. The figures show how the exposure values of the mesothelioma deaths relate to the
10   exposure values of the subcohort of workers hired after 1959. Better fitting models are expected
11   to show higher exposure values for the mesothelioma cases relative to those who did not die
12   from mesothelioma, while poorer fitting models are expected to show mesothelioma cases
13   scattered with equivalent density to the distribution as a whole and, thus, closer to the center of
14   the distribution of exposure metric.

Peto metric and mesothelioma deaths
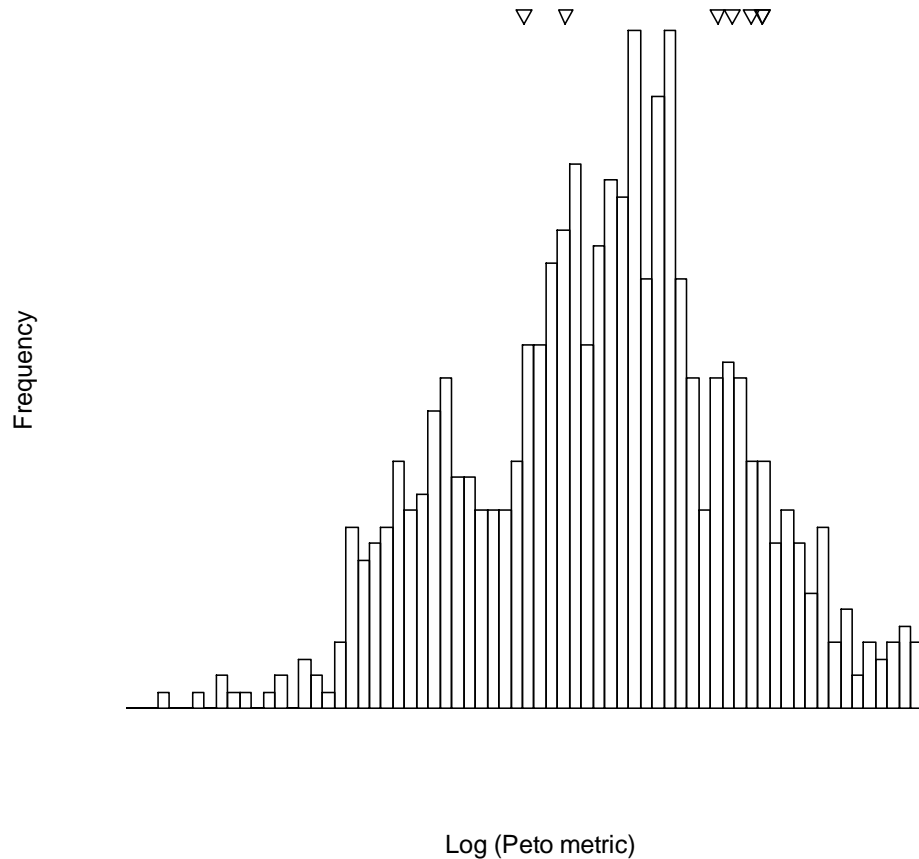
Figure 5-6. Distribution of values of the Peto metric and Peto metric values of mesothelioma deaths (shown as inverted triangles) in the subcohort of employees hired after 1959.

1   From comparing Figures 5-6 (above) and Figures 5-7, and 5-8 (below), exposure values
2 of the mesothelioma deaths based on the Peto exposure metric are clearly closer to the center of
3 the distribution and, therefore, more like the values of those that did not die of mesothelioma.
4 Thus Peto exposure metric does not reveal a higher likelihood of death from mesothelioma
5 compared to the other exposure metrics. This is consistent with what was observed in
6 Tables 5-34 through 5-38—the Peto model does not fit the subcohort data as well as CE metrics
7 with decay fit. For the CE-based exposure metrics (see Figures 5-7 and 5-8), unlike the Peto
8 exposure metric (see Figure 5-6), mesothelioma deaths are concentrated at high values of the
9 exposure metrics and not as close to the center of the distribution.

CE with lag 15 and half-life 5 years and mesothelioma deaths
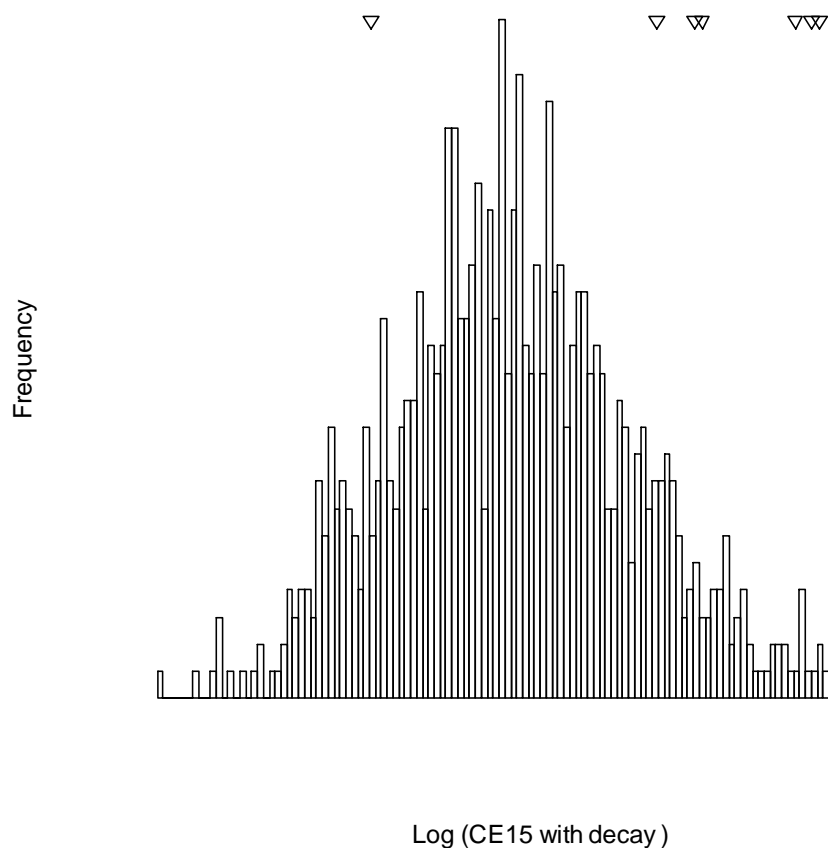
Figure 5-7. Distribution of observed values of cumulative exposure (CE) with 15-year lag and 5-year half-life and CE with 15-yr lag and 5-yr half-life values of mesothelioma deaths (shown as inverted triangles) in the subcohort of employees hired after 1959.

CE with lag 10 and half-life 5 years and mesothelioma deaths

Frequency

Log (CE10 with decay)
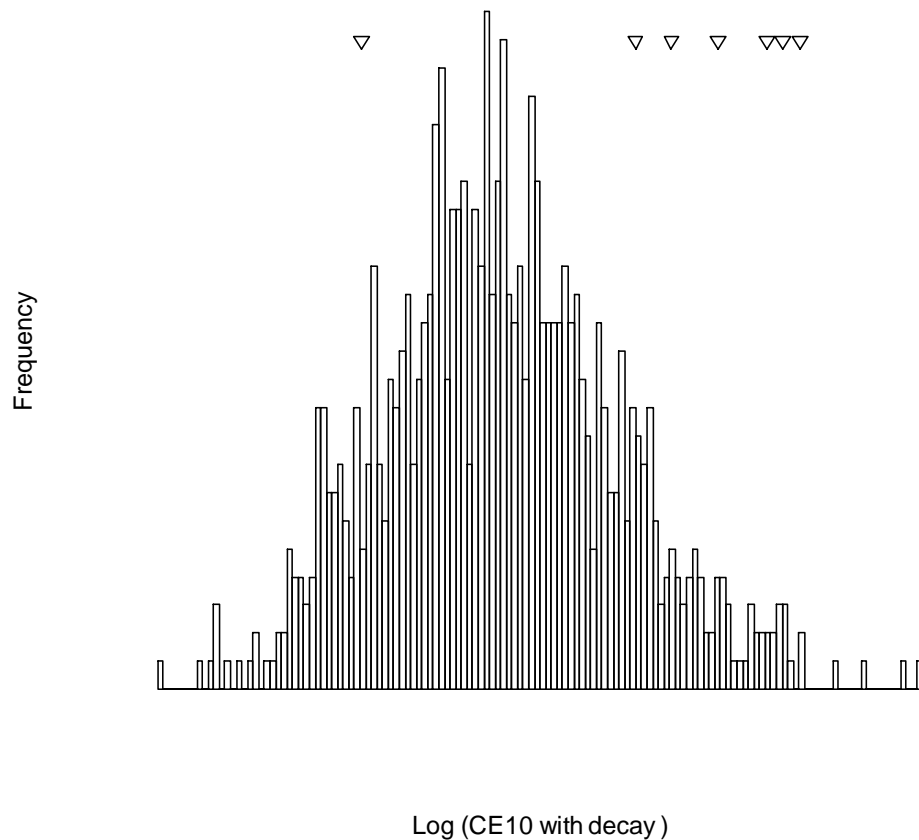
Figure 5-8. Distribution of observed values of cumulative exposure (CE) with 10-year lag and 5-year half-life and CE with 10-yr lag and 5-yr half-life values of mesothelioma deaths (shown as inverted triangles) in the subcohort of employees hired after 1959.

1   As discussed above and seen in Tables 5-34 through 5-38 and Figures 5-6 through 5-8:

2

3   1)   While TSFE by itself, without personal exposure information, shows a clear
4   relationship with increases in mesothelioma rates with increasing TSFE (see
5   Table 5-32), adding information on concentration of fibers to the model (as the Peto
6   model does) appears to degrade the fit (compare Table 5-36 to Table 5-32). The
7   amphibole cohorts (amosite and crocidolite), which were used to derive the Peto
8   model and the Peto model with clearance had little, if any, personal exposure data.
9   Therefore, those models were predominantly based on the power of TSFE and
10   demonstrated a good fit to the exposure timing data from those cohorts. Lack of good
11   exposure data, and in particular personal exposure information, was a limitation of
12   these analyses. In the case of the Libby workers subcohort, personal exposure data is
13   available and when personal exposure is taken into account, the models do not appear
14   to fit as well.

1   2) The tabular fit of the best models from Table 5-33 (see Tables 5-34 to 5-35)
2   compared to the fit in Tables 5-36 to 5-38, demonstrates somewhat better alignment
3   for the subcohort. The tabular results are consistent with overall model fit statistics.
4
5   Comparing the relative fits of the empirical models based on individual-level exposure
6   estimates (but just seven cases) with those literature-based models (Peto and Peto with clearance
7   based on hundreds of cases but little actual individual-level exposure data) reveals uncertainties
8   related to model selection. While there is understandable uncertainty in using empirical models
9   based on a small number of cases, there is also uncertainty in applying literature-based models
10 based on different type of amphibole asbestos without individual-levels exposure estimates. This
11 uncertainty is discussed below in the section describing the derivation of the IUR (see
12 Section 5.4.5.3). As described in Section 5.4.2.5, only metrics with nonzero lag were retained
13 for derivation of unit risks. Table 5-39 shows KM (slope) and credible intervals for all metrics
14 retained from Table 5-33.
15

Table 5-39. **Mesothelioma mortality exposure metrics fits, slopes per day,
and credible intervals in the subcohort of employees hired after 1959**

Exposure metric	Lag yr	DIC	Slope $\times$ 10^{-5}	90% Credible interval for slope $\times$ 10^{-5}
CE—5-yr half-life	15	70.6	20.6	(10.2, 34.3)
CE—5-yr half-life	10	72.8	31.1	(15.2, 50.8)
CE—10-yr half-life	10	73.9	9.93	(5.00, 16.3)
CE—10-yr half-life	15	74.0	7.78	(3.72, 12.9)
CE—15-yr half-life	10	75.7	6.17	(3.04, 10.1)
CE—15-yr half-life	15	76.1	5.30	(2.63, 8.69)
CE—20-yr half-life	10	76.7	4.71	(2.34, 7.71)
CE—20-yr half-life	15	77.2	4.27	(2.12, 6.98)

16
17   Table 5-40 shows fits (DIC), KM (slope), and credible intervals for the Peto model and
18 the Peto model with clearance (note that these slopes are not directly comparable with those in
19 Table 5-39 because of difference in the units of time due to the use of different powers).

Table 5-40. Peto model and Peto model with clearance fits, slopes per year, and credible intervals in the subcohort of employees hired after 1959

Power (k)	Decay	DIC	Slope $\times 10^{-8}$	90% Credible interval for slope $\times 10^{-8}$
5.4	0.15	95.3	0.09	(0.04, 0.15)
3.9	0.068	95.4	0.66	(0.34, 1.09)
3	No	98.4	1.06	(0.52, 1.72)

1   Issues related to uncertainty in the choice of exposure metric are described further in the

2 section on the derivation of the combined IUR of mesothelioma and lung cancer (see

3 Section 5.4.5.3).

4

5 **5.4.3.6.** *Results of the Analysis of the Lung Cancer Mortality in the Subcohort*

6   EPA based its final analyses for lung cancer mortality on the subset of workers hired after

7 1959. Thus, this analysis is based on 32 deaths from lung cancer[27] (ICD-8: 2 deaths with the

8 code 162.1; ICD-9: 1 death with the code 162.2, 20 deaths with the code 162.9; ICD-10:

9 9 deaths with the code C349) out of 230 total deaths that occurred in the subcohort of

10 880 workers.

11   Tables 5-41 to 5-43 show lung cancer mortality rates by duration of exposure, age of first

12 exposure, and TSFE. As in the full cohort, duration of exposure, age at first exposure, and TSFE

13 all show relationships with lung cancer mortality rate.

---

[27]Note that in the full cohort, it was unclear whether cases of tracheal cancer were included in the definition of lung cancer as many of the recorded ICD codes on death certificates did not provide sufficient detail to distinguish tracheal cancer cases from lung cancer cases. However, among the subcohort of workers hired after 1959, all the deaths from the broader category of cancers of the lung, bronchus, and trachea did provide sufficient detail to show that no deaths occurred from tracheal cancer.

Table 5-41. Lung cancer mortality rate in the subcohort of employees hired after 1959 shown by duration of exposure (yr)

	Duration			
	0−1 yr	**1−2 yr**	**2−5 yr**	**5+ yr**
Deaths/PY	13/14,942	5/4,129	2/4,614	12/4,669
Rate × 10^{-4}	8.7	12.1	4.3	25.7
White male deaths/white male PY	12/13,779	5/3,848	2/4,251	12/4,601
White male rate × 10^{-4}	8.7	13.0	4.7	26.1
White male SMR$_{Montana}$	1.4	2.0	0.7	4.1
White male SMR$_{United States}$	1.1	1.7	0.6	3.4

SMR standardized to white male lung cancer mortality rates obtained from NCI (2012).

Table 5-42. Lung cancer mortality rate in the subcohort of employees hired after 1959 shown by age at first exposure

	Age		
	15−25 yr old	**25−35 yr old**	**35+ yr old**
Deaths/PY	1/14,104	12/9,029	19/5,222
Rate × 10^{-4}	0.7	13.3	36.4

SMR not computed due to lack of comparable rates.

Table 5-43. Lung cancer mortality rate in the subcohort of employees hired after 1959 shown by time since first exposure (TSFE)

	Time since first exposure			
	<15 yr	**15−25 yr**	**25−35 yr**	**35+yr**
Deaths/PY	4/12,954	11/8,155	13/5,731	4/1,514
Rate × 10^{-4}	3.1	13.5	22.7	26.4
White male deaths/white male PY	4/12,054	11/7,560	12/5,404	4/1,461
White male rate × 10^{-4}	3.3	14.6	22.2	27.4
White male SMR$_{Montana}$	0.5	2.3	3.5	4.3
White male SMR$_{United States}$	0.4	1.9	2.9	3.5

SMR standardized to white male lung cancer mortality rates obtained from NCI (2012).

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1   As noted in Section 5.4.3.5, these marginal analyses do not specifically include the
2   effects of the exposure as well as both the duration and the TSFE. Therefore, EPA investigated
3   the overall fit of different exposure models and tabulated the results of several models that
4   include personal exposure information.
5   All multivariate Cox proportional hazards models with time-varying exposures were
6   initially fit, using one exposure metric at a time, to the subcohort hired after 1959 with covariates
7   for gender, race, and date of birth. Lung cancer mortality was modeled using CE and RTW
8   exposure, where each metric was potentially modified by four different half-lives (5, 10, 15, or
9   20 years). Each of these exposure metrics was also evaluated with four different lag periods to
10   allow for cancer latencies of 0, 10, 15, or 20 years. In all, 40 multivariate exposure-response
11   models were evaluated for the adequacy of the exposure metric to fit the epidemiologic data.
12   Each model and the comparative model fit statistics are presented in Table 5-44.

Table 5-44. Model fit comparison for different exposure metrics and lung cancer mortality associated with LAA, controlling for age, gender, race, and date of birth. Results ordered at left by exposure metric and at right by model fit.

Ordered by exposure metric			Ordered by model fit				
Exposure metric	Lag (yr)	AIC	Exposure metric	Lag (yr)	AIC	Multivariate model *p*-value†	Exposure *p*-value
CE	0	361.610	CE—10-yr half-life	10	358.400	0.0071	0.0009
CE	10	361.073	CE—5-yr half-life	10	358.502	0.0075	0.0010
CE	15	363.124	CE—15-yr half-life	10	358.777	0.0084	0.0015
CE	20	364.964	CE—20-yr half-life	10	359.122	0.0098	0.0022
CE—20-yr half-life	0	361.123	CE—5-yr half-life	15	359.910	0.0138	0.0032
CE 20-yr half-life	10	359.122	CE—10-yr half-life	15	360.543	0.0181	0.0079
CE—20-yr half-life	15	361.533	CE	10	361.073	0.0227	0.0188
CE—20-yr half-life	20	364.703	CE—20-yr half-life	0	361.123	0.0232	0.0155
CE—15-yr half-life	0	361.382	CE—15-yr half-life	15	361.129	0.0232	0.0162
CE—15-yr half-life	10	358.777	CE—15-yr half-life	0	361.382	0.0258	0.0184
CE—15-yr half-life	15	361.129	CE—20-yr half-life	15	361.533	0.0276	0.0254
CE—15-yr half-life	20	364.588	RTW 5-yr half-life	0	361.593	0.0283	0.0309
CE—10-yr half-life	0	362.169	CE	0	361.610	0.0285	0.0307
CE—10-yr half-life	10	358.400	CE—10-yr half-life	0	362.169	0.0360	0.0358
CE—10-yr half-life	15	360.543	RTW 10-yr half-life	0	362.283	0.0378	0.0588
CE—10-yr half-life	20	364.342	RTW 15-yr half-life	0	362.714	0.0452	0.0863
CE—5-yr half-life	0	364.225	RTW 20-yr half-life	0	362.973	0.0503	0.1084
CE—5-yr half-life	10	358.502	CE	15	363.124	0.0535	0.1215
CE—5-yr half-life	15	359.910	RTW 5-yr half-life	10	363.224	0.0558	0.1343
CE—5-yr half-life	20	363.644	CE—5-yr half-life	20	363.644	0.0662	0.1751
RTW	0	363.869	RTW	0	363.869	0.0726	0.2397
RTW	10	364.835	RTW 10-yr half-life	10	364.041	0.0778	0.2810
RTW	15	364.990	CE—5-yr half-life	0	364.225	0.0838	0.2908
RTW	20	364.502	RTW 15-yr half-life	10	364.336	0.0876	0.3733
RTW 20-yr half-life	0	362.973	CE—10-yr half-life	20	364.342	0.0878	0.3661
RTW 20-yr half-life	10	364.477	RTW 20-yr half-life	10	364.477	0.0927	0.4314
RTW 20-yr half-life	15	365.011	RTW	20	364.502	0.0936	0.5307
RTW 20-yr half-life	20	364.628	CE—15-yr half-life	20	364.588	0.0969	0.4815
RTW 15-yr half-life	0	362.714	RTW 20-yr half-life	20	364.628	0.0985	0.5763
RTW 15-yr half-life	10	364.336	RTW 15-yr half-life	20	364.662	0.0998	0.5909

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Table 5-44. Model fit comparison for different exposure metrics and lung cancer mortality associated with LAA, controlling for age, gender, race, and date of birth. Results ordered at left by exposure metric and at right by model fit. (continued)

Ordered by exposure metric				**Ordered by model fit**			
Exposure metric	**Lag (yr)**	**AIC**		**Exposure metric**	**Lag (yr)**	**AIC**	**Multivariate model _p_-value†**	**Exposure _p_-value**
RTW 15-yr half-life	15	365.001		CE—20-yr half-life	20	364.703	0.1014	0.5530
RTW 15-yr half-life	20	364.662		RTW 10-yr half-life	20	364.719	0.1021	0.6188
RTW 10-yr half-life	0	362.283		RTW 5-yr half-life	15	364.768	0.1041	0.6021
RTW 10-yr half-life	10	364.041		RTW 5-yr half-life	20	364.831	0.1067	0.6884
RTW 10-yr half-life	15	364.962		RTW	10	364.835	0.1069	0.6586
RTW 10-yr half-life	20	364.719		RTW 10-yr half-life	15	364.962	0.1124	0.8173
RTW 5-yr half-life	0	361.593		CE	20	364.964	0.1125	0.8204
RTW 5-yr half-life	10	363.224		RTW	15	364.990	0.1136	0.8809
RTW 5-yr half-life	15	364.768		RTW 15-yr half-life	15	365.001	0.1141	0.9100
RTW 5-yr half-life	20	364.831		RTW 20-yr half-life	15	365.011	0.1146	0.9599

CE = Cumulative exposure with or without exponential decay modeled with different half-lives.
RTW = Residence time-weighted exposure with or without exponential decay with different half-lives.
†Likelihood ratio test (overall model fit where $p < 0.05$ indicated an adequate fit).

1   The assumptions of the Cox proportional hazards model were reevaluated for the

2   subcohort. Restricting the cohort addressed each of the previously listed potential explanations

3   for the lack of hazard proportionality (see Section 5.4.3.3). First, measurement error for

4   exposures is likely to have been smaller after 1959 for several reasons. One reason is that

5   706 workers were removed from the analysis because job category and department code

6   information were missing during all of their employment prior to 1960. Also, beginning in 1968,

7   fiber concentrations by PCM analysis of site-specific air samples were available for all location

8   operations to inform the JEM.

9   Second, prior to 1968, the exposure intensity for 23 of 25 location operations was

10   estimated based on assumptions informed by employee interviews in the early 1980s. It is likely

11   the uncertainty of these assumptions increased the farther back in time that exposures were

12   estimated, making the earliest exposure estimates (1940s and 1950s) less certain than those only

1	a few years before fiber count data were available. Further, between 1956 and 1967,
2	dust-to-PCM extrapolation data were used to estimate exposures in the dry mill based on
3	measurements taken in the late 1960s. Although there is some uncertainty in the conversion ratio
4	selected by Amandus et al. (1987b), dust-to-fiber conversions are likely to be less uncertain than
5	extrapolations further back in time to the 1950s and 1940s, where only one air sample for dust
6	was available in 1944. Thus, the potential attenuation effect of nondifferential measurement
7	error is likely to be reduced by examining the post-1959 cohort alone compared to the entire
8	cohort.
9	Third, smoking rates among this more narrowly defined subcohort are likely to have been
10	more homogeneous; thus, restricting analysis to this subcohort would help to limit any potential
11	confounding due to smoking.
12	Finally, EPA conducted goodness-of-fit testing of the extended Cox proportional hazards
13	model as applied to the subcohort hired post-1959. There was no evidence to reject the
14	hypothesis of proportionality, and the exposure models demonstrated adequate fits to the data,
15	with statistically significant effect estimates. In each of the Cox proportional hazards model
16	analyses with time-varying exposures—across all the exposure metrics and across all the lag
17	lengths—no violations of the assumption of proportionality of hazards were found.
18	As the exposure-response models cannot strictly be considered to be nested, a standard
19	measure of fit called the AIC (Burnham and Anderson, 2002) was used for comparison of
20	goodness of fit across models based on the same data set. In their text on model selection,
21	Claeskens and Hjort (2008) state that "…for selecting a model among a list of candidates, AIC is
22	among the most popular and versatile strategies." Claeskens and Hjort (2008) also state that the
23	model yielding the smallest AIC is judged the best fitting and it is a common practice in
24	environmental epidemiology to simply select the single model with the best statistical fit (i.e., the
25	lowest AIC) among the models evaluated. While large differences in AIC values can reveal
26	important differences in model fit, small differences are less conclusive. For example, in a set of
27	models differing in AIC by two or fewer units, each can be considered to have a substantially
28	similar level of empirical support (Burnham and Anderson, 2002 ; p. 70).
29	Table 5-44 shows the models and exposure metrics ordered by fit. Of interest is whether
30	there are models with distinct exposure metrics that adequately fit these data (as measured by
31	statistical significance of the model p-value) and then whether a measure of relative fit exists
32	among these adequately fitting models. Of the 40 exposure-response metrics, 14 demonstrated
33	an adequate fit to the data as measured by the overall model fit, with the standard likelihood ratio
34	test being statistically significant ($p < 0.05$), as well as having statistically significant exposure
35	metrics ($p < 0.05$). However, note that only the nine models that demonstrated adequate model
36	and exposure metric fit and incorporated a lag period to account for lung cancer mortality latency
37	were advanced for potential use in developing a unit risk. While metrics that did not include an
38	adjustment for lag on the exposure metric to account for cancer mortality latency were fit to

1   these data for the sake of completeness, they were dropped from further consideration because
2   they implicitly assume no passage of time between the initiation of cancer, subsequent promotion
3   of that cancer, and mortality.

4   Several general patterns were discernible with respect to which exposure metric(s) best
5   predicted lung cancer mortality when comparing AICs for relative model fit. The data show that
6   lagging exposure by 10 years best predicts lung cancer mortality compared to other lags. This
7   trend is seen across both the cumulative exposure without decay and the various half-life
8   cumulative exposure metrics where a 10-year lag of exposure best predicts lung cancer mortality
9   for all cumulative exposure metrics compared to other lags. Metrics with 15-year lags were
10   generally the next best in terms of fit. Another conclusion is that the models that included RTW
11   exposure metrics, regardless of half-life or lag, did not fit as well as the models that employed
12   cumulative exposure with different half-lives and lags.

13   Among the 40 exposure metric models that were evaluated, the exposure model with the
14   lowest AIC value was for cumulative exposure with a 10-year half-life for decay and a 10-year
15   lag for cancer mortality latency and had a model *p*-value based on the likelihood ratio test of
16   0.0071 (see Table 5-44). This multivariate model controlled for age, gender, race, and date of
17   birth. This model estimated a KL (slope) of 1.26×10^{-2} per fibers/cc-yr based on a 365-day
18   calendar year,[28] and the 95th percentile upper bound on this parameter was 1.88×10^{-2} per
19   fibers/cc-yr. The *p*-value for the LAA regression coefficient (slope) was <0.001, indicating that
20   this parameter was statistically significantly greater than zero. Table 5-45 shows the slopes and
21   confidence intervals for all retained metrics from Table 5-44. Figure 5-9 shows the model
22   residuals (in this case, the Schoenfeld residuals for Cox models) for the retained models in Table
23   5-45. Patterns in such residuals such as an increasing or decreasing slope overall can indicate
24   lack of fit. Attention is directed at the pattern of residuals with respect to age at death (the
25   *x*-axis). None of the plots appears to show a meaningful deviation from a linear function of age
26   which indicates a lack of interaction between the model-predicted effect of exposure on lung
27   cancer mortality risk and age. That is, the risk of lung cancer mortality does not appear to vary
28   by age within the subcohort of workers at the Libby facility. There is no indication of a
29   systematic lack of fit across these models excepting the nonlinear departure in the center of each
30   residual plot which appears to be random and is minimized with the pattern in the residuals if
31   smoothed out to a greater extent. The model fit residuals are consistent with the similarity of the
32   AIC values in demonstrating similar model fit.

---

[28]The two-sided 90% confidence interval is $(6.00 \times 10^{-3}, 1.88 \times 10^{-2})$.

Table 5-45. Lung cancer mortality exposure metrics fits, slopes, and confidence intervals (CI) for all retained metrics from Table 5-44. Subset of lung cancer models with lagged exposures that yielded statistically significant model fit ($p < 0.05$) and exposure metric fit ($p < 0.05$) to the epidemiologic data

Exposure metric	Lag yr	AIC	Slope	SE	Exposure p-value	90% CI for the slope
CE—10-yr half-life	10	358.400	0.0126	0.0038	0.0009	(0.0063, 0.0188)
CE—5-yr half-life	10	358.502	0.0179	0.0055	0.0010	(0.0089, 0.0269)
CE—15-yr half-life	10	358.777	0.0106	0.0033	0.0015	(0.0052, 0.0160)
CE—20-yr half-life	10	359.122	0.0095	0.0031	0.0022	(0.0044, 0.0146)
CE—5-yr half-life	15	359.910	0.0155	0.0052	0.0032	(0.0069, 0.0241)
CE—10-yr half-life	15	360.543	0.0115	0.0043	0.0079	(0.0044, 0.0186)
CE	10	361.073	0.0058	0.0025	0.0188	(0.0017, 0.0099)
CE—15-yr half-life	15	361.129	0.0097	0.0040	0.0162	(0.0031, 0.0163)
CE—20-yr half-life	15	361.533	0.0087	0.0039	0.0254	(0.0023, 0.0151)

Exposure Metric	Less smoothing	More smoothing
CE—no half-life; 10-yr lag		
CE—5-yr half-life; 10-yr lag		
CE—10-yr half-life; 10-yr lag		
CE—15-yr half-life; 10-yr lag		
CE—20-yr half-life; 10-yr lag		

| CE—5-yr half-life; 15-yr lag | | |
CE—10-yr half-life; 15-yr lag		
CE—15-yr half-life; 15-yr lag		
CE—20-yr half-life; 15-yr lag		
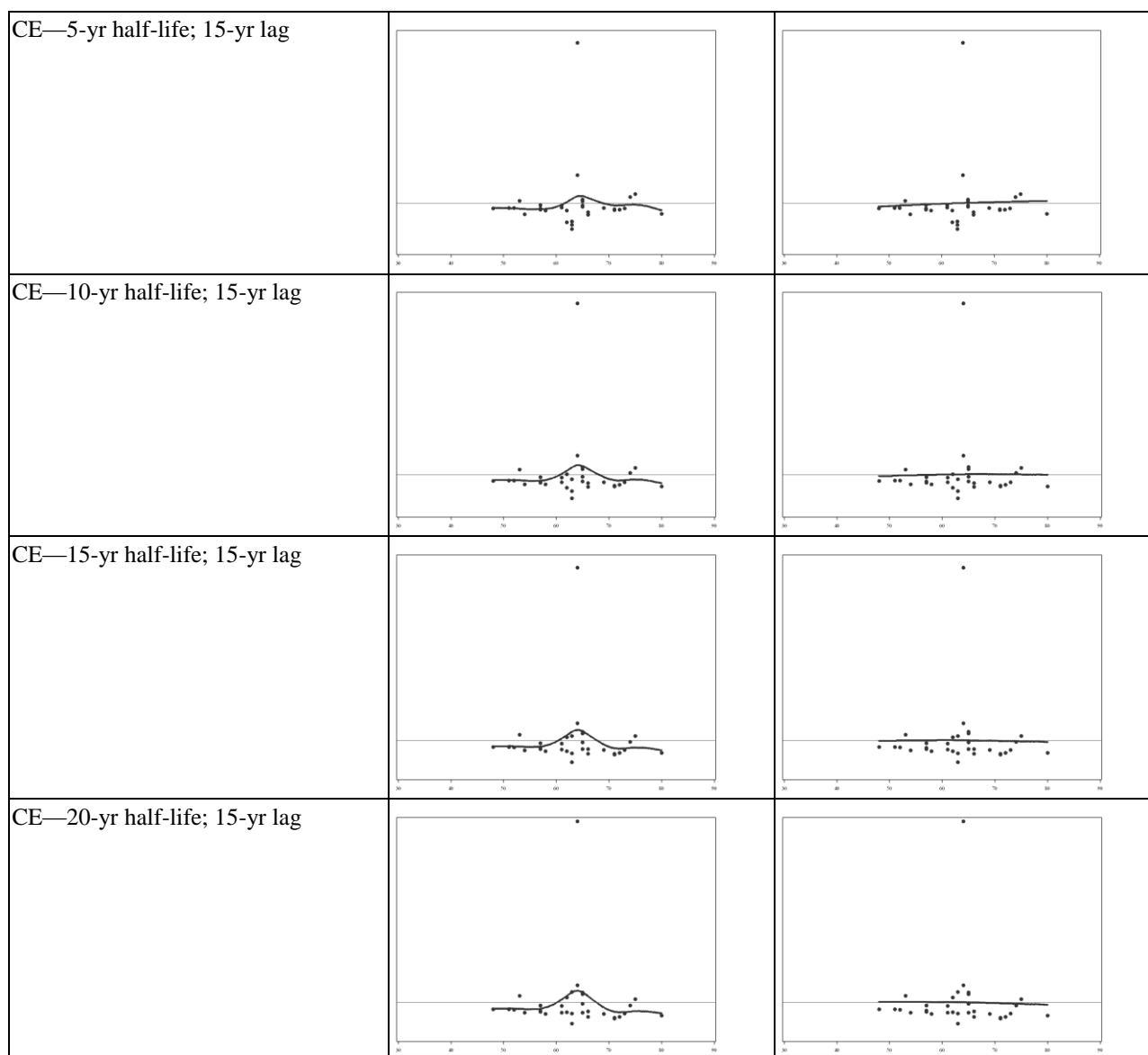
Figure 5-9. Regression diagnostics showing model fit based on the Schoenfeld residuals with two levels of nonparametric smoothing (using cubic splines) to show any patterns of departures from the model predicted values. In each plot, age at lung cancer mortality is shown against the model residuals. The *x*-axis shows the age of death while the *y*-axis shows the scaled residuals (predicted minus observed) according to the scale of the specific exposure metric.

1   According to the model results presented in Table 5-44, there were multiple exposure
2 metrics that predicted lung cancer mortality and exhibited statistically significant effect
3 estimates. Several other metrics were considered to fit nearly as well as the model with the
4 smallest AIC because their AIC values were within two units of the exposure model with the
5 lowest AIC, a proximity that can be considered to be a range that cannot clearly differentiate
6 among models (Burnham and Anderson, 2002). As each of the other exposure metrics was
7 based on a different configuration of the same exposure data, the different slopes (KLs) are not
8 directly comparable, but all adequately fitting lagged models also produce statistically significant
9 slopes for the exposure-response relationship ($p < 0.05$). Of particular note are the results of the
10 cumulative exposure model with a 10-year lag for latency but without a decay function because
11 this model showed the lowest AIC among nondecay models.
12   The AIC values for models that included lag and/or half-life adjustments to the exposure
13 metrics were not penalized in the regression analyses for using these extra parameters because
14 these factors were not represented as covariates but rather were embedded in the computation of
15 the exposure metric. While these results were obtained using each instance of lag and/or half-life
16 terms in separate model fit, it may be appropriate to mathematically penalize the AICs for
17 inclusion of these additional parameters. AIC values, as typically computed by regression
18 software, include the addition of a penalty for model complexity as measured by the number of
19 parameters that are fit in the regression model (thereby increasing the AIC). In the AIC
20 calculations presented in Table 5-44, the models are treated as having the same number of
21 parameters because each model represents the same individual's time-varying exposures in a
22 different way but with a single exposure parameter in the regression models. For that reason, the
23 models are equally penalized in the software's AIC calculation. However, because an argument
24 can be made that exposure metrics that do not include a decay function, with an explicit half-life
25 term, are implicitly more parsimonious (simpler), a comparison of the AICs is not
26 straightforward. If the decay model fits were penalized for the inclusion of the decay function in
27 the computation of the exposure metric, then with such an adjustment, the relative fit of the CE
28 models would be somewhat improved in terms of their comparison with the values in Table 5-44
29 (AICs are generally penalized two units for each additional parameter).
30   Table 5-45 displays the lagged exposure-response models and metrics with adequate
31 model fit ($p < 0.05$) to the epidemiologic data that were further considered. The units of the
32 slopes are fiber/cc-yr. These slopes and confidence intervals represent calendar year continuous
33 environmental exposure as described above and define the "Exposed Hazard Rate" in the
34 life-table procedure when multiplied by the exposure level (see Appendix G for details). The
35 plots in Figure 5-9 do not suggest a meaningful difference in model fits among the nine different
36 parameterizations of exposure with adequate fit.
37   As presented in Table 5-45, the CE model with 10-year half-life and lag provided an
38 adequate fit to the data based on the likelihood ratio test ($p < 0.05$) and had the lowest AIC value.

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1   The cumulative exposure model with a 10-year lag also yielded a statistically adequate fit to

2   these data ($p < 0.05$), as did several decay models with a 15-year lag. These results demonstrate

3   reasonable uncertainty in the metric of exposure such that no single exposure model can be

4   definitively selected based on goodness of fit alone. Issues related to uncertainty in the choice of

5   exposure metric are described further in the section explaining the derivation of the combined

6   IUR of mesothelioma and lung cancer (see Section 5.4.5.3).

7

8   **5.4.3.7.** *Sensitivity Analysis of the Influence of High Exposures in Early 1960s on the Model*
9   *Fit in the Subcohort*

10   As discussed in Section 5.4.2.5, the comparison of model fit among various exposure

11 metrics is an empirical process and does not necessarily reflect a specific biological or other

12 factor as an underlying cause for model fit. Although data do not exist to evaluate biological

13 bases for model fit, other potential factors can be explored where data allow. For example,

14 because of concerns that very high (>100 fibers/cc) 8-hour TWA exposures during 1960−1963

15 (see Table 5-21) could have influenced the relative fit of the various exposure metrics, EPA

16 conducted a sensitivity analysis of the impact on the relative model fit of reducing all estimated

17 exposure intensities for 1960−1963 by 50%.

18   For modeling mesothelioma mortality on this revised data set, one change occurred in the

19 relative fit of 3rd and 4th best fit decay models, but the observation that exposure metrics

20 including decay fit better than exposure metrics without decay was unchanged (see Table 5-46).

21 However, the fit of all the metrics decreased slightly, with each DIC increased between 0.3 and

22 1.1. The metrics without decay and RTW metrics had DIC values higher than those in

23 Table 5-46. The revised data set DIC for the model used in IRIS IUR (U.S. EPA, 1988a)

24 was 97.9.

Table 5-46. Sensitivity analysis of model fit comparison for different exposure metrics and mesothelioma mortality associated with LAA. Estimated exposure intensities for all jobs during 1960−1963 were reduced by 50%.

Exposure metric	Lag (yr)	All workers hired after 1959 (*n* = 880). Based on seven mesothelioma deaths (as shown in Table 5-33).	All workers hired after 1959 (*n* = 880). Based on seven mesothelioma deaths. Exposures during 1960−1963 at 50%.
		DIC	DIC
CE—5-yr half-life	15	70.6	71.2
CE—5-yr half-life	10	72.8	73.9
CE—10-yr half-life	10	73.9	74.9
CE—10-yr half-life	15	74.0	74.6
CE—15-yr half-life	10	75.7	76.4
CE—15-yr half-life	15	76.1	76.7
CE—20-yr half-life	10	76.7	77.3
CE—20-yr half-life	15	77.2	77.7

CE = Cumulative exposure with exponential decay modeled with different half-lives.

1   For modeling lung cancer mortality on this revised data set, no difference was present in
2   the order of the relative fit between the same exposure metrics that fit the subcohort of workers
3   hired after 1959 and those exposures estimated by Amandus et al. (1987b) for 1960−1963 (see
4   Table 5-47). The metrics based on the revised data set fit marginally better based on AIC.

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Table 5-47. Sensitivity analysis of model fit comparison for different exposure metrics and lung cancer mortality associated with LAA, controlling for age, gender, race, and date of birth. Estimated exposure intensities for all jobs during 1960−1963 were reduced by 50%. Lung cancer models presented include those with statistically significant multivariate model *p*-value and nonzero lag in exposure.

Exposure metric	Lag (yr)	All workers hired after 1959 (*n* = 880) based on 32 deaths from lung cancer (as shown in Table 5-44)			All workers hired after 1959 (*n* = 880) based on 32 deaths from lung cancer. Exposures during 1960−1963 at 50%.		
		AIC	Multivariate model *p*-value	Exposure *p*-value	AIC	Multivariate model *p*-value	Exposure *p*-value
CE—10-yr half-life	10	358.400	0.0071	0.0009	357.644	0.0051	0.0004
CE—5-yr half-life	10	358.502	0.0075	0.0010	357.781	0.0054	0.0005
CE—15-yr half-life	10	358.777	0.0084	0.0015	357.966	0.0059	0.0006
CE—20-yr half-life	10	359.122	0.0098	0.0022	358.283	0.0068	0.0009
CE—5-yr half-life	15	359.910	0.0138	0.0032	359.456	0.0113	0.0025
CE—10-yr half-life	15	360.543	0.0181	0.0079	360.167	0.0154	0.0067
CE	10	361.073	0.0227	0.0188	360.238	0.0159	0.0086
CE—15-yr half-life	15	361.129	0.0232	0.0162	360.810	0.0203	0.0138
CE—20-yr half-life	15	361.533	0.0276	0.0254	361.245	0.0244	0.0217

CE = Cumulative exposure with or without exponential decay modeled with different half-lives.

1 This sensitivity analysis reduces some of the potential uncertainty in the results that may
2 have been attributed to exposure measurement error specific to the 1960−1963 time period when
3 some of the estimated exposures were particularly high.
4
5 **5.4.3.8.** *Additional Analysis of the Potential for Confounding of Lung Cancer Results by*
6 *Smoking in the Subcohort*
7 In the full cohort analysis, the proportional hazard assumption was not found to hold, and
8 one of the reasons for this failure was the possible presence of confounding by smoking, which
9 altered the proportionality of the hazard rate in the exposed workers compared to the baseline
10 hazard rate over time. Confounding, which can bias observed results when there is an
11 uncontrolled variable that is correlated with both the explanatory variable and the outcome
12 variable, is a distinct concept from effect-measure modification (e.g., synergy), which might
13 reflect different observed effects of exposure to LAA among smokers as compared to
14 nonsmokers. The extent of effect-measure modification cannot be assessed without adequate
15 data on smoking; however, the potential for effect-measure modification is discussed in
16 Section 5.4.6.

1   As an additional check on the potential for confounding, a novel method was evaluated to
2   test for confounding by smoking in occupational cohorts that do not have data on smoking. A
3   method has been described by Richardson (2010) to determine if an identified exposure
4   relationship with lung cancer is confounded by unmeasured smoking in an occupational cohort
5   study. Richardson (2010) demonstrated that an exposure of interest (i.e., LAA) can be used to
6   predict an outcome other than lung cancer such as COPD, which is known to be caused by
7   smoking, but not thought to be related to the exposure of concern.[29] If a positive relationship is
8   identified where no causal association is suspected, this would suggest that smoking and the
9   exposure metric (LAA) were positively correlated and that the identified exposure-response
10   relationship was, in fact, confounded by smoking. EPA implemented this methodology to model
11   the potential effects of LAA on the risk of COPD mortality ($n = 18$) on the subcohort of workers
12   hired after 1959. Using the exposure metric defined as cumulative exposure with a 10-year lag,
13   the extended Cox proportional hazards model with time-varying exposures estimated a slope
14   (beta) for COPD of -0.056 per fiber/cc-yr based on a 365-day calendar year. The p-value for the
15   coefficient (slope) was 0.102, indicating that this parameter was not statistically significantly
16   different from zero. Using the exposure metric defined as cumulative exposure with a 10-year
17   half-life for decay and a 10-year lag for cancer latency, the extended Cox proportional hazards
18   model with time-varying exposures estimated a slope (beta) of -0.135 per fiber/cc-yr based on a
19   365-day calendar year. The p-value for the coefficient (slope) was 0.116, indicating that this
20   parameter was not statistically significantly different from zero.
21   Summarizing these findings, EPA used the method described by Richardson (2010) to
22   evaluate whether exposures to LAA predicted mortality from COPD as an indication of potential
23   confounding by smoking and found a nonsignificant negative relationship, which was
24   inconsistent with confounding by smoking in the subcohort of workers hired after 1959.
25
26   **5.4.4. Exposure Adjustments and Extrapolation Methods**
27   The estimated exposures based on the JEM and work histories are discussed in
28   Section 5.4.2.5. Note that all potency estimates (i.e., KM or KL) presented with units of
29   fiber/cc-yr are for calendar year and not for occupational year, so no additional adjustment is
30   needed to address this difference as may have been found in other evaluations based on
31   occupational epidemiology cohort analyses. Adjustments for differences in breathing rates and
32   the number of hours of exposure in an occupational (8-hour) day as compared to a whole
33   (24-hour) day are not incorporated directly into the slope but rather applied in the derivation of
34   the central risk and unit risk estimates.

---

[29]Richardson (2010) cited literature with possible associations between asbestos and COPD which, if true, would
have explained a positive association among the Libby workers cohort but should not detract from the use of the
Richardson method as applied to these Libby workers, where a negative association is found.

1 **5.4.5. Inhalation Unit Risk (IUR) of Cancer Mortality**

2   The derivation of the unit risk estimates, defined as the lifetime risk of mortality from

3 either mesothelioma or lung cancer from chronic inhalation of LAA at a concentration of

4 1 fiber/cc of air, is presented in the following subsections.

5

6 **5.4.5.1. *Unit Risk Estimates for Mesothelioma Mortality***

7   Computational details of the methodology and tables for deriving the lifetime unit risk for

8 mesothelioma mortality are presented in Appendix G. For mesothelioma, the life-table

9 procedure involves applying the absolute rates of mesothelioma mortality estimated in the Libby

10 workers to the age-specific survival distribution of the general population to compute the

11 age-specific risks of mesothelioma mortality expected at specific LAA exposure concentrations.

12 The modeling analysis presented above showed that metrics including lag and half-life

13 parameters provided the best empirical fit to the Libby worker subcohort data. Although there is

14 uncertainty in applying these models for occupational mortality to estimate risks for different

15 exposure levels and time patterns (see Section 5.4.6), following the recommendations of the

16 *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a), a linear low-dose extrapolation

17 below the POD was used because the mode of action for LAA for mesothelioma is largely

18 unknown. Lifetime unit risk estimates from the Peto model and the Peto model with clearance

19 are presented in Table 5-48.

20

Table 5-48. Unit risks for the Peto model and Peto model with clearance

Model	Power	Decay	DIC	Central risk estimate	Unit risk
Peto with clearance	5.4	0.15	95.3	0.015	0.025
	3.9	0.068	95.4	0.035	0.058
Peto	3	No	98.4	0.117	0.191

21   The mesothelioma unit risks for model results presented in Table 5-39 and discussed in

22 Section 5.4.3.5 are presented in Table 5-49. All of the metrics in Table 5-49 are CE metrics

23 lagged 10−15 years (the fit of 20-year lag models was much worse because one of seven

24 mesothelioma deaths occurred before 20 years; lags longer than 15 years are possible, and this is

25 an uncertainty described in Section 5.4.6). Issues related to uncertainty in the choice of exposure

26 metric are described further in the section on the derivation of the combined IUR of

27 mesothelioma and lung cancer (see Section 5.4.5.3).

Table 5-49. Mesothelioma mortality exposure metrics unit risks for the subcohort hired after 1959

Exposure metric	Lag yr	DIC	Central risk estimate	Unit risk
CE—5-yr half-life	15	70.6	0.032	0.053
CE—5-yr half-life	10	72.8	0.054	0.088
CE—10-yr half-life	10	73.9	0.028	0.047
CE—10-yr half-life	15	74.0	0.020	0.032
CE—15-yr half-life	10	75.7	0.022	0.036
CE—15-yr half-life	15	76.1	0.017	0.027
CE—20-yr half-life	10	76.7	0.020	0.032
CE—20-yr half-life	15	77.2	0.015	0.025

1   **5.4.5.1.1. *Adjustment for mesothelioma underascertainment.*** For mesothelioma, the
2   undercounting of cases (underascertainment) is a particular concern given the limitations of the
3   ICD classification systems used prior to 1999. In practical terms, this means that some true
4   occurrences of mortality due to mesothelioma are missed on death certificates and in almost all
5   administrative databases such as the National Death Index. Even after the introduction of a
6   special ICD code for mesothelioma with the introduction of ICD-10 in 1999, detection rates are
7   still imperfect (Camidge et al., 2006; Pinheiro et al., 2004), and the reported numbers of cases
8   typically reflect an undercount of the true number.
9   Kopylev et al. (2011) reviewed the literature on this underascertainment and developed a
10 general methodology to account for the likely numbers of undocumented mesothelioma deaths
11 using the Libby worker cohort as an example. Because the analysis of mesothelioma mortality
12 was based on absolute risk, it was possible to compensate for mesothelioma underascertainment
13 in the Libby worker subcohort. Kopylev et al. (2011) considered analyses when mesothelioma
14 type (i.e., pleural and peritoneal) is unknown and when it is known. As the number of peritoneal
15 mesotheliomas is partially known in the Libby worker subcohort, the method for known
16 proportion of pleural and peritoneal mesothelioma deaths is briefly described here.
17   Selikoff and Seidman (1992) provided information on the likelihood that individuals who
18 have been diagnosed as having mesothelioma will have that disease recorded (in some field) on
19 their death certificate. Their results are based on histopathological analysis (Ribak et al., 1991)
20 of a very large cohort of insulators, with more than 450 mesothelioma cases. Despite medical
21 advances, diagnosis of mesothelioma is still very challenging, and histopathology is still a
22 standard diagnostic tool today (e.g., Mossman et al., 2013). Using their results on the most
23 common misdiagnoses of mesothelioma (mesothelioma diagnosed as lung, colon, and pancreatic
24 cancers; and conversely, other diseases misdiagnosed as mesothelioma) and likelihoods of
25 corresponding misdiagnoses, Kopylev et al. (2011) conducted a simulation study randomly

1   creating a new data set with the number of mesothelioma deaths simulated in the full Libby

2   cohort to match the Selikoff and Seidman (1992) results. That simulated data set included

3   24 mesothelioma cases that were obtained using the underascertainment estimate of 37% derived

4   from Selikoff and Seidman (1992). The full cohort was used for the simulation study because of

5   the larger number of mesothelioma cases and because limitations of exposure information is not

6   relevant for that analysis. Using the Poisson model and MCMC simulation similarly to that

7   described in Section 5.1.3.1, Kopylev et al. (2011) calculated the mean of underascertainment of

8   risk and its 90% confidence interval to be 1.39 and (0.80; 2.17).

9   This method to adjust for underascertainment was applied to the Libby workers

10   subcohort; mesothelioma mortality-adjusted unit risks are listed in Table 5-50.

11

Table 5-50. Mesothelioma unit risks for the subcohort hired after 1959 adjusted for underascertainment

Exposure metric	Lag yr	DIC	Adjusted central risk estimate	Adjusted unit risk
CE—5-yr half-life	15	70.6	0.044	0.074
CE—5-yr half-life	10	72.8	0.075	0.122
CE—10-yr half-life	10	73.9	0.039	0.065
CE—10-yr half-life	15	74.0	0.028	0.044
CE—15-yr half-life	10	75.7	0.031	0.050
CE—15-yr half-life	15	76.1	0.024	0.038
CE—20-yr half-life	10	76.7	0.028	0.044
CE—20-yr half-life	15	77.2	0.022	0.035

12   Similarly, for the subcohort data, the Peto model and the Peto model with clearance unit

13   risks are presented in Table 5-51.

Table 5-51. Mesothelioma unit risks for the subcohort hired after 1959 based on the Peto model and the Peto model with clearance adjusted for mesothelioma underascertainment

Model	Power	Decay %	DIC	Adjusted central risk estimate	Adjusted unit risk
Peto with clearance	5.4	0.15	95.3	0.021	0.035
	3.9	0.068	95.4	0.049	0.086
Peto	3	No	98.4	0.163	0.265

1 **5.4.5.2.** *Unit Risk Estimates for Lung Cancer Mortality*

2   Computational details of the methodology and tables for deriving the unit risk for lung

3   cancer mortality are presented in Appendix G. For lung cancer, the life-table procedure involves

4   application of the hazard rates of lung cancer mortality estimated in the Libby workers to the

5   age-specific background rates of lung cancer in the general population (accounting for the

6   age-specific survival distribution of the general population) to compute the age-specific risks of

7   lung cancer mortality expected at specific LAA exposure concentrations. Although there is

8   uncertainty in applying these models for occupational mortality to the estimation of risks for

9   different exposure levels and time patterns (see Section 5.4.6), following the recommendations

10 of the *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a), a linear low-dose

11 extrapolation below the POD was used because the mode of action for LAA for lung cancer is

12 undetermined. The nine exposure-response models shown in Table 5-45 all had reasonably

13 similar goodness of fits. No single model stands out as statistically superior; however, there is a

14 range of quality of fit within the set that could be considered adequate. The lung cancer

15 mortality unit risks are shown in Table 5-52.

16

**Table 5-52. Unit risks for subset of lung cancer models with lagged
exposures that yielded statistically significant model fit ($p < 0.05$) and
exposure metric fit ($p < 0.05$) to the epidemiologic data**

Exposure metric	Lag	AIC	Exposure p-value	Central risk estimate (based on EC_{01})	Unit risk (based on LEC_{01})
C—10-yr half-life	10	358.400	0.0009	0.0260	0.0389
CE—5-yr half-life	10	358.502	0.0010	0.0195	0.0293
CE—15-yr half-life	10	358.777	0.0015	0.0300	0.0455
CE—20-yr half-life	10	359.122	0.0022	0.0326	0.0501
CE—5-yr half-life	15	359.910	0.0032	0.0167	0.0260
CE—10-yr half-life	15	360.543	0.0079	0.0231	0.0375
CE	10	361.073	0.0188	0.0399	0.0679
CE—15-yr half-life	15	361.129	0.0162	0.0258	0.0434
CE—20-yr half-life	15	361.533	0.0254	0.0280	0.0486

LEC_{01} = 95% lower confidence limit of the exposure concentration associated with a 1% increased risk.

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 95%

19 lower confidence limit of the exposure concentration associated with a 1% increased risk

20 (LEC_{01}) yielded a lifetime unit risk of 0.0389 per fiber/cc. The value of the risk that would

1 correspond to the measure of central tendency involves EC_{01} rather than LEC_{01}. The EC_{01}

2 yielded a lifetime central estimate of 0.0260 per fiber/cc.

3 Using the results of the exposure model based on cumulative exposure with a 10-year lag

4 for cancer latency, the LEC_{01} for the adult-only exposures was determined to be 0.191 fiber/cc.

5 This LEC_{01} yielded a lifetime unit risk of 0.0679 per fiber/cc. The EC_{01} for the adult-only

6 exposures was determined to be 0.325 per fiber/cc. When divided into a POD of 1%, this EC_{01}

7 yielded a lifetime central estimate of 0.0399 per fiber/cc.

8 The resulting unit risks in Table 5-52 ranged from 0.0260 to 0.0679 per fiber/cc. This

9 shows that the unit risk (i.e., 0.0389 per fiber/cc) based on the exposure metric with the lowest

10 AIC value (i.e., cumulative exposure with a 10-year half-life for decay and a 10-year lag for

11 cancer latency) is in the center of this range, and is thus statistically robust. However, because

12 this estimate is in the middle of the range, it does not capture the uncertainty across metrics with

13 similar goodness of fit. As noted (see Section 5.4.3.6., an argument can be made that the CE

14 metric with a 10-year lag and no half-life is implicitly more parsimonious (simpler) because it

15 was not explicitly adjusted to include decay, although this metric is mathematically equivalent to

16 CE metric with a 10-year lag and an infinitely long decay half-life. Conceptually, the AIC

17 values are penalized for increased model complexity (thereby increasing the AIC). The CE

18 metric with a 10-year lag does fit these data—both statistically and by examination of the

19 residuals. Further, the CE metric is a simpler and more straightforward metric, and has an

20 extensive tradition of use in the epidemiologic literature and in the practice of risk assessment.

21

22 **5.4.5.3. *Inhalation Unit Risk (IUR) Derivation for Combined Mesothelioma and Lung Cancer***

23   ***Mortality***

24 For mesothelioma, the exposure-response models developed by EPA using personal

25 exposure data on the subcohort (see Table 5-50) provided better fit to the subcohort data than the

26 Peto model and the Peto model with clearance that have been proposed in the asbestos literature

27 (see Table 5-51). These variations of the Peto model have been shown to predict mesothelioma

28 mortality more precisely than the original Peto model in a large crocidolite-exposed cohort of

29 6,908 workers with 329 mesothelioma deaths from Wittenoom, Australia (Berry et al.,

30 2012)—specifically, the best fitting models for that cohort was the Peto model with a power

31 $k = 3.9$ and decay rate of $\lambda = 0.068$ (approximately 10-year half-life) and Peto model with a

32 power $k = 5.4$ and decay rate of $\lambda = 0.15$ (approximately 5-year half-life).

33 The exposure-response models developed by EPA using personal exposure data on the

34 subcohort (see Table 5-50) show estimated lifetime unit risks of 0.074 and 0.122 per fiber/cc.

35 The two Peto models with different clearances and powers of k show lifetime unit risks of 0.086

36 and 0.035 per fiber/cc, respectively (see Table 5-51). The results of the two different approaches

37 to modeling, the first based only on the LAA data and the second based on a much larger

38 population of workers exposed to another but different amphibole asbestos, reveal a relatively

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1   small degree of uncertainty in the derivation of the mesothelioma lifetime unit risk. Therefore,

2   EPA selected the model derived directly from the Libby data with the strong support of the

3   model that best fit the mesothelioma risk in a much larger cohort of amphibole-exposed workers.

4   EPA's selected model based on cumulative exposure with a 10-year lag and 5-year half-life

5   yielded a lifetime unit risk for mesothelioma of 0.122 per fiber/cc which encompasses other three

6   risk estimates. Table 5-53 shows the combined IUR for mesothelioma and lung cancer based on

7   the selected mesothelioma model, the two best-fitting mesothelioma models from the

8   epidemiologic literature (the Peto model with clearance), as well as the combined IUR based on

9   Peto model.

Table 5-53. Estimates of the combined central estimate of the unit risk for mesothelioma and lung cancer and the combined upper-bound lifetime unit risks for mesothelioma and lung cancer risks (the Inhalation Unit Risk) for different combination of mesothelioma and lung cancer models[a]

Lung cancer	Mesothelioma	Combined central estimate (per fiber/cc)	Combined upper bound (per fiber/cc)
Selected IUR based directly on the Libby data			
CE10 Subcohort	**CE10 5-yr half-life**	**0.115**	**0.169**
Best models from the epidemiologic literature (Peto model with clearance)			

CE10 Subcohort	Peto with clearance
	   Decay rate of 6.8%/yr
	   Power of time = 3.9
	   Subcohort
		0.089	0.135

CE10 Subcohort	Peto with clearance
	   Decay rate of 15%/yr
	   Power of time = 5.4
	   Subcohort
		0.061	0.092

Alternative model from the epidemiologic literature (Peto model)			

CE10 Subcohort	Peto
	   No decay
	   Power of time = 3
	   Subcohort
		0.203	0.308

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

For lung cancer, this assessment selected the upper bound among the lung cancer lifetime unit risks from the plausible exposure metrics (regardless of the small residual differences in quality of fit). Because there were few metrics with unit risks higher than the best fitting metric's unit risk for lung cancer mortality endpoint, this method effectively selects the highest lifetime unit risk among those considered for the lung cancer mortality endpoint. Based on the selected model for lung cancer mortality using the cumulative exposure with a 10-year lag in the Libby subcohort data yields a central unit risk estimate of 0.040 per fiber/cc and upper-bound lifetime unit risk of 0.0680 per fiber/cc.

Once the cancer-specific lifetime unit risks are selected, the two are then combined. It is important to note that this estimate of overall potency describes the risk of mortality from cancer at either of the considered sites and is not just the risk of both cancers simultaneously. Because each of the unit risks is itself an upper-bound estimate, summing such upper-bound estimates across mesothelioma and lung cancer mortality is likely to overpredict the overall risk. Therefore, following the recommendations of the *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a), a statistically appropriate upper bound on combined risk was derived in order to gain an understanding of the overall risk of mortality resulting from mesothelioma and from lung cancer.

Because the estimated risks for mesothelioma and lung cancer mortality were derived using Poisson and Cox proportional hazards models, respectively, it follows from statistical theory that each of these estimates of risk is approximately normally distributed. For independent normal random variables, a standard deviation for a sum is easily derived from individual standard deviations, which are estimated from confidence intervals: standard deviation = (unit risk – central risk) ÷ $Z_{0.95}$, where $Z_{0.95}$ is a standard normal quantile equal to 1.645. For normal random variables, the standard deviation of a sum is the square root of the sum of the squares of individual standard deviations.

As shown in Table 5-50, the upper bound of the selected mesothelioma mortality unit risks was 0.122 per fiber/cc (highest adjusted unit risk value). The associated central estimate of risk was 0.075 per fiber/cc for mesothelioma mortality. Table 5-52 shows the upper bound of the selected lung cancer mortality unit risk was 0.068 per fiber/cc (highest unit risk value based on LEC_{01}). The associated central estimate of risk was 0.040 per fiber/cc for lung cancer mortality.

It is important to mention here that the assumption of independence of the estimated risks for mesothelioma and lung cancer mortality (note above) is a theoretical assumption, as there is insufficient data on independence of mesothelioma and cancer risks for LAA. However, in a somewhat similar context of different tumors in animals, NRC (1994) stated: "…a general assumption of statistical independence of tumor-type occurrences within animals is not likely to introduce substantial error in assessing carcinogenic potency." To provide numerical bounding analysis of impact of this assumption, EPA used results of Chiu and Crump (2012) on the upper and lower limits on the ratio of the true probability of a tumor of any type and the corresponding

1   probability assuming independence of tumors. The lower limit is calculated by

2    $[1 - \min(p1,p2)]/(1 - p1 \times p2)$ and the upper limit is $\min(1,2 - p1 - p2)/(1 - p1 \times p2)$.

3   Substituting the risk of lung cancer ($p1$) is 0.040 and the risk of mesothelioma ($p2$) is 0.075, the

4   lower limit is 0.963 and the upper limit is 1.003. A value of 1.0 indicates independence.

5   Because lower and upper values are both very close to the value of 1.0, this demonstrates that the

6   assumption of independence in this case does not introduce substantial error, consistent with

7   what NRC (1994) has stated.

8   In order to combine the unit risks, first obtain an estimate of the standard deviation of the

9   sum of the individual unit risks as:

10

11   $$\sqrt{\left[\,[[(0.122 - 0.075) \div 1.645]^2 + (0.068 - 0.040) \div 1.645]^2\,\right]} = 0.033 \text{ per fiber/cc} \quad (5\text{-}15)$$

12

13   Then, the combined central estimate of risk of mortality from either mesothelioma or

14   lung cancer is $0.040 + 0.075 = 0.115$ per fiber/cc, and the combined IUR is

15   $0.115 + 0.033 \times 1.645 = 0.169$ per fibers/cc.

16   To illustrate the uncertainty in the selected IUR, Table 5-53 shows central risks and upper

17   bounds for the combined IUR for selected metrics for each cancer (CE10 for lung cancer and

18   CE10 with 5-year half-life for mesothelioma) and for selected lung cancer model (CE10) with

19   other mesothelioma models suggested in the literature from Tables 5-51. The selected IUR does

20   address issues of model uncertainty because a higher risk is only given by the Peto model, but

21   the Peto model tends to overestimate mortality from mesothelioma in asbestos cohorts with long

22   follow-up (e.g., Berry et al., 2012; Barone-Adesi et al., 2008).

23

24   *Age-dependent adjustment factor*

25   As discussed in Section 4.7.1.1, there is no chemical-specific information for LAA, or

26   general asbestos, that would allow for the computation of a chemical-specific age-dependent

27   adjustment factor for assessing the risk of exposure that include early-life exposures.

28   The review of mode-of-action information in this assessment (see Section 4.6.2.2)

29   concluded that the available information on the mode of action by which LAA causes lung

30   cancer or mesothelioma is complex and a mode of action is not established at this time. Thus, in

31   accordance with EPA's *Supplemental Guidance for Assessing Susceptibility from Early-Life*

32   *Exposure to Carcinogens* (U.S. EPA, 2005b), the application of the age-dependent adjustment

33   factors for substances that act through a mutagenic mode of action is not recommended.

34

35   **5.4.5.3.1. *Comparison with other published studies of Libby workers cohort.*** For lung cancer,

36   two alternative analytic approaches to the use of EPA's extended Cox proportional hazards

37   models are considered here for the calculation of a unit risk of lung cancer mortality. All of the

1   choices are based on different analyses of the Libby worker cohort; however, inclusion criteria

2   differ among the analyses as does the length of mortality follow-up. Each of the two alternative

3   approaches has two options to estimate the slope of the exposure-response relationship in place

4   of the regression slope estimated from the Cox proportional hazards model.

5   The first approach would be to use the published categorical results based on Sullivan

6   (2007), which offers two options: (1) estimate a slope to those categorical data or (2) use the

7   slope estimated in a published reanalysis of categorical data of the Sullivan (2007) cohort by

8   Berman and Crump (2008). The second approach would be to use the published regression

9   results of other researchers who modeled the underlying continuous data. There are two options

10   under this approach: (1) use the slope estimated by Larson et al. (2010b) or (2) use the slope

11   estimated by Moolgavkar et al. (2010).

12   For comparison purposes, the lung cancer unit risk from these alternatives is computed;

13   however, as all analyses are based upon different subsets of the Libby workers cohort and used

14   different analytic methods, the results are not necessarily interchangeable. Table 5-54

15   summarizes lung cancer risks derived from these studies.

16

Table 5-54. Lung cancer regression results from different analyses of cumulative exposure in the cohort of workers in Libby, MT. All analyses used NIOSH-collected exposure data but used different cohort definitions, lengths of follow-up, and lengths of exposure lags to account for cancer latency.

Lung cancer analysis	Cohort definition	Follow-up	Lung cancer cases/N	Slope per fiber/cc-yr $\times 10^{-3}$ (calendar yr)	Risk based on upper confidence limit (UCL) on the slope (per fiber/cc)
This current assessment	Hired post-1959 Exposures 1960−1982	2006	32/880	5.8	0.068
Sullivan (2007)	Still alive post-1959 White males Exposures 1960−1982	2001	99/1,672	4.2	0.037
Moolgavkar et al. (2010)[a]	Still alive post-1959 White males Exposures 1960−1982	2001	95/1,662	1.69	0.011
Berman and Crump (2008)[b]	Still alive post-1959 White males Exposures 1960−1982	2001	93/1,672	3.96	0.079
Larson et al. (2010b)	Full cohort Exposures 1935−1993	2006	98/1,862	1.61	0.010

[a]Reanalysis of Sullivan (2007).
[b]Sullivan (2007) and reanalysis of Sullivan (2007) state slightly different number of lung cancers. It is impossible to reconcile these numbers from published information.

1   The first alternative analytical approach to estimating the extra risk from a linear

2   regression of individual mortality data was to use a technique that is standard in EPA cancer risk

3   assessments (U.S. EPA, 2005a) when individual-level data are not available. This approach used

4   a weighted linear regression of standardized risk ratio (SRR) estimators for lung cancer mortality

5   in white males, as calculated in the NIOSH cohort analysis (Sullivan, 2007), with categorical

6   cumulative exposure and a 15-year lag. The Sullivan (2007) analysis was based only on those

7   workers who had not died or been lost to follow-up before January 1, 1960 (in contrast to

8   employment beginning after January 1, 1960), because the NIOSH software program (Life-Table

9   Analysis System) used for this analysis only has statistics on external comparison rates for

10   asbestosis (one of the primary outcomes of interest in the Sullivan (2007) analysis) beginning in

11   1960. The SRR analysis involves internal comparisons of lung cancer mortality rates in the

12   higher exposure categories to the lung cancer mortality rates in the lowest exposure category.

13   The weights used for the SRRs were the inverses of the variances. Midpoints of the exposure

14   intervals were used, and for the unbounded interval, the midpoint was assumed to be twice the

15   starting point of that interval.

16   Using this approach, a regression coefficient of 4.2×10^{-3} per fibers/cc-yr (standard error

17   [SE] $= 7.7 \times 10^{-4}$ per fibers/cc-yr, $p = 0.03$) was obtained from the weighted linear regression of

18   the categorical SRR results. Because the data from Sullivan (2007) were already adjusted for the

19   length of an occupational year (240 days) to the length of a calendar year (365 days), only the

20   standard adjustment for inhaled air volume was performed. The concentration estimate obtained

21   using this regression modeling and the life-table analysis procedure was $LEC_{01} = 0.272$ fiber/cc,

22   resulting in the lung cancer unit risk of 0.0368 per fiber/cc.

23   The Berman and Crump (2008) reanalysis was based on the Sullivan (2007) summary

24   results except the authors used a lag of 10 years (personal communication with Sullivan in 2008

25   as cited by Berman and Crump [2008]). They fit the IRIS IUR (U.S. EPA, 1988a) lung cancer

26   model to aggregate data using an extra multiplicative parameter α. In this model, the relative

27   risk at zero exposure is α rather than 1 (unity). With $\alpha = 1$, their model did not fit, and with α

28   estimated, the fit was satisfactory. Berman and Crump (2008) chose the central estimate of the

29   slope from the fit with α estimated, but constructed an "informal" 90% confidence interval by the

30   union of two confidence intervals (this upper bound is shown in Table 5-54). This was done to

31   address uncertainty in the estimated parameter α, similar to what is done in this current

32   assessment with estimated lag and decay. Note also that Berman and Crump (2008) provided a

33   UF to adjust for several sources of uncertainty in exposures, resulting in an upper-bound risk of

34   0.3162.

35   The second alternative analytic approach to estimating the extra risk of lung cancer from

36   a Cox regression with time-dependent covariates of individual mortality data was to use the

37   results published by Larson et al. (2010b), with cumulative exposure and a 20-year lag. This

38   analysis of lung cancer mortality was based on the full cohort of 1,862 workers, updated until

1　2006 and using the same model form as the current EPA analysis (the extended Cox proportional

2　hazards model). Larson et al. (2010b) reported a regression coefficient of 1.06×10^{-3} per

3　fibers/cc-yr (SE = 3.1×10^{-4} per fibers/cc-yr, p = 0.0006).[30] EPA assumed that the cumulative

4　exposures reported by Larson et al. (2010b) were based on years of occupational exposure

5　(240 days per year) during a 365-day calendar year. In order to account for exposure on every

6　day of the year for a calculation of unit risk, an adjustment for exposures during the length of an

7　occupational year (240 days) to the length of an calendar year (365 days) and an adjustment for

8　the volume of inhaled air were performed to match EPA's analyses. The concentration estimate

9　obtained using the Larson et al. (2010b) regression modeling and the life-table analysis

10　procedure was LEC$_{01}$ = 1.26 fibers/cc, resulting in a lung cancer unit risk of 0.0103 per fiber/cc.

11　　　　Moolgavkar et al. (2010) also used the Cox proportional hazards model with

12　time-dependent covariates for analysis of the Sullivan (2007) cohort with a 15-year lag. The

13　parameter in this study estimates 1.11×10^{-3} per fibers/cc-yr (SE = 2.5×10^{-4} per fibers/cc-yr),

14　which is very close to the Larson et al. (2010b) value, and therefore, the lung cancer unit risk

15　based on their analysis would be very close to the Larson et al. (2010b) value. Comparison with

16　McDonald et al. (2004) is difficult because in that articleoutcome is defined as respiratory cancer

17　(ICD-9 160−165), which is more expansive than other researchers' definitions of the outcome as

18　lung cancer, and their subcohort of 406 white men employed before 1963—a time period when

19　exposure assessment was less reliable and more likely to include significant

20　exposure-measurement error. Nonetheless, the parameter estimate resulting from the Poisson

21　analysis by McDonald et al. (2004) was 3.6×10^{-3} per fibers/cc-yr.

22　　　　The differences in the results in Table 5-54 appear to be mostly attributable to the time

23　periods of analysis and various degrees of exposure measurement error corresponding to these

24　time periods rather than the analytic approach. EPA based their analyses on the exposures that

25　occurred after 1959, while the Sullivan (2007), Larson et al. (2010b), and Moolgavkar et al.

26　(2010) analyses were based on the cohort including those hired before 1960, and McDonald et al.

27　(2004) included only workers hired before 1964. The small discrepancy between observed lung

28　cancer deaths between this current assessment and Larson et al. (2010b), described in

29　Section 4.1.1.1, is unlikely to play a role in the difference among risk estimates. Moreover, for

30　the subcohort hired after 1959, all deaths are included in the Larson et al. (2010b) lung cancer

31　counting rules.

32　　　　As explained in detail in the discussion on uncertainty in the exposure assessment (see

33　Section 5.4.6), there were only several measurements from the 1950s and one from 1942, and

34　most of the exposure estimation for the early years of the cohort's experience was based on

35　estimates of the ratio of dust to fibers estimated in the late 1960s and extrapolated backwards in

---

[30]Note that EPA results based on the subcohort hired after 1959 were from the same model form but based on the cumulative exposure with a 10-year lag and had a slope of 5.81×10^{-3} per fiber/cc-yr (SE = 2.48×10^{-3} per fiber/cc-yr, p = 0.018).

1   time for several decades. Moreover, 706 of the workers hired before 1960 (not necessarily short-

2   term workers) did not have an exposure measurement assigned to them at all, leading to a much

3   larger measurement error. These limitations in the underlying exposure assessment for the years

4   before 1968 likely resulted in exposure measurement error that could have attenuated the

5   analytic regression results (see the discussion in Lenters et al. (2012; 2011) on the impact the

6   quality of the exposure information has on estimates of dose-response; also Bateson and Kopylev

7   (2014)), thereby yielding a smaller effect estimate for the whole cohort compared to the

8   subcohort hired after 1959.

9   None of the approaches used by McDonald et al. (2004), Sullivan (2007), or Larson et al.

10   (2010b) could have been appropriately used for the unit risk of mesothelioma because these

11   approaches are not based on absolute risk metrics of association, which the current assessment

12   considered to be the relevant metric of association. Berman and Crump (2008) did not evaluate

13   the risk of mesothelioma. Moolgavkar et al. (2010) used an absolute risk model for

14   mesothelioma. These results are summarized in Table 5-55. The upper-bound results for the full

15   cohort presented by Moolgavkar et al. (2010) are about 80% of the U.S. EPA (1988a) estimate of

16   the mesothelioma slope factor, leading to an approximately 80% estimate of the mesothelioma

17   unit risk as dependence is linear in the mesothelioma slope factor (see eq 5-11). This is very

18   close to the current assessment's estimate based on the subcohort, which is also about 80% of the

19   U.S. EPA (1988a) estimate of mesothelioma risk. Duration of exposure, but neither department

20   code nor job category, was known for 706 of 991 (71%) workers hired from 1935 to 1959.

21   Because of that limitation, duration of employment is the best metric for the full cohort, and it

22   does not support exposure-response estimation.

Table 5-55. Mesothelioma analysis results from different analyses of cumulative exposure in the Libby workers cohort. All analyses used NIOSH-collected exposure data but different cohort definitions, lengths of follow-up, and lengths of exposure lags to account for cancer latency.

Mesothelioma analysis	Cohort definition	Follow-up	Mesothelioma cases/*N*	Mesothelioma risk (absolute risk model) (per fiber/cc)
This current assessment	Hired post-1959 Exposures 1960−1982	2006	7/880	Upper Bound = 0.122 Central = 0.075
Sullivan (2007)	Still employed post-1959 White males Exposures 1960−1982	2001	15/1,672	No estimates of absolute risk
Moolgavkar et al. (2010)[a]	Still employed post-1959 White males Exposures 1960−1982	2001	15/1,662	Upper Bound ≈ 0.13 Central ≈ 0.08
Larson et al. (2010b)	Full cohort Exposures 1935−1993	2006	19/1,862	No estimates of absolute risk
Berman and Crump (2008)[a]	Still employed post-1959 White males Exposures 1960−1982	2001	15/1,672	No estimates provided

[a]Reanalysis of Sullivan (2007).

5.4.6. Uncertainties in the Cancer Risk Values

Uncertainties in the derivation of the IUR are important to consider. This assessment does not involve extrapolation from high doses in animals to low doses in humans. It is based on a well-documented and well-studied cohort of workers with adequate years of follow-up to evaluate mesothelioma and lung cancer mortality risks with PODs within the range of the data. The discussions below explore uncertainty in the derivation of the IUR to provide a comprehensive and transparent context for the resulting cancer mortality risk estimates.

5.4.6.1. *Sources of Uncertainty*

Sources of uncertainty in this assessment include:

1) Uncertainty in low-dose extrapolation,

2) Uncertainty in exposure assessment, including analytical measurements uncertainty,

3) Uncertainty in model form,

4) Uncertainty in selection of exposure metric,

5) Uncertainty in assessing mortality corresponding to other cancer endpoints,

6) *Uncertainty in control of potential confounding in modeling lung cancer mortality,*

7) *Uncertainty due to potential effect modification,*

8) *Uncertainty due to length of follow-up,*

9) *Uncertainty in use of life tables to calculate cancer mortality inhalation unit risks,*

10) *Uncertainty in combining of risks to derive a composite cancer inhalation unit risk (IUR), and*

11) *Uncertainty in extrapolation of findings in adults to children.*

5.4.6.1.1. *Uncertainty in low-dose extrapolation.* A common source of uncertainty in quantitative cancer risk assessments generally derives from extrapolating from high doses in animals to low doses in humans. Compared to assessments based on animal data, the uncertainty from low-dose extrapolation in this assessment, which uses occupational epidemiology data, is considered to be lower for the following reasons. The NIOSH worker cohort developed by Sullivan (2007) includes 410 workers employed less than 1 year among the 880 workers hired on or after January 1, 1960. Although short-term workers on average experience a mean exposure intensity per day worked greater than workers employed more than a year (Sullivan, 2007), the cohort nevertheless includes many short-term workers with relatively low cumulative occupational exposures. Further, inclusion of salaried workers in the NIOSH cohort (Sullivan, 2007) adds many workers with lower workplace exposure. Thus, while occupational exposure concentrations may be generally higher than typical ongoing environmental concentrations, the low-dose exposures in this occupational database may be more representative of nonoccupational exposures.

While many occupational epidemiology studies are based on relatively high exposure levels that are beyond the range of common environmental exposures, many in the Libby worker cohort experienced exposures that were near or below the PODs derived from the life-table analysis (i.e., the estimated PODs are in the range of the observed data). The POD for the selected lung cancer mortality exposure metric was 0.191 fiber/cc. The POD for the selected mesothelioma mortality exposure metric was 0.106 fiber/cc. Among the workers hired after 1959 who had at least 1 year of occupational exposure (*n* = 470; 20 lung cancer deaths), there were 19 (4%) with average occupational exposure concentrations of less than 0.3 fiber/cc, including one lung cancer death (5%).

Although data might have been modeled down to a very low cumulative exposure level, the *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a) recommends defining a POD for low-dose extrapolation to increase the stability of the IUR estimate at lower exposures where fewer cancers might be expected. Thus, the uncertainty associated with low-dose extrapolation is somewhat mitigated because the linear extrapolation from the dose associated with the POD

1   from the life-table analyses of each cancer endpoint was encompassed within the observed data

2   range. Nonetheless, some uncertainty remains in the extrapolation from occupational exposures

3   to lower environmental exposures when using a POD.

4

5   **5.4.6.1.2. *Uncertainty in exposure assessment.*** Accurate exposure assessment is generally

6   considered to be a major challenge for occupational epidemiologic studies and is a challenge

7   well recognized by the NIOSH investigators (Amandus et al., 1987b). As stated previously in

8   Section 5.4.3.3, while it is generally true that the use of more data is an advantage in statistical

9   analyses because it allows for the computation of more statistically precise effect estimates, this

10   advantage in precision may be offset by a negative impact on the accuracy of the effect estimate

11   if an increase in sample size is accompanied by greater exposure misclassification or other

12   biases. In this case, EPA decided to base this LAA-specific human health risk assessment upon

13   the mortality experience of workers hired on or after January 1, 1960. EPA's use of the

14   subcohort analysis is based on the belief that it is important to accurately estimate the true

15   underlying exposure-response relationships by relying on the most accurate exposure data. The

16   use of this subcohort greatly reduces the uncertainty in exposure error compared to evaluations

17   based on the full cohort. More specifically:

18

19   a) Job category and department codes were completely unknown for 706 of the
20   991 workers' jobs from 1935 to 1959 (71% of the cohort for this time period). These
21   workers were assigned by Sullivan (2007) the same exposure concentration
22   (66.5 fibers/cc) for all years without this information. Examination of the post-1959
23   cohort removes this significant source of exposure misclassification (only 9 of
24   880 subcohort workers did not have department code and job category information).

25   b) Using the more recently hired cohort minimizes the uncertainty in estimated worker
26   exposures based on the JEM, which was informed by air sampling data available in
27   1956 and later years. Although uncertainties still exist in the task-specific exposure
28   estimates from 1960−1967, uncertainty in the assessment of earlier exposure levels is
29   considerably greater.

30   c) Exposure measurements were collected from the area samples and represented
31   exposures for all the workers with the same job code. Statistically, this causes the
32   Berkson measurement error effect, which is described later in this section.
33

34   As EPA exposure-response modeling for mesothelioma and lung cancer mortality is

35   based on the post-1959 subcohort, the remaining discussion of uncertainty in exposure

36   measurement will address these data.

37

38   **5.4.6.1.2.1. *Sources of uncertainty in job history information.*** Worker exposures for EPA

39   exposure-response modeling were calculated based on job histories and the JEM from 1960

40   through 1982 (see Figure 5-5). Overall, there is little uncertainty in the job history information.

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1   Regarding exposure estimation for the occupational cohort, the NIOSH investigators (Amandus
2   et al., 1987b) conducted a detailed retrospective exposure assessment to estimate the individual
3   worker exposures. NIOSH used extensive occupational exposure data to construct the
4   time-specific JEM, spanning decades (Amandus et al., 1987b). These data were reabstracted
5   from the workers' employment records for quality assurance (Sullivan, 2007). NIOSH records
6   on work histories and job-specific exposure extended from the 1930s through May 1982.
7   However, the vermiculite mining and milling operation continued on for several years, and some
8   workers were retained through 1993 for plant close-out activities. Only 148 members of the
9   post-1959 cohort ($n = 880$) were employed as of the May 1982 employment records when the
10   cohort was enumerated by NIOSH (Sullivan, 2007). Because exposure concentrations in 1982
11   (see Table 5-21) were generally below 1 fiber/cc with only two locations having concentrations
12   of 1.2 fibers/cc, it is unlikely that these workers' exposures were significantly underestimated.
13
14   *Sources of uncertainty in exposure intensity for the identified location operations*
15   The available exposure data that inform the JEM include over 4,000 air samples, the
16   majority of which were collected after 1967 (see Table 4-1). All of the job location exposure
17   estimates (see Table 5-21) from 1968−1982 were directly informed from air samples collected
18   on membrane filters and analyzed for fibers by PCM. The availability of site-and task-specific
19   air samples for these years provides a good basis for the exposure estimates. However, some
20   uncertainties exist in estimating asbestos exposures using air samples analyzed by PCM.
21

22   1) PCM analysis does not determine the mineral or chemical make-up of the fiber: The
23   PCM method defines and counts fibers based on the size (length, width, and aspect
24   ratio) of the particle without regard for the material that makes up the particle being
25   viewed. The PCM method was developed for use in occupational environments
26   where asbestos was present, and the nature of the fibers should be further evaluated to
27   confirm the fibers viewed under PCM are asbestos. McGill University researchers
28   evaluated the fibers collected on membrane filters in the early 1980s and confirmed
29   the presence of asbestos fibers in the tremolite-actinolite solution series consistent
30   with the LAA (McDonald et al., 1986a). NIOSH researchers confirmed the presence
31   of tremolite asbestos in bulk dust samples but not in air samples from the facility
32   (Amandus et al., 1987b). Although less specific to fibers, 60−80% of the airborne
33   dust in the mills in 1968 was tremolite, further supporting the presence of asbestos in
34   the air (based on State of Montana air sampling, and x-ray diffraction analysis by the
35   Public Health Service [correspondence, October 17, 1968]). However, although the
36   presence of mineral fibers in the actinolite-tremolite series was confirmed in the work
37   environment, it is possible that fibers were also counted by PCM from other materials
38   (such as textiles from clothes and packaging materials). Therefore, it is unknown
39   from these data what proportion of the counted PCM fibers were mineralogically
40   asbestos and what proportion were other materials present in the air workplace.

41   2) PCM defines fibers as particles with an aspect ratio of 3:1 or greater. There is an
42   ongoing debate in the literature on asbestos toxicity regarding the influence of aspect

ratio on relative toxicity. Specifically, in mining environments, it has been speculated that a larger proportion of low aspect ratio fibers from mineral dusts may significantly impact the apparent cancer potency of the measured PCM fibers in those environments (Berman, 2010; U.S. EPA, 1988a). Few data are available to understand fiber morphology and fiber aspect ratios in the Libby cohort working environment. Considering the post-1959 cohort, PCM fiber size distribution and aspect ratio data only exist for a set of eight air samples (599 fibers) collected from the wet mill and screening operations and analyzed by the NIOSH researchers (Amandus et al., 1987b). For these air samples, over 96% of the fibers viewed by PCM had an aspect ratio greater than 10:1 (see Table 4-2) (Amandus et al., 1987b).[31.] However, because these samples were provided by the company in the early 1980s, they do not represent conditions in the old wet mill or dry mill operations, which were significantly dustier environments (Amandus et al., 1987b). It is possible that prior to IH modifications in 1974, the dry and old wet mills generated proportionally more mineral dusts than the screening plant and new wet mill operations after IH modifications. No data are available for the mining environment, which would also be expected to generate a range of mineral dusts. Therefore, there is a significant uncertainty about the size and aspect ratio of fibers included in PCM fiber counts for the majority of the post-1960 workers cohort, but it is not possible to judge the direction or magnitude of such uncertainty.

3) The resolution of visible PCM fibers: Current analytical instruments used for PCM analysis have resulted in a standardization of minimum fiber width considered visible by PCM between 0.2 and 0.25 µm. Historical PCM analysis (1960s and early 1970s) generally had less resolution, and fibers with minimum widths of 0.4 or 0.44 µm were considered visible by PCM (Amandus et al., 1987b; Rendall and Skikne, 1980). McDonald et al. (1986a) compared fibers viewed by PCM and TEM and estimated that approximately one-third of the total fibers could be viewed by PCM. Because 38% of the fibers were <5 µm in length, this implies approximately 30% were not viewable by optical microscopy for other reasons, such as width. However, it is unknown what proportion of that 30% would be viewed with the minimum width resolution of 0.25 µm for later optical microscopy. It is likely that early PCM counts were underestimated relative to the later data for the cohort but by less than a factor of 2.

Before 1968, no air sampling data were available for 23 of the 25 job location operations (see Table 4-2), and the exposure estimates were extrapolated from later air sampling data. Amandus et al. (1987b) recognized there was significant uncertainty in the extrapolation of available air sampling data to previous time periods. The researchers considered major changes in operations and interviewed employees in the early 1980s regarding previous years of operation. The assumptions used to make these extrapolations are clearly stated for each of the plant operations. For four operations, high and low estimates of pre-1968 exposures were

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[31]Although Amandus et al. (1987b) report the sizing of PCM fibers, the details of the methodology are not given regarding how these fibers were identified. No method is cited, and it is unclear if the sizing was done by PCM or TEM for fibers in the reported size categories.

1   provided based on different sets of exposure assumptions (see Table 5-21). For ore loading,

2   there were negligible differences in the exposure estimates for the period from 1960−1967 (10.7

3   versus 9 fibers/cc). For drilling, the river dock, and the bagging plant, there were 3.4-, 2.6-, and

4   2.8-fold differences, respectively, between the high and low estimates of exposure between 1960

5   and 1968.

6   Dry mill exposures between 1960 and 1968 were informed by air sampling for total dust

7   collected in the dry mill facility from 1956−1969 (where total dust was collected by midget

8   impingers). Amandus et al. (1987b) derived a conversion factor of 4.0 fibers/cc per mppcf to

9   apply to the two location operations in the dry mill during these years. A range of conversion

10 factors was considered for the dry mill depending on how the dust and fiber air samples (PCM)

11 were grouped and averaged (1.2 to 11.5 fibers/cc per mppcf). A subset of dust and fiber samples

12 available over the same time period (1967−1968) resulted in a ratio of 8.0 fibers/cc per mppcf.

13 In contrast, a ratio of 1.9 fibers/cc resulted when total dust samples from 1969 were compared

14 with fiber samples from 1970. However, both of these subsets had limited numbers of samples

15 available. Therefore, the conversion factor of 4.0 fibers/cc per mppcf was selected based on

16 using the maximum samples available over a time period when the dry mill exposures were

17 considered similar: dust samples (1965−1969) and fiber samples (1967−1971).

18

19 **5.4.6.1.2.2.** *__Sources of uncertainty in the calculation of the job-exposure matrix (JEM).__* The

20 exposures in the JEM (see Figure 5-5) were calculated from the exposure intensities of the

21 various task-specific exposure intensities shown by job location operation (see Table 5-21). The

22 uncertainties in the exposure intensity for the job location operations will impact the JEM.

23 Additionally, for each of the job categories in the JEM, NIOSH researchers defined which tasks

24 (job location operations) were conducted and for what proportion of the work day. A TWA

25 exposure for each job category across time was calculated based upon these assumptions and the

26 task-specific exposure estimates. There is a measure of uncertainty in these assumptions for

27 each job category. Additionally, there is interindividual variation within the job categories.

28 These uncertainties are common to exposure reconstruction for epidemiological cohorts.

29

30 **5.4.6.1.2.3.** *__Uncertainty in the exposure metric.__* The PCM measurement is the available

31 exposure metric for analysis of the Libby worker cohort at this time. Currently, there is no

32 optimal choice of the best dose metric for asbestos, in general, and for LAA, in particular.

33 Uncertainties related to PCM analytical method are discussed in Section 2. Briefly, PCM cannot

34 distinguish between asbestos and nonasbestos material or differentiate among specific types of

35 asbestos. Further, due to limitations of this methodology, PCM does not take into account fibers

36 shorter than 5 μm in length.

1   **5.4.6.1.2.4.** ***Evaluation of the effects of uncertainties in exposure measurement.*** An

2   understanding of the effects of exposure measurement error on the risks estimated from

3   epidemiologic analyses is important to place these possible exposure measurement errors in

4   context. The effect of exposure measurement error on estimates of the risk of mesothelioma or

5   lung cancer mortality attributable to exposure depends upon the degree to which that error may

6   be related to the likelihood of the outcome of interest (mesothelioma or lung cancer mortality).

7   Exposure measurement error that is similar among workers who died of lung cancer, and those

8   who did not die of lung cancer, is termed nondifferential exposure measurement error. Exposure

9   measurement error that is associated with the outcome (error that is differential with respect to

10   disease status) can cause bias in an effect estimate towards or away from the null, while

11   nondifferential exposure error typically results in bias towards the null (Rothman and Greenland,

12   1998). From the above evaluation of uncertainties, there is no indication that the uncertainties in

13   job history information, exposure estimates for specific tasks, or calculation of the JEM would be

14   differential based on the cancer health outcome data. Therefore, these uncertainties are

15   considered unrelated to disease status and the general result is likely to be an attenuation in risk

16   estimates towards the null (i.e., the addition of random noise to a clear signal tends to reduce the

17   clarity of the observed signal, and the avoidance of random noise results in a stronger observed

18   signal).

19   Generally speaking, if the exposure concentrations estimated by NIOSH were

20   systematically too high, then the associated risks of exposure estimated in the regression analysis

21   would be low because the same actual risk would be spread across a larger magnitude of

22   exposure. Similarly, if the exposure concentrations estimated by NIOSH were systematically too

23   low, then the associated risks of exposure estimated in the regression analysis would be too high.

24   From the above evaluation, the majority of the sources of uncertainty are not systematic. There

25   are a few areas of uncertainty that may be classified as biased:

26

27   1) High- and low-exposure estimates for four job location operations were provided
28   between 1960 and 1967. Amandus et al. (1987b) chose the high estimates of
29   exposure for these job location operations when calculating the JEM. Therefore,
30   there will be a bias towards the high end for the job categories informed by these
31   data. There was a 1.1- to 3.4-fold difference between the high and low estimates.
32   This difference will be less pronounced where these exposure concentrations are
33   averaged with other job location operations in the JEM, and across multiple jobs (as
34   was the case for the majority of the workers; see Figure 5-5).

35   2) Current PCM analysis would count more fibers relative to early PCM methods based
36   on minimum fiber width resolution. For example, Amandus et al. (1987b) used a
37   minimum width cutoff of 0.44 µm in their review of PCM fibers in the 1980s, which
38   may have resulted in as much as a twofold underestimate compared to current PCM
39   methods with a width resolution of 0.25 µm or less. Additionally, as PCM
40   methodology has developed over time, it is unknown when PCM results from

company records would be considered relatively standard to a minimum width resolution between 0.2 and 0.25 µm. Also, prior to standardization of PCM to 0.25-µm minimum width, there was interlaboratory variability as well. Therefore, the size distribution of PCM fibers (e.g., minimum width) reported in the JEM may have changed over time. Although theoretically a systematic bias, given the years for which PCM data are available, this is likely an insignificant effect.

3) Asbestos was a contaminant of vermiculite that was the primary object of production. Mine, old dry mill, and wet mill ambient air may have contained material other than asbestos that could have contributed to PCM fiber count. The exposures in the old dry and wet mills and mine location may have included a greater proportion of dust to fibers than tasks using the ore and refined vermiculite after the new wet mill became operational. It is possible there is a systematic overcount of fibers in the dusty environment due to interference from nonmineral fragments. This likely affects the exposure intensity for 23 of 25 job location operations within the mine and old dry mill. Estimated exposures from job categories that include these operations may be biased upwards.

Nondifferential measurement error in a continuous exposure can be of the classical or Berkson type and typically arises in environmental and occupational settings as a mixture of the two forms (Zeger et al., 2000). Classical measurement error occurs when true exposures are measured with additive error (Carroll et al., 2006) and the average of many replicate measurements, conditional on the true value, equals the true exposure (Armstrong, 1998). This error is statistically independent of the true exposure being measured and attenuates true linear effects of exposure, resulting in effect estimates in epidemiologic studies that are biased towards the null (Heid et al., 2004; Zeger et al., 2000; Armstrong, 1998). Such errors occur, for example, when the mean values of multiple local air samples are used.

Berkson measurement error is independent of the surrogate measure of exposure (Heid et al., 2004; Berkson, 1950) and is present when the average of individuals' true exposures, conditional on the assigned measurement, equals the assigned measurement. Berkson measurement error can arise from the use of local area mean sampled exposures to represent the individual exposures of people in that area—even when the estimated area mean is equal to the true underlying mean (i.e., no classical measurement error). Examples of random variability in personal behavior that may produce Berkson measurement error in personal exposure estimates include the volume of air breathed per day among the workers and the effectiveness of an individual's nasal filtration at removing contaminants. In general, Berkson measurement error is not thought to bias effect estimates but rather increases their standard errors (Zeger et al., 2000). However, some epidemiologic studies have suggested that Berkson measurement error can produce a quantitatively small bias towards the null in some analyses (Bateson and Wright, 2010; Kim et al., 2006; Reeves et al., 1998; Burr, 1988). Uncertainties in the levels and time course of asbestos exposure for the Libby workers also adds uncertainty in evaluating the relative fit of different exposure metrics.

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1   **5.4.6.1.2.5.** *Exposure to other kinds of asbestos and residential exposure.* Another source of

2   uncertainty in the estimation of exposures in the Libby workers cohort is the potential

3   contribution of nonoccupational or residential exposures as well as exposures to other kinds of

4   asbestos in employment before or after working in Libby.

5   Many of the workers resided in Libby, MT before and/or after their employment at the

6   mining and milling facilities ended. The vermiculite from the mine had been used at numerous

7   sites around the town including baseball fields around the expansion plant, high- and

8   middle-school tracks, attic and wall insulation in homes, and as a soil amendment in gardens

9   (U.S. EPA, 2010a, 2001). Exposure to asbestos could have occurred among individuals outside

10 of the workplace, particularly through activities with the potential of stirring up soil or other

11 materials that had been mixed with the vermiculite (Weis, 2001). The results of community

12 sampling indicated that even 10 years after mill operations ceased, asbestos fiber concentrations

13 in the air could exceed OSHA standards established for the protection of workers during some

14 activities (Weis, 2001).

15   Therefore, the workers' actual personal exposures as the sum of occupational and

16 nonoccupational exposures are likely to have been underestimated by the use of estimated

17 Libby-related occupational exposure alone. The difficulty stems from the lack of data on

18 residential exposures and lack of information on pre- and postemployment residence of the

19 Libby workers. Nonoccupational exposures were likely to have been smaller in magnitude than

20 the occupational exposures, but workers may have lived in and around Libby, MT for many

21 more years than they were exposed occupationally. The effect of residential exposure could be

22 more prominent for workers with lower occupational exposure who resided in Libby for a long

23 time. Whitehouse et al. (2008) has reported several cases of mesothelioma among residents of

24 the Libby, MT region who were not occupationally exposed. However, because the report by

25 Whitehouse et al. (2008) details only the cases and does not define or enumerate the population

26 from which those cases were derived, computed relative risks from nonoccupational exposures

27 were not available. ATSDR (2000) reported higher relative risks of mesothelioma among the

28 population of Libby, MT, including former workers residing in Libby, but did not provide

29 relative risk for nonoccupational exposure. Instead, the ATSDR report on mortality ATSDR

30 (2000) grouped cases among the former workers with nonoccupationally exposed cases.

31 Therefore, it is not clear what the magnitude of the contribution of workers' nonoccupational

32 exposures was to their overall risk.

33   Some of the occupational workers with lower exposures, such as short-term workers, may

34 have either been high school or college students working during the summer or may have been

35 transient workers who may not have stayed for a long time in Libby. It is interesting to note that

36 the lung cancer rates by age at first exposure show very low rates for those first exposed before

37 age 25 (see Table 5-42). Sullivan (2007) analyzed differences between short- and long-term

38 workers and reported little difference among the groups except for age at hire. As the short-term

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1   workers were younger on average, this supported the suggestions that some of the short-term
2   workers may have been college students working during the summer. This population of
3   short-term workers is not well defined; however, while it is possible that short-term transient
4   workers could potentially have been exposed to other kinds of asbestos or other lung carcinogens
5   in their non-Libby occupational career, which might have affected their pre- and post-Libby risk
6   profile for asbestos exposure, lung cancer rates for those with less than 1 year of exposure are in
7   line with those with less than 5 years of exposure (see Table 5-27). While their occupational
8   histories other than working in Libby are unknown, it is very unlikely that they include
9   exposures of the magnitude that were encountered in the Libby mine and mill. The impact of
10 these uncertainties on regression slopes is difficult to evaluate. However, the slope may be
11 somewhat underestimated, as an observed increase in risk would be attributed to a larger
12 exposure differential than might have been present due to the addition of nonoccupational
13 exposures. There will also be a downward bias from random exposure measurement error with
14 lower occupational exposure affected disproportionately; however, the magnitude of this bias
15 would be expected to be small.
16
17 **5.4.6.1.2.6. _Conclusion regarding uncertainty in exposure assessment._** Overall, there are
18 likely to be multiple sources of uncertainty attributable to exposure measurement error. It is
19 possible that systematic error may have been introduced into the exposure intensities assigned to
20 several of the job location operations discussed above. In each case, these errors in estimating
21 exposures were overestimates, which in general, might lead to underestimations of risk for lung
22 cancer, but the results are unclear for the risk of mesothelioma. The magnitude of the potential
23 overestimates of drilling and dry and old wet mill exposures is uncertain. The dust-to-fiber
24 conversion ratio applied to the dry mill during 1960−1967 could be an over- or underestimate by
25 as much as twofold, as Amandus et al. (1987b) derived a conversion factor of 4.0 fibers/cc per
26 mppcf, but subsequent samples available during 1967−1968 resulted in a ratio of 8.0 fibers/cc
27 per mppcf, while samples from 1970 yielded a ratio of 1.9 fibers/cc. Random error in the
28 measurement of dust or fibers would likely have produced an underestimation of risk. There is
29 no known bias in the assumptions to extrapolate exposure to pre-1968 location operations
30 outside of the dry mill, and random bias would also likely have produced an underestimation of
31 risk.
32

1 **5.4.6.1.3.** *Uncertainty in model form.* For mesothelioma mortality, the Poisson model is
2 commonly used for rare outcomes and has been applied by McDonald et al. (2004) to model
3 mesothelioma risk in the Libby worker cohort. For lung cancer mortality, the Cox proportional
4 hazards model is a well-established method that is commonly used in cohort studies, including
5 by Larson et al. (2010b) and Moolgavkar et al. (2010) for the Libby worker cohort, because this
6 type of survival analysis takes into account differences in follow-up time among the cohort.
7 Larson et al. (2010b) conducted Poisson analyses and reported that their lung cancer results
8 using this different model form were similar to those from their extended Cox proportional
9 hazards models, but those results were not shown.
10   Both of these model forms allow for the evaluation and control of important potential
11 confounding factors such as age, gender, and race, and for the modeling of exposure as a
12 continuous variable. Both model forms yielded exposure-response results with good fit to the
13 occupational exposure data. The default assumption of the extended Cox proportional hazards
14 model as well as the Poisson model is that all censoring (due to death or loss to follow-up) is
15 assumed to be independent of exposure to the LAA. However, exposure to LAA may cause
16 death from other causes such as asbestosis or nonmalignant respiratory disease (Larson et al.,
17 2010b), which is referred to as dependent censoring. The concern is that the observation of lung
18 cancer mortality may be precluded by mortality from other causes.
19   In the cohort of 880 workers hired after 1959, 32 died of lung cancer, while 10 died of
20 asbestosis, and 21 died of nonmalignant respiratory disease. The mean length of follow-up from
21 the date of hire until death for the workers who died of lung cancer was 24.9 years. However,
22 the mean length of follow-up for the workers who died of asbestosis or nonmalignant respiratory
23 disease was 30.4 years, so it does not appear that early deaths from other causes associated with
24 exposure to the LAA (Larson et al., 2010b) would have precluded many cases of lung cancer.
25 This implies that any potential bias in the lung cancer risk estimates due to dependent competing
26 risks is small.
27   With respect to mesothelioma mortality, it should be noted that the exposure-response
28 modeling is limited by the number of deaths. However, dependent censoring, as described
29 above, is not accounted for in the Poisson model and likely causes a downward bias in the
30 estimation of risk. The mean length of follow-up for the workers who died of mesothelioma was
31 30.1 years, and there is some evidence that early deaths from other exposure-related causes
32 precluded an individual's risk of death from mesothelioma; only lung cancer exhibited a shorter
33 average follow-up time compared to mesothelioma, and in 419 cases of mesothelioma,
34 mesothelioma and lung cancer were never coidentified (Roggli and Vollmer, 2008).
35

1   **5.4.6.1.4. *Uncertainty in selection of exposure metric.*** There is uncertainty about what metric

2   should be used for modeling exposure to LAA. This current assessment evaluated models

3   proposed in the asbestos literature for modeling mesothelioma and models that include unlagged

4   and lagged cumulative exposure with and without a half-life of various lengths, and RTW

5   exposure with and without a half-life. In the analysis of comparative model fit based on the

6   empirical data, lagged cumulative exposure with a half-life provided the best fits for both

7   mesothelioma and lung cancer mortality associated with LAA. However, evaluation of 20-year

8   lag and longer lag times for mesothelioma was not possible, as the earliest mesothelioma death

9   happened less than 20 years from the start of the exposure; hence, exposure was zeroed out, and

10   the fit of any model with 20-year lag was very poor. Latency time for mesothelioma may be as

11   long as 60−70 years (e.g., Bianchi and Bianchi, 2009), so the precise lag time is uncertain.

12   In evaluating the data on lung fiber burden, Berry et al. (2009) estimated the range of the

13   half-life for crocidolite to be between 5 and 10 years. That range is consistent with the finding of

14   a 5- to 10-year half-life with 10−15 years lag that provided the best fit to the Libby workers

15   cohort mesothelioma mortality data. Similarly, recent publications indicate that the relative risk

16   of lung cancer due to asbestos exposure declines 15−20 years after the cessation of exposure to

17   asbestos (Magnani et al., 2008; Hauptmann et al., 2002). The marginally best fit for the Libby

18   workers cohort lung cancer mortality data was for CE models with a 5- to 20-year half-life and

19   10-year lag. However, the precise lag and half-life times are somewhat uncertain. Sensitivity

20   analysis that excluded people with high exposure during 1960−1963 (see Section 5.4.3.6.4)

21   provides further evidence that distinguishing between various lags and decays may be difficult

22   with these data. A limitation of this sensitivity analysis is the decrease in the number of cases,

23   especially for mesothelioma. Resolving this uncertainty would require longer follow-up time,

24   which would allow for a subcohort analysis of workers hired in 1967 or afterwards (when

25   exposure estimates began to be based on PCM measurements) until a sufficient number of cases

26   would be available for additional analysis.

27   These simulated decay models were derived mathematically to approximate underlying

28   biological processes that are not well understood, and are based on maximizing the likelihood for

29   the workers cohort and may not necessarily apply to the environmental exposure patterns.

30   Nonetheless, while the mode of action for carcinogenicity is unknown, the models incorporating

31   a half-life in the exposure metric were clearly preferable for mesothelioma mortality, and the

32   goal of the regression modeling effort was to identify the best fitting exposure model for the

33   Libby worker cohort.

34   Table 5-53 illustrates uncertainty in the IUR due to exposure metric selection. The

35   quantitative uncertainty is about threefold.

36

1   **5.4.6.1.5.** *Uncertainty in assessing of mortality corresponding to other cancer endpoints.*

2   There is evidence that other cancer endpoints may also be associated with exposure to the

3   commercial forms of asbestos. IARC concluded that there was sufficient evidence in humans

4   that commercial asbestos (chrysotile, crocidolite, amosite, tremolite, actinolite, and

5   anthophyllite) was causally associated with lung cancer and mesothelioma, as well as cancer of

6   the larynx and the ovary (Straif et al., 2009). Among the entire Libby workers cohort, only

7   two deaths were found to be due to laryngeal cancer, and there were no deaths from ovarian

8   cancer among the 24 deaths of 84 female workers. The lack of sufficient number of workers to

9   estimate risk of ovarian cancer is an uncertainty in an overall cancer health assessment.

10   The remaining uncertainties attributed to assessing mortality corresponding to the cancer

11   endpoints are considered to be low.

12

13   **5.4.6.1.6.** *Uncertainty in control of potential confounding in modeling lung cancer mortality.*

14   It is well known that smoking is a strong independent risk factor for lung cancer and may have a

15   synergistic effect with asbestos exposure (Wraith and Mengersen, 2007). In contrast, smoking is

16   not considered a risk factor for mesothelioma (Selikoff and Lee, 1978; Anderson et al., 1976).

17   As an important potential confounder of the lung cancer mortality analysis, the possible

18   effect of smoking on the estimated risk of lung cancer mortality associated with exposure to

19   LAA needs to be evaluated to the fullest extent possible. This consideration was discussed in

20   Amandus and Wheeler (1987) and in Section 4.1.1.3.

21   Additionally, W.R. Grace and Co. instituted a smoking ban on the property in 1979

22   (Peacock, 2003). Information is not available as to the effect of this smoking ban at work on

23   smoking patterns outside of the work environment. About 30% of the subcohort was still

24   employed in 1979 and all of the post-1959 cohort had been terminated by May 1982, so the

25   effect of a workplace smoking ban on cohort smoking history may explain the higher proportion

26   of former smokers in the Amandus and Wheeler (1987) data. Lung cancer risks in ex-smokers

27   decrease over time compared to lung cancer risks in continued smokers. A reduction of smoking

28   in the Libby worker population may lead to fewer observations of lung cancer deaths in later

29   years of the cohort study than would have occurred in the absence of the smoking restrictions.

30   Changes in smoking behavior during the course of the epidemiological observation period would

31   lead to changes in the observed time course of lung cancer death rates. This issue is related to

32   potential effect modification of lung cancer mortality described in Section 5.4.6.1.7.

33   Without high-quality individual-level data on smoking that could be used to control for

34   potential confounding, it is still possible to comment upon the likelihood and potential magnitude

35   of confounding and the impact any confounding would be expected to have on the lung cancer

36   mortality risk estimates. Confounding can be controlled for in a number of ways including by

37   modeling and by restriction. Restriction of the study population can reduce any potential

38   confounding by making the resulting population more similar. For instance, there can be no

confounding by gender when a study population is restricted to only men. This assessment
restricted the study population to those workers hired after 1959. Smoking habits have changed
over time, and it can reasonably be assumed that the range of smoking habits among those hired
after 1959 is less variable than that among the whole cohort, particularly because of the narrower
range of birth cohorts represented in this subcohort. This should have the effect of reducing
some of the potential for confounding. Analytic examinations of potential confounding are
discussed below.

Richardson (2010) describes a method to determine if an identified exposure relationship
with lung cancer is confounded by unmeasured smoking in an occupational cohort study. EPA
implemented this methodology to model the potential effects of LAA on the risk of COPD
mortality on the subcohort of workers hired after 1959 (see Section 5.4.3.8). Summarizing these
findings, EPA used the method described by Richardson (2010) to evaluate whether exposures to
LAA predicted mortality from COPD as an indication of potential confounding by smoking and
found a statistically nonsignificant negative relationship, which was inconsistent with
confounding by smoking.

5.4.6.1.7. *Uncertainty due to potential effect modification.* Among the 32 deaths from lung
cancer in workers hired after 1959 that were used to estimate the unit risk of lung cancer
mortality (see Section 5.4.5.2), data on smoking listed 16 as smokers, 4 as former smokers, and
12 of the 32 had missing data. Thus, data to support an estimate of the risk of LAA among
known nonsmokers were not available.

It is theoretically possible that the risk of lung cancer mortality estimated in this current
assessment is a reflection of a positive synergy between smoking and asbestos, and that the
adverse effect of LAA among the potentially nonsmoking workers has been overestimated. The
unit risk of the lung cancer estimate herein and the combined mesothelioma and lung cancer
mortality IUR would then be health protective for any population that had a lower prevalence of
smoking than that of the Libby worker cohort. However, if the smoking ban did diminish the
effect of smoking, then any overestimation would be somewhat mitigated.

5.4.6.1.8. *Uncertainty due to length of follow-up.* There is some potential uncertainty regarding
the length of follow-up for cancer mortality, even more so with the restriction of the cohort to
those workers hired after 1959. The hire dates among this subset of the cohort ranged from
January 1960 to November 1981 (the mean date of hire was May 1971). Follow-up continued
until the date of death or December 31, 2006, whichever occurred first. Therefore, the range of
follow-up was from 25 to 46 years, with a mean of more than 35 years.

However, for mesothelioma mortality, the length of the latency period is considerably
longer. Suzuki and Yuen (2001) reviewed 1,517 mesothelioma cases from 1975 through 2000
and was able to estimate the latency for 800. Suzuki and Yuen (2001) reported 17% of cases had

a latency of less than 30 years with 52% of cases with a latency of less than 40 years. Bianchi and Bianchi (2009) estimated the mesothelioma latency in 552 cases and reported mean latency periods of 35 years among insulators, 46 years among various industries, and 49 years among shipyard workers.

According to the results of Suzuki and Yuen (2001) and of Bianchi and Bianchi (2009) a mean length of follow-up of 35 years may only have captured half of all eventual mesothelioma mortality cases among the Libby workers hired after 1959. If this were so, then the unit risk of mesothelioma mortality could be larger than was estimated from existing data, suggesting continued examination.

5.4.6.1.9. *Uncertainty in use of life tables to calculate cancer mortality inhalation unit risk (IUR).* The life-table procedure computes the extra risk of death from birth up to 85 years of age, in part, because this is how national cancer incidence and mortality rate data that are one basis of the life tables are made available (see SEER, 2010, Table 15.10, age-specific U.S. death rates). Because the prevalence of cancer mortality is a function of increasing age, this cut-off at age 85 ignores a small additional risk of lung cancer mortality among a small percentage of people who have the higher background risk. This has the effect of slightly underestimating the IUR that would be derived if the life table were extended for an additional period of time, accounting for longer life spans. Extension of the life-table analysis to people over the age of 85 requires an additional assumption. Assuming that having attained the age of 85 years, the additional life expectancy is 5 years, then the lung cancer mortality unit risk based on the LEC_{01} would be somewhat larger―on the order of 5−10%―slightly more than the additional mesothelioma mortality risk if the life tables were extended.

5.4.6.1.10. *Uncertainty in combining of risk for composite cancer inhalation unit risk (IUR).* For the purpose of combining risks, it is assumed that the unit risks of mesothelioma and lung cancer mortality are normally distributed. Because risks were derived from a large epidemiological cohort, this is a reasonable assumption supported by the statistical theory. EPA conducted a bounding analysis and showed that the related uncertainty is very low.

5.4.6.1.11. *Uncertainty in extrapolation of findings in adults to children.* The analysis of lung cancer mortality specifically tested the assumption that the relative risk of exposure is independent of age within the observed age range of the occupational subcohort hired after 1959 and did not find evidence of age dependence, although such a dependence among a working-age study population has been reported in another asbestos-exposed cohort (Richardson, 2009). However, it should be noted that no comparable data are available to estimate the lifetime risk from early life exposures. Note that default age-dependent adjustment factors (ADAFs) are not recommended because a mutagenic MOA was not identified.

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5.4.6.2. *Summary*

Section 5.4.6.1 details the several sources of uncertainty in the assessment of the cancer exposure-response relationships and the use of those data to derive the inhalation unit risk. The text that follows summarizes the primary sources of uncertainty and, where possible, the expected direction of effect on the exposure-response risk estimates and the inhalation units risk.

1) *Uncertainty in low-dose extrapolation (see Section 5.4.6.1.1)*

- There remains some uncertainty in the extrapolation of risks based on occupational exposure to environmental exposure levels but this uncertainty is considered to be low as the lower range of occupational exposure overlaps with expected environmental exposure levels.

2) *Uncertainty in exposure assessment, including analytical measurements uncertainty (see Section 5.4.6.1.2)*

- The JEM was based on the "high" exposure estimate for each job according to Amandus et al. (1987b) and to some extent this could be an overestimate of exposure. The associated cancer risk would be somewhat underestimated resulting in a somewhat underestimated IUR.

- The JEM was largely based on estimated fiber concentration using PCM measurement (with some extrapolations in time), and because PCM may count all long and thin objects as fibers, these measurement could overestimate the true LAA fiber concentrations leading to an overestimate of exposure and a somewhat underestimated cancer risk resulting in a somewhat underestimated IUR.

- PCM measurements in the era of NIOSH measurements in Libby used a lower resolution, and therefore, included only somewhat thicker fibers thereby counting fewer fibers than would have been counted by later PCM standards. These earlier measurement could underestimate the true LAA fiber concentrations leading to an underestimate of exposure and an overestimate of cancer risk resulting in a somewhat overestimated IUR.

- The PCM measurement is the available exposure metric for analysis of the Libby worker cohort at the time of this assessment. Currently, there is no optimal choice of the best dose metric for asbestos, in general and in particular, for LAA. Uncertainties related to PCM analytical method are discussed in Section 2 and such uncertainties cannot be related to the IUR at the time of this assessment.

- Random measurement error in the assignment of exposures could have the effect of underestimating the risk of lung cancer mortality as that measure of risk is based on a relative measure. The effect would be to somewhat underestimate the risk of lung cancer resulting in a somewhat underestimated unit risk for lung cancer. It is unclear what the impact of such measurement error would be on the absolute risk of mesothelioma.

- Exposure to other kinds of asbestos and residential exposure to LAA may have caused workers' actual personal exposures (as the sum of occupational and nonoccupational exposures) to have been underestimated by the use of estimated Libby occupational exposure information alone. This could underestimate the true LAA fiber exposures leading to an overestimate of the associated cancer risk resulting in a somewhat overestimated IUR.

3) *Uncertainty in model form (see Section 5.6.4.1.3)*

- For mesothelioma, the Poisson model is the standard epidemiologic form and it is considered to be the most appropriate model form for rare health outcomes; therefore, uncertainty is considered to be low. For lung cancer mortality, the Cox proportional hazards model is the standard epidemiologic form. It is considered to be the most appropriate model form for health outcomes with time-varying exposure data, and thus, uncertainty is considered to be low.

4) *Uncertainty in selection of exposure metric (see Section 5.6.4.1.4)*

- There is uncertainty about what metric should be used for modeling exposures to LAA. Table 5-53 illustrates the uncertainty in the IUR due to exposure metric selection. The quantitative uncertainty is about threefold.

5) *Uncertainty in assessing mortality corresponding to other cancer endpoints (see Section 5.6.4.1.5)*

- The lack of sufficient numbers of workers to estimate the risk of other cancers potentially related to LAA exposure is an uncertainty of unclear direction but is considered to be low due to the rarity of those cancers.

6) *Uncertainty in control of potential confounding in modeling lung cancer mortality (see Section 5.4.6.1.6)*

- The uncertainty in control of potential confounding by smoking is considered to be low, as the described sensitivity analysis did not show evidence of potential confounding.

7) *Uncertainty due to potential effect modification (see Section 5.4.6.1.7)*

- Smoking was not considered to be related to LAA exposure, and therefore, smoking is not considered to be a likely effect modifier of cancer risk. Age has been shown to be a potential effect modifier of lung cancer risk but there was no evidence of this relationship in the subcohort.

8) *Uncertainty due to length of follow-up (see Section 5.4.6.1.8)*

- There is uncertainty related to the limited follow-up for cancer mortality, and it is possible that with subsequent mortality follow-up the IUR could change in a direction that is unknown.

1   *9) Uncertainty in the use of life tables to calculate cancer mortality IUR (see*
2   *Section 5.4.6.1.9)*

3   • The life-table procedure computes the extra risk of death from birth to 85 years of
4   age. If the life tables were extended from 85 to 90 years to account for longer life
5   spans, the selected lung cancer mortality unit risk (Table 5-52 shows this as
6   0.068) would be somewhat larger, about 5−10%, and the selected mesothelioma
7   unit risk (Table 5-50 shows this as 0.122) would be slightly less (about 3%).
8   Taking both effects into consideration, the uncertainty in the IUR is considered to
9   be low.

10   *10) Uncertainty in combining of mortality risks to derive a composite cancer mortality*
11   *inhalation unit risk (IUR) (see Section 5.4.6.1.10)*

12   • EPA assumed that the cancer risks were independent, conducted a bounding
13   analysis and showed the related uncertainty to be very low.

14   *11) Uncertainty due to extrapolation of findings in adults to children (see*
15   *Section 5.4.6.1.11)*

16   • There is uncertainty in the assumption that risks are independent of age and that
17   children are at the same exposure-related risk as adults. The lack of published
18   information on cancer risks associated with exposures during childhood remains an
19   uncertainty of unclear magnitude.
20

6. MAJOR CONCLUSIONS IN THE CHARACTERIZATION OF HAZARD AND EXPOSURE RESPONSE

Libby Amphibole asbestos (LAA),[32] present in vermiculite ore from the mine near Libby, MT, is a complex mixture of amphibole fibers—both mineralogically and morphologically (see Section 2.2). The mixture primarily includes winchite, richterite, tremolite, magnesio-riebeckite, magnesio-arfvedsonite, and edenite (84:11:6:1:1:1) amphibole minerals that exhibit a range of fiber morphologies (e.g., asbestiform, acicular, prismatic) (Meeker et al., 2003). Given the exposure potential to LAA—and its characteristic mineral composition—a hazard characterization and cancer exposure-response assessment are presented.

As discussed in Section 1, no RfC for asbestos currently exists, and the EPA IRIS IUR for asbestos is based on a synthesis of 14 epidemiologic studies that included occupational exposure to chrysotile, amosite, or mixed mineral fibers (chrysotile, amosite, and crocidolite) (U.S. EPA, 1988a). Some uncertainty exists in applying the resulting IUR to environments and minerals not included in the studies considered for the asbestos IUR derivation (U.S. EPA, 1988a). Published mortality studies on the Libby, MT worker cohort have become available since the derivation of the IRIS asbestos IUR (i.e., Larson et al., 2010b; Sullivan, 2007; McDonald et al., 2004; Amandus and Wheeler, 1987; McDonald et al., 1986a). This assessment documents noncancer and cancer health effects from inhalation exposure to LAA. Data are not available to support derivation of either a RfD or a cancer oral slope factor (OSF) following oral exposures to LAA.

6.1. HUMAN HAZARD POTENTIAL

6.1.1. Exposure

Several different groups of humans have the potential for exposure to fibers from vermiculite ore from the mine in Libby, MT, and hence the potential for exposure to the LAA associated with this material. These groups include not only the former workers at the mine and mill site, but also residents in the community of Libby, MT, as well as workers at other locations who processed the vermiculite product. When the mine in Libby, MT, was active, miners, mill workers, and those working in the processing plants were exposed to vermiculite ore, silica dust, and amphibole structures released to air from the ore during the mining and processing operations (Meeker et al., 2003; Amandus et al., 1987b; McDonald et al., 1986a). In some cases, workers may have inadvertently transported contaminated materials from the workplace to vehicles, homes, and other establishments, typically on the clothing, shoes, and hair. This

---

[32]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   transported material may have resulted in "take-home exposure" for the workers, their families,

2   and other coresidents. The magnitude of these historic take-home exposures was not measured,

3   so the levels at which individuals in the home might have been exposed are unknown.

4   While some vermiculite concentrate was exfoliated and used in Libby, MT, most of the

5   concentrate was transported to expansion plants at other locations across the country where it

6   was exfoliated and distributed. A review of company records from 1964−1990 indicates that

7   more than 6 million tons of vermiculite concentrate was shipped to over 200 facilities outside of

8   Libby, MT (ATSDR, 2008). Because expanded vermiculite from Libby was widely used in

9   numerous consumer and construction products in the United States, even people not associated

10 with Libby or other communities with expansion plants may also have the potential for exposure

11 to LAA (see Table 2-2). Vermiculite was most notably used as attic insulation (VAI, Versar,

12 2003), as a soil amendment for gardening, fireproofing agent, and in the manufacturing of

13 gypsum wallboard. Other residents living in communities near the expansion plants may also

14 have been subjected to some of the same exposure pathways as was the Libby community. The

15 2008 ATSDR Summary Report observed that individuals in a community with a vermiculite

16 expansion and processing plant could have been exposed by breathing airborne emissions from

17 the facility or by inhalation exposure to contaminants brought into the home on workers'

18 clothing or from outdoor sources (ATSDR, 2008).

19

20 **6.1.2. Fiber Toxicokinetics**

21   Although oral and dermal exposure to fibers does occur, inhalation is considered the main

22 route of human exposure to mineral fibers, and therefore, has been the focus of more fiber

23 toxicokinetic analyses in the literature. As with other forms of asbestos, exposure to LAA is

24 presumed to be through all three routes of exposure; however, this assessment specifically

25 focuses on the inhalation pathway of exposure. Generally, fiber deposition in the respiratory

26 tract is fairly well defined based on fiber dimensions and density, although the same cannot be

27 said for fiber translocation to extrapulmonary sites (e.g., pleura). The deposition location within

28 the pulmonary and extrapulmonary tissues plays a role in the clearance of the fibers from the

29 organism.

30   Fiber clearance from the respiratory tract can occur through physical and biological

31 mechanisms. Limited mechanistic information is available on fiber clearance mechanisms in

32 general, and no information specific to clearance of LAA fibers is available. Fibers have been

33 observed in various pulmonary and extrapulmonary tissues following exposure, suggesting

34 translocation occurs to a variety of tissues. Studies have also demonstrated that fibers may be

35 cleared through physical mechanisms (coughing, sneezing) or through dissolution of fibers.

36   Multiple fiber characteristics (e.g., dimensions, density, and durability) play a role in the

37 toxicokinetics and toxicity of fibers. The literature examining a variety of fiber determinants and

38 their role in disease is extensive, with a focus on fiber length, width, and durability; however,

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1 these studies are often contradictory, making conclusions difficult for fibers in general. This is

2 in part due to the variety of fibers analyzed, inadequate study design, and/or lack of information

3 on fiber dimensions in earlier studies. However, due to the importance in understanding the role

4 of these fiber determinants in the biological response, careful attention has been paid to these

5 fiber characteristics when analyzing research studies on LAA and asbestiform tremolite, an

6 amphibole fiber that comprises part of LAA (see Appendix D). No toxicokinetic data are

7 currently available specific to LAA or its components (e.g., winchite, richterite, tremolite,

8 magnesio-riebeckite, magnesio-arfvedsonite, and edenite). When available, fiber characteristic

9 data are presented in the discussion of each study in relation to the toxic endpoints described.

10

6.1.3. Noncancer Health Effects in Humans and Laboratory Animals

12   The predominant noncancer health effects observed following inhalation exposure to

13 LAA are on the lungs and pleural lining surrounding the lungs. These effects have been

14 observed primarily in studies of exposed workers and community members, and are supported by

15 laboratory animal studies. Recent studies have also examined other noncancer health effects

16 following exposure to Libby Amphibole, including autoimmune effects and cardiovascular

17 disease; this research base is currently not as well developed as that of respiratory noncancer

18 effects. Adequate data are not available to differentiate the health effects of the predominant

19 mineralogical forms composing LAA. Although the adverse effects of tremolite are reported in

20 the literature, the contribution of winchite and richterite to the aggregate effects of LAA has not

21 been determined.

22   Noncancer health effects identified in humans following inhalation exposure to LAA

23 include pleural abnormalities, asbestosis, and reduced lung function, as well as increased

24 mortality from noncancer causes. Two cohorts of workers exposed to LAA have been studied:

25 workers at the mine and related operations in Libby, MT and employees in the O.M. Scott plant

26 in Marysville, OH, where the vermiculite ore was exfoliated and used as an inert carrier in lawn

27 care products. Radiographic assessments of study participants in both cohorts indicate

28 radiographic abnormalities consistent with asbestos-related disease, specifically pleural effects

29 and small interstitial opacities (indicative of interstitial fibrosis) (Rohs et al., 2008; Amandus et

30 al., 1987a; McDonald et al., 1986b; Lockey et al., 1984). These studies provided quantitative

31 exposure estimates and were considered suitable for exposure-response analysis to support an

32 RfC derivation. Additionally, five cohort mortality studies of Libby, MT workers identified an

33 increased risk of mortality from noncancer causes, including nonmalignant respiratory disease

34 (e.g., asbestosis) (Larson et al., 2010b; Sullivan, 2007; McDonald et al., 2004; Amandus and

35 Wheeler, 1987; McDonald et al., 1986a) and cardiovascular disease (Larson et al., 2010b).

36   ATSDR conducted health screening of community members in and around Libby, MT

37 (including past workers), and identified an increase in radiographic abnormalities with an

38 increased number of exposure pathways (Peipins et al., 2004a; Peipins et al., 2003; ATSDR,

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1   2001b). Other researchers have also used these data to identify the increased prevalence of

2   respiratory symptoms in children (Vinikoor et al., 2010) and to evaluate the prevalence of

3   radiographic abnormalities and reduced lung function in nonworker participants (Weill et al.,

4   2011). Radiographic abnormalities were more prevalent in mine/mill workers versus other

5   exposure categories (i.e., household contacts, 'dusty trades', and community-only exposures)

6   (Weill et al., 2011). Prevalence of pleural effects increased with age and within each exposure

7   group. Decreased pulmonary function (as percentage of the predicted forced vital capacity) is

8   reported for participants with radiographic abnormalities (Weill et al., 2011). A nested

9   case-control study based on ATSDR community health screening also identified a potential for

10   increased prevalence of autoimmune disease (Noonan et al., 2006), and other experimental work

11   has examined mechanistic steps relating to autoimmunity (Marchand et al., 2012; Pfau et al.,

12   2005). Further development of this area of research could provide additional insights into the

13   range of health effects possibly linked to LAA.

14   Laboratory animal and mechanistic studies of LAA are consistent with the noncancer

15   health effects observed in workers exposed to LAA in Libby, MT and Marysville, OH, as well as

16   exposed community members. Pleural fibrosis was increased in hamsters after intrapleural

17   injections of LAA (Smith, 1978). More recent studies have demonstrated increased collagen

18   deposition and inflammation consistent with fibrosis following intratracheal instillation of LAA

19   fibers in mice and rats (Cyphert et al., 2012b; Cyphert et al., 2012a; Padilla-Carlin et al., 2011;

20   Shannahan et al., 2011a; Shannahan et al., 2011b; Smartt et al., 2010; Putnam et al., 2008).

21   Pulmonary fibrosis, inflammation, and granulomas were observed after tremolite inhalation

22   exposure in Wistar rats (Bernstein et al., 2005; Bernstein et al., 2003) and intratracheal

23   instillation in albino Swiss mice (Sahu et al., 1975). Davis et al. (1985) also reported pulmonary

24   effects after inhalation exposure in Wistar rats, including increases in peribronchiolar fibrosis,

25   alveolar wall thickening, and interstitial fibrosis.

26   Limited research is available on noncancer health effects occurring outside the

27   respiratory system and pleura. Larson et al. (2010b) examined cardiovascular disease-related

28   mortality in the cohort of exposed workers from Libby (see Section 4.1). Mechanistic studies

29   have examined the potential role of iron and the associated inflammation for both respiratory and

30   cardiovascular disease (Shannahan et al., 2012a; Shannahan et al., 2012c; Shannahan et al.,

31   2012b; Shannahan et al., 2012d; Shannahan et al., 2011b). Recent studies in the Libby, MT

32   community examined the association between asbestos exposure and autoimmune disease

33   (Noonan et al., 2006) or autoantibodies and other immune markers (Pfau et al., 2005; see Table

34   4-16). Mechanistic studies examining the role of LAA exposure in autoimmune disease have

35   shown limited effects but did observe an increase in autoantibodies in the serum of exposed

36   animals (Salazar et al., 2013; Salazar et al., 2012). These results are supported by recent in vitro

37   studies demonstrating increased autoantibodies to mesothelial cells, leading to collagen

38   deposition (Serve et al., 2013). These recent studies have examined the association between

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1 asbestos exposure and autoimmune disease; additional research in this area could enhance
2 understanding of this potential mode of action for noncancer effects (Salazar et al., 2013; Serve
3 et al., 2013; Rasmussen and Pfau, 2012; Salazar et al., 2012; Blake et al., 2008; Pfau et al., 2008;
4 Hamilton et al., 2004). However, limitations in the number, scope, and design of these studies
5 make it difficult to reach conclusions as to the role of asbestos exposure in either cardiovascular
6 disease or autoimmune disease.
7   Limited in vitro studies have demonstrated oxidative stress following LAA exposures in
8 various cell types (Duncan et al., 2014; Duncan et al., 2010; Hillegass et al., 2010; Pietruska et
9 al., 2010; Blake et al., 2007). LAA fibers increased intracellular ROS in both murine
10 macrophages and human epithelial cells (Duncan et al., 2010; Blake et al., 2007). The role of
11 surface iron on inflammatory marker gene expression and inflammasome activation was shown
12 to be increased following exposure to LAA in human epithelial cells (Duncan et al., 2014;
13 Shannahan et al., 2012a; Shannahan et al., 2012c; Shannahan et al., 2012b; Shannahan et al.,
14 2012d; Shannahan et al., 2011b; Duncan et al., 2010; Pietruska et al., 2010; see Table 4-18).
15 Tremolite studies also demonstrate cytotoxicity in various cell culture systems (see Table 4-22).
16 However, evidence is currently insufficient to establish the noncancer mode of action for LAA.
17

6.1.4. Carcinogenicity in Humans and Laboratory Animals

19   There is convincing evidence of a causal association between exposure to LAA
20 mesothelioma and lung cancer in workers from the Libby, MT vermiculite mining and milling
21 operations as well as workers from the Marysville, OH plant (Larson et al., 2010b; Sullivan,
22 2007; McDonald et al., 2004; Amandus et al., 1988; Amandus and Wheeler, 1987; McDonald et
23 al., 1986a). Whitehouse et al. (2008) documented 11 mesothelioma cases in nonworkers
24 exposed to LAA in Libby, MT. Increased lung cancer and mesothelioma deaths are also
25 reported for worker cohorts exposed to other forms of amphibole fibers (amosite and crocidolite)
26 (de Klerk et al., 1989; Seidman et al., 1986; Henderson and Enterline, 1979). These findings are
27 consistent with the increased cancers reported for communities exposed to various rocks and
28 soils containing tremolite fibers (Hasanoglu et al., 2006; Sichletidis et al., 1992b; Baris et al.,
29 1987; Langer et al., 1987; Baris et al., 1979; Yazicioglu, 1976). Although potency, fiber
30 dimension, and mineralogy differ among amphiboles, these studies are supportive of the hazard
31 identification of LAA fibers described in this assessment.
32   Although experimental data in animals and data on toxicity mechanisms are limited for
33 LAA, tumors were observed in tissues similar to those seen in humans (e.g., mesotheliomas, lung
34 cancer) indicating that the existing data are consistent with the cancer effects observed in humans
35 exposed to LAA. Smith (1978) reported increased incidence of mesotheliomas in hamsters after
36 intrapleural injections of LAA. Additionally, studies in laboratory animals (rats and hamsters)
37 exposed to tremolite via inhalation (Bernstein et al., 2005; Bernstein et al., 2003; Davis et al.,
38 1985), intrapleural injection (Roller et al., 1997, 1996; Davis et al., 1991; Wagner et al., 1982;

1   Smith et al., 1979), or implantation (Stanton et al., 1981) have shown increases in mesotheliomas

2   and lung cancers. The tremolite used in these studies was from various sources and varied in

3   fiber content and potency (see Section 4.2, Appendix D). Although McConnell et al. (1983a)

4   observed no increase in carcinogenicity following oral exposure to nonfibrous tremolite, the

5   ability of this study to inform the carcinogenic potential of fibrous tremolite through inhalation is

6   unclear, and the study results contribute little weight to the evaluation of the carcinogenicity of

7   fibrous LAA.

8   The available mechanistic information suggests LAA induces effects that may play a role

9   in carcinogenicity (see Section 4.2, Appendix D). Several in vitro studies have demonstrated

10 oxidative stress and genotoxicity following LAA exposures in various cell types (Duncan et al.,

11 2010; Hillegass et al., 2010; Pietruska et al., 2010; Blake et al., 2007). LAA increased

12 intracellular ROS in both murine macrophages and human epithelial cells (Duncan et al., 2010;

13 Blake et al., 2007). Additionally, surface iron, inflammatory marker gene expression,

14 inflammasome, and aneugenic micronuclei were increased following exposure to LAA in human

15 epithelial cells (Duncan et al., 2010; Pietruska et al., 2010). Tremolite studies demonstrate

16 cytotoxic and clastogenic effects (e.g., micronucleus induction and chromosomal aberrations) of

17 the fibers in various cell culture systems.

18

19 **6.1.5. Susceptible Populations**

20   Certain populations could be more susceptible than the general population to adverse

21 health effects from exposure to LAA. In general, factors that may contribute to increased

22 susceptibility from environmental exposures include lifestage, gender, race/ethnicity, genetic

23 polymorphisms, health status, and lifestyle. However, little data exist to address the potential of

24 increased susceptibility to cancer or noncancer effects from exposure to the LAA.

25   Most occupational studies of workers exposed to LAA have examined the effects only in

26 men because this group represents the vast majority of workers in these settings (Moolgavkar et

27 al., 2010; Sullivan, 2007; McDonald et al., 2004; Amandus et al., 1988; Amandus et al., 1987b;

28 Amandus and Wheeler, 1987; Amandus et al., 1987a; McDonald et al., 1986a; McDonald et al.,

29 1986b). The analysis presented here includes all workers; however, there were few women in

30 the cohort, and therefore, no determination can be made regarding increased susceptibility to

31 lung cancer or mesothelioma by gender. Gender-related differences in exposure patterns,

32 physiology, and dose-response are some of the factors that may contribute to gender-related

33 differences in risk from asbestos exposure (Smith, 2002). The limited data available from

34 community-based studies (ATSDR, 2000) do not provide a basis for drawing conclusions

35 regarding gender-related differences in carcinogenic effects from LAA. Racial diversity among

36 workers exposed to LAA is also limited, and data on ethnic groups are absent, precluding the

37 ability to examine racial and ethnicity-related differences in the mortality risks within the Libby,

38 MT worker cohort. Finally, the potential modifying effects of genetic polymorphisms,

1 preexisting health conditions, nutritional status, and other lifestyle factors have not been studied
2 sufficiently to determine their potential contribution to variation in risk in the population.
3

4 **6.1.6. Mode-of-Action Information**

5   Research on multiple types of elongate mineral fibers supports the role of multiple modes
6 of action following exposure to LAA. Of the MOAs described in Section 4.4, the evidence that
7 chronic inflammation, genotoxicity and cytotoxicity, and cellular proliferation may all play a role
8 in the carcinogenic response to LAA is only suggestive (see Table 4-23). In vitro studies provide
9 evidence that amphibole asbestos is capable of eliciting genotoxic and mutagenic effects in
10 mammalian respiratory cells; however, direct evidence linking mutagenicity to respiratory cells
11 following inhalation exposure is lacking. Results of the in vivo studies described here are
12 consistent with the hypothesis that some forms of amphibole asbestos act through a MOA
13 dependent on cellular toxicity, based on the observations that cytotoxicity and reparative
14 proliferation occur following subchronic exposure and that bronchiolar tumors are produced at
15 exposure levels that produce cytotoxicity and reparative proliferation. However, dose-response
16 data in laboratory animal studies for damage/repair and tumor development are limited due to the
17 limited number of inhalation studies that used multiple doses of fibers. Although evidence is
18 generally supportive of a MOA involving chronic inflammation or cellular toxicity and repair,
19 there is insufficient evidence to establish a MOA; thus, a linear approach is used to calculate the
20 inhalation cancer unit risk in accordance with the default recommendation of the 2005
21 *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a). It is possible that multiple MOA
22 discussed above, or an alternative MOA, may be responsible for tumor induction.
23

24 **6.1.7. Weight-of-Evidence Descriptor for Cancer Hazard**

25   Under the EPA *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a), LAA is
26 *carcinogenic to humans* following inhalation exposure based on epidemiologic evidence that
27 shows a convincing association between exposure to LAA fibers and increased lung cancer and
28 mesothelioma mortality (Larson et al., 2010b; Moolgavkar et al., 2010; Sullivan, 2007;
29 McDonald et al., 2004; Amandus and Wheeler, 1987; McDonald et al., 1986a). These results are
30 further supported by animal studies that demonstrate the carcinogenic potential of LAA fibers
31 and tremolite fibers in rodent bioassays (see Section 4.1, 4.2, Appendix D). As LAA is a durable
32 mineral fiber of respirable size, this weight-of-evidence descriptor is consistent with the
33 extensive published literature that documents the carcinogenicity of amphibole fibers (as
34 reviewed in Aust et al., 2011; Broaddus et al., 2011; Bunderson-Schelvan et al., 2011; Huang et
35 al., 2011; Mossman et al., 2011).
36   EPA's *Guidelines for Carcinogenic Risk Assessment* (U.S. EPA, 2005a) indicate that for
37 tumors occurring at a site other than the initial point of contact, the weight of evidence for

1 carcinogenic potential may apply to all routes of exposure that have not been adequately tested at
2 sufficient doses. An exception occurs when there is convincing information (e.g., toxicokinetic
3 data) that absorption does not occur by other routes. Information on the carcinogenic effects of
4 LAA via the oral and dermal routes in humans or animals is absent. The increased risk of lung
5 cancer and mesothelioma following inhalation exposure to LAA has been established by studies
6 in humans, but these studies do not provide a basis for determining the risk from other routes of
7 exposure. Mesothelioma occurs in the pleural and peritoneal cavities, and therefore, is not
8 considered a portal-of-entry effect. However, the role of indirect or direct interaction of asbestos
9 fibers in disease at these extrapulmonary sites is still unknown. There is no information on the
10 translocation of LAA to extrapulmonary tissues following either oral or dermal exposure, and
11 limited studies have examined the role of these routes of exposure in cancer. Therefore, LAA is
12 considered *carcinogenic to humans* by the inhalation route of exposure.
13
14 **6.2. EXPOSURE-RESPONSE**
15 **6.2.1. Noncancer/Inhalation**
16   There were three potential candidate studies for the derivation of the RfC—two of these
17 were occupationally exposed cohorts, that is, the Libby worker cohort (Larson et al., 2012a) and
18 the Marysville worker cohort (Rohs et al., 2008) and the third was of community residents in
19 Minneapolis, MN (Minneapolis cohort, Alexander et al., 2012). Each of these studies provided
20 individual exposure estimates and documented increased hazard of pleural effects. As detailed in
21 Section 5.2.1, each of the available studies has strengths and weaknesses. The cohort of
22 Marysville, OH workers (Lockey et al. (1984) and the follow-up by Rohs et al. (2008)) was
23 selected as the principal cohort over the Libby worker cohort for several reasons: (1) lack of
24 confounding by residential and community exposure; (2) availability of information on important
25 covariates (e.g., BMI); (3) an exposure-response relationship defined for lower cumulative
26 exposure levels (particularly the workers hired in 1972 or later and evaluated in 2002−2005);
27 (4) adequate length of follow-up; (5) use of more recent criteria for evaluating radiographs (ILO,
28 2002); (6) availability of high-quality exposure estimates based on numerous industrial hygiene
29 samples and work records (see Section 5.2.1 for details); and (7) availability of data on TSFE
30 matched to the exposure data. The study of Libby workers (Larson et al., 2012a) had many of
31 these same attributes (e.g., adequate follow-up and high-quality exposure estimates), but
32 exposure levels were generally higher in this group compared to the Marysville workers, and the
33 Libby workers may have experienced greater levels of undocumented "take home" and other
34 nonoccupational exposure for which TSFE data were more uncertain. The main limitation in the
35 study of Minneapolis community residents (Alexander et al., 2012) was relatively lower quality
36 exposure information; exposure estimates were based on a small number of total dust
37 measurements from stack emissions combined with air dispersion modeling, and the authors

1   estimate that the individual exposure estimates are likely to have an order of magnitude of
2   uncertainty. Thus, the study of Marysville workers ([Rohs et al., 2008](#)) was selected as the
3   principal study for RfC derivation.
4   The MOA for LPT and the results of other asbestos epidemiology studies could
5   potentially inform noncancer modeling decisions and suggest exposure metrics to use in
6   modeling. However, the conclusion of Section 3 of this assessment is that the data are not
7   sufficient to establish a MOA for the pleural and/or pulmonary effects of exposure to LAA. A
8   general understanding of the biology and epidemiology of pleural health endpoints suggests that
9   the timing of exposure, the exposure intensity, and the duration of exposure may be important
10 explanatory variables and these variables were carried forward for modeling using three
11 exposure metrics called "mean exposure" or "mean concentration" (C), "cumulative exposure"
12 (CE), and "residence time-weighted exposure" (RTW).
13   LPT was selected as the critical effect for derivation of the RfC, with a BMR of 10%
14 extra risk. LPT was selected because, among the noncancer radiographic endpoints evaluated in
15 the principal study, it is the endpoint that generally appears soonest after exposure and at the
16 lowest levels of exposure, and it was deemed the most sensitive endpoint. LPT is a pathological
17 change associated with decreased pulmonary function, and thus is considered an appropriate
18 adverse effect for deriving the RfC (see Section 5.2.2.3 and Appendix I).
19   The RfC is derived based on data from the Marysville workers who were evaluated in
20 2002−2005 and hired in 1972 or later. These workers were selected due to the greater certainty
21 in their exposure assessment. BMC modeling was used to derive the POD. Statistical models
22 were evaluated based on biological and epidemiological considerations (see Section 5.2.2.6.1)
23 and EPA's Benchmark Dose Technical Guidance ([U.S. EPA, 2012](#)). Considerations included
24 (1) the nature of the data set (i.e., cross-sectional, dichotomous health outcome data), (2) ability
25 to estimate the effect of exposure and of covariates, (3) appropriate inclusion of a plateau term
26 representing theoretical maximal prevalence of the outcome, and (4) appropriate estimation of
27 the background rate of the outcome. A number of models were evaluated, and the Dichotomous
28 Hill model with the plateau parameter fixed at a literature-derived value of 85% was selected for
29 the derivation of a POD and sensitivity analyses. This model had very similar fit to others
30 evaluated and was thought to provide the greatest flexibility and ability to determine sensitivity
31 of model results to various assumptions. EPA considered several exposure metrics informed by
32 general biology and the epidemiologic literature, including mean exposure intensity, cumulative
33 exposure (which incorporates duration of exposure), and RTW exposure (which incorporates
34 TSFE by weighting more heavily exposures occurring in the more distant past).
35   Another important feature of the exposure-response analysis is the ability to include
36 effects of TSFE in the modeling. TSFE has been shown in the literature to be important in
37 evaluating risk of LPT, and studies have shown that prevalence of LPT can increase with
38 increasing TSFE even after cessation of exposure. EPA evaluated TSFE as a predictor in the

1   primary analytic group of workers hired after 1972 and evaluated in 2002−2005, but found that
2   TSFE was not significantly associated with LPT in this group—likely due to the very low
3   variability in TSFE for this particular population. Thus, EPA used a hybrid modeling approach
4   to "borrow" information on the effect of TSFE from a larger subset of the Marysville workers
5   with greater variability in TSFE. The model was fit in the group of all workers evaluated in
6   2002−2005 (regardless of hire date), including both LAA exposure and TSFE as predictors. The
7   regression coefficient corresponding to TSFE was then set as a fixed parameter in the model for
8   the primary analytic group of workers hired in 1972 or later. In this hybrid modeling, mean
9   exposure was used due to its superior model fit compared to cumulative exposure. RTW
10   exposure was not used since TSFE was included as a separate covariate (to avoid collinearity of
11   predictors). Using this modeling approach (details in Section 5.2.2.6.2), the resulting BMC_{10}
12   under these modeling assumptions is 0.0.0923 fiber/cc; the corresponding lower 95% confidence
13   limit of the BMC_{10} ($BMCL_{10}$) is 0.026 fiber/cc.
14   The RfC is obtained by applying uncertainty factors as needed. Three UFs have been
15   applied for a composite UF of 300 (intraspecies uncertainty factor, $UF_H = 10$; database
16   uncertainty factor, $UF_D = 3$; subchronic-to-chronic uncertainty factor, $UF_S = 10$) (see
17   Section 5.2.5). As shown below, the chronic RfC is 9×10^{-5} fiber/cc for LAA, calculated by
18   dividing the POD by a composite UF of 300:
19
20   Chronic RfC   = POD ÷ UF   (6-1)
21   = 0.026 fiber/cc ÷ 300
22   = 8.67×10^{-5} fiber/cc, rounded to 9×10^{-5} fiber/cc
23
24   Note that for the primary RfC as well as for all the alternative RfCs, the fiber concentration are
25   presented here as continuous lifetime exposure in fiber/cc, where exposure measurements are
26   based on analysis of air filters by PCM. Current analytical instruments used for PCM analysis
27   have resulted in a standardization of minimum fiber width considered visible by PCM between
28   0.2 and 0.25 μm. Historical PCM analysis (1960s and early 1970s) generally had less resolution,
29   and fibers with minimum widths of 0.4 or 0.44 μm were considered visible by PCM (Amandus
30   et al., 1987b; Rendall and Skikne, 1980). Methods are available to translate exposure
31   concentrations measured in other units into PCM units for comparison.
32   EPA conducted RfC derivation from the same subcohort with alternative definitions of
33   the health endpoint (see Section 5.2.3.1 and 5.2.3.2). The chronic RfC value for "any pleural
34   thickening" (APT) was also 9×10^{-5} fiber/cc and the same value was derived for "any
35   radiographic change" (ARC). Although EPA based the primary value of the RfC on the model
36   based on mean exposure, Section 5.2.4 illustrates an alternative derivation of an RfC of 1×10^{-4}
37   fiber/cc from the same cohort with an alternative exposure metric of cumulative exposure. EPA
38   also conducted alternative modeling of the Marysville cohort, including all individuals who

1   participated in the health examination in 1980 (Lockey et al., 1984) and 2002−2005 (Rohs et al.,

2   2008) and who were not exposed to asbestos from a source outside of the Marysville facility (see

3   Section 5.2.4 and Appendix E). The modeling of this full cohort (n = 434 individuals) was

4   performed using an alternative critical effect of "any pleural thickening" (APT), a slightly

5   different definition of LPT (diagnostic criteria changed slightly over time) and with "any

6   radiographic change" (ARC). These analyses yielded five other RfC values. A summary table

7   of the primary and alternative derivation of the RfC is provided in Table 5-11 in Section 5.2.5;

8   all eight alternative derivations of the RfC were within threefold of the primary RfC, ranging

9   from 3×10^{-5} fiber/cc up to 2×10^{-4} fiber/cc. This series of derivations further substantiates the

10   primary RfC derived from the Marysville workers evaluated in 2002−2005, and hired in 1972 or

11   later.

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 (Rohs et

14   al., 2008) is conducted in a population of occupationally exposed workers with long term,

15   relatively low intensity, exposures. While deriving the primary analysis from the group of

16   workers evaluated in 2002−2005 and hired after 1972 resulted in a smaller data set with fewer

17   cases to model, alternative RfC derivations based on the larger group of workers without

18   restriction on the date of hire (and many more cases) yielded similar values of the RfC. The

19   exposure assessment in the principal study is based on measured data. The main source of

20   uncertainty in the exposure estimates is incomplete exposure measurements for some of the

21   occupations/tasks before industrial hygiene improvements that started about 1973 or 1974 and

22   continued throughout the 1970s (see Appendix F, Figure F-1). The principal study assessed the

23   health outcome cross sectionally and this may underrepresent the true health burden as

24   individuals with more severe disease could have left employment or may have died and not been

25   included in the follow up study, resulting in an underestimation of overall toxicity. However, for

26   health outcomes not considered to be frank effects, such as LPT, this underestimation should be

27   minimal. Further, Rohs et al. (2008) compared the study participants with the complete study

28   population and there was no evidence of major differences in the two group's exposure

29   distributions. Thus, the potential for selection bias is considered to be low. In terms of the

30   sensitivity of the principal study to detect the critical effect (LPT) by radiograph, it is known that

31   HRCT can identify asbestos related lesions in the respiratory tract, which cannot be identified by

32   standard radiographs (e.g., Lebedova et al., 2003; Janković et al., 2002; Šimundić et al., 2002).

33   Thus, the technology employed for determining the prevalence of radiographic changes in the

34   Marysville cohort will likely underestimate the prevalence of pleural lesions that could be

35   detected using HRCT.

36   Confidence in the completeness of the overall database is medium. The database consists

37   of long term mortality and morbidity studies in humans exposed via inhalation to LAA. The

38   mortality studies do not provide appropriate data for RfC derivation for pleural abnormalities,

1   although the two other morbidity studies ([Alexander et al., 2012](#); [Larson et al., 2012a](#)) do support

2   the conclusion that low levels of exposure to LAA is associated with increased prevalence of

3   LPT. It is known that inhaled asbestos fibers migrate out of the lung and into other tissues (see

4   Section 3.1), which leads to uncertainty regarding the assumption that other health effects would

5   not be expected. While a potential for autoimmune effects and cardiovascular disease is noted in

6   exposed individuals, there are insufficient data to provide a quantitative exposure response

7   relationship for these endpoints. It is unknown whether an RfC based on these other health

8   would result in a higher or lower estimate for the RfC. Nor is there evidence as to whether any

9   of these other effects would occur earlier following exposure to LAA than LPT occurs. There

10   are no data in laboratory animals or humans on general systemic effects. Therefore, overall

11   confidence in the RfC is medium, reflecting medium confidence in the principal study and

12   medium confidence in the completeness of the overall database.

13

14   **6.2.1.1. *Uncertainty and Sensitivity Analyses for Reference Concentration (RfC) Derivation***

15   It is important to consider the sources of uncertainties in the derivation of the RfC for

16   LAA. These include the following:

17

18   *Measurement error in exposure assessment and assignment.* The estimated exposure for
19   each individual relied on self-reported employment history, which may be subject to
20   recall error. Only data from 1972 and later were used for an RfC derivation based on
21   lack of fiber measurements prior to this date, but some uncertainty remains due to the
22   limited amount of industrial hygiene data collected in 1972−1973. There is also
23   uncertainty in the post-1972 data regarding asbestos content and potency of fibers
24   originating from other ore sources (Virginia, South Carolina, and South Africa).
25   Although LAA was not used in the facility after 1980, industrial hygiene measurements
26   collected after 1980 showed low levels of fibers. Regarding nonoccupational exposure,
27   any exposure to LAA outside of the workplace is not likely to contribute significantly to
28   cumulative exposure—~10% of workers reported bringing raw vermiculite home, and the
29   majority showered and changed clothes before leaving the workplace. As a sensitivity
30   analysis, EPA evaluated the change in the POD when setting all exposure measurements
31   after 1980 to zero, and when using the geometric mean rather than the arithmetic mean to
32   summarize multiple fiber measurements for a given task/location/time period. These
33   analyses showed a difference of −65 to +50% in the POD.

34   *Radiographic assessment of localized pleural thickening.* Conventional
35   radiographs―rather than the more sensitive high-resolution computed
36   tomography―were used to determine the health outcome. Localized pleural thickening
37   may be difficult to detect on these radiographs, leading to the potential for outcome
38   misclassification. However, uncertainty in the detection of LPT in each individual is
39   considered minimal due to the use of a team of highly qualified chest radiologists
40   evaluating the radiographic films and the use of consensus diagnosis.

41   *Use of an alternative critical effect.* In addition to the primary analysis using a critical
42   effect of LPT, EPA also derived an RfC based on the alternative endpoint of any pleural

thickening (APT), and based on any radiographic change (ARC). In the primary analytic group of workers evaluated in 2002−2005 and hired in 1972 or later, the two alternative endpoints are identical to the critical effect of LPT, because the one individual with DPT also had LPT, and none had interstitial changes. In the larger group of workers used to estimate the effect of TSFE (all evaluated in 2002−2005), there were 69 cases of APT and 71 with ARC, of which the majority ($n = 66$) were LPT. Consequently, the RfC derived using these two alternative endpoints of APT or ARC were identical (to one significant digit) to that derived for LPT, 9×10^{-5} fibers/cc.

Length of follow-up. Time from first exposure to x-ray was 23.2−32.7 years in the primary analytic group of workers evaluated in 2002−2005, and hired in 1972 or later (mean of 28.2 years). The literature shows that the prevalence of LPT may increase with time, beyond this observed range of time from first exposure. The lack of observed data beyond ~30 years after first exposure (on average) is a source of uncertainty when characterizing the exposure-response relationship for a full lifetime of exposure (e.g., 70 years).

Model Form. A number of model forms were explored in the initial stages of analysis, and generally showed reasonably close fits as measured by the AIC. The Dichotomous Hill model with a plateau fixed at 85% was selected for RfC derivation due to its greater flexibility and ability to evaluate sensitivity to model assumptions. EPA also evaluated the sensitivity of the fixed plateau parameter and found that the POD changed very little (<16%) when fixing the plateau at different values (70, 100%) or when estimating the plateau from the Marysville data.

Effect of covariates. Information on a number of covariates was available for the Marysville workers, including demographic characteristics (gender, smoking status, BMI) as well as potentially exposure-related factors (hire year, job tenure, exposure duration, and age at x-ray). The potential for these factors to confound the association between LAA exposure and LPT was investigated in two ways. First, each was evaluated for association with the exposure, association with the outcome, and whether it was an intermediate in the pathway between exposure and outcome (i.e., did they meet the theoretical definition for a confounder). By these standards, none of the covariates was a confounder. Second, each covariate was included in the final model to evaluate the impact on the estimated effects of LAA exposure and TSFE; the differences were quite small, and none of the covariates were significantly associated with risk of LPT in these models.

6.2.2. Cancer/Inhalation

6.2.2.1. *Background and Methods*

The most appropriate data set for deriving quantitative cancer risk estimates based on LAA exposure in humans is the cohort of workers employed at the vermiculite mining and milling operation near Libby, MT (see Section 4.1.1.1). The Libby, MT worker cohort has been the focus of two epidemiologic investigations by the NIOSH scientists. A database created by NIOSH in the 1980s contains demographic data, work history, and vital status at the end of May of 1982 for 1,881 workers at the vermiculite mine, mill, and processing plant in Libby, MT (see

1 Section 4.1.1.1). Vital status follow-up was completed by NIOSH through 2006 using the
2 National Death Index (Bilgrad, 1997). Nearly 54% of workers in the cohort ($n = 1,009$) had died
3 by December 31, 2006. The data from this update (provided by NIOSH) is the basis of EPA
4 exposure-response modeling.

5   EPA does not have sufficient information to select models for the epidemiology data on
6 the basis of the biological mechanism of action for lung cancer or mesothelioma (see Section 3).
7 In this situation, EPA's practice is to investigate several modeling options to determine how to
8 best empirically model the exposure-response relationship in the range of the observed data, as
9 well as to consider exposure-response models suggested in the epidemiologic literature. For
10 LAA, possible exposure metrics were explored for model fit to the chosen models forms. The
11 exposure metric options were selected to provide a range of shapes that was sufficiently flexible
12 to allow for a variety of ways that time and duration might relate to cancer risk in the data being
13 modeled. EPA then evaluated how well the models and exposure metric combinations fit the
14 data being modeled. Then EPA calculated a reasonable upper bound on risk using selected
15 exposure metrics. This is explained in more detail below and in Section 5.4.5. However, there
16 are uncertainties in the modeling of the epidemiological data that may impact the IUR and these
17 are described in Section 6.2.8 below and in greater detail in Section 5.4.6.

18   In the Libby, MT worker cohort data developed by NIOSH and used by EPA in this
19 assessment, detailed work histories, together with job-specific exposure estimates, allowed for
20 the reconstruction of each individual's occupational exposure experience over time to define
21 multiple exposure metrics. From this information-rich, individual-level data set from NIOSH,
22 EPA constructed a suite of the different metrics of occupational exposure which had been
23 proposed in the asbestos literature or used in EPA health assessment on general asbestos
24 exposures (U.S. EPA, 1988a) as well as modifications proposed (Berry et al., 2012). This suite
25 of models was defined a priori to encompass a reasonable set of proposed exposure metrics to
26 allow sufficient flexibility in model fit to these data. These exposure metrics were evaluated in
27 analytic-regression models to test which exposure metrics were the best empirical predictors of
28 observed cancer mortality, and the better fitting models were advanced for consideration as the
29 basis of the exposure-response relationship for the IUR. The types of exposure metrics evaluated
30 were intended to allow for variations of the classic metric of cumulative exposure, allowing for
31 more or less weight to be placed on earlier or later exposures. These simulated exposure metrics
32 were derived mathematically to approximate underlying processes that are not well understood.
33 Thus, the empirical fit of various exposure metrics to the observed epidemiologic data is
34 evaluated statistically, and the exposure metrics have epidemiological interpretation but do not
35 necessarily have direct biological interpretations.

36   Exposure estimates for all exposure metrics were adjusted to account for the time period
37 between the onset of cancer and mortality. The lag period defines an interval before death, or
38 end of follow-up, during which any exposure is excluded from the calculation of the exposure

metric. There was one important limitation of the NIOSH JEM. Of the 991 workers hired before 1960, 706 workers with unknown department code and unknown job assignments hired between 1935 and 1959 were assigned the same average estimated exposure intensity. The lack of information on specific job assignments for such a large portion of these early workers when exposures were higher resulted in the misclassification of the exposure and effectively yielded exposure metrics that were differentiated only by the duration of each worker's employment. For this reason and because there was little measured fiber exposure data during the earlier period, identifying an adequate exposure-response model fit was unsuccessful. The two biggest problems were that the duration of employment was the best-fitting metric for modeling mesothelioma and that the Cox model assumptions were violated in modeling lung cancer mortality (see Section 5.4.3.4). As a result, this assessment developed a subcohort analysis by dividing the whole cohort into two groups: those hired before 1960 and those hired after 1959. This removed all but nine cohort members with missing department code and job category information and lessened the effect of estimates of early exposures where no air sampling data were available. For the subcohort of those hired after 1959, those two biggest problems were resolved: the assumptions of the Cox model were satisfied, and a lagged cumulative exposure with a decay (rather than duration of exposure, as for the full cohort) was the best-fitting metric for mesothelioma.

Of the 880 workers hired after 1959, 230 (26%) had died by December 31, 2006. The number of mesothelioma deaths in the subcohort is relatively small ($n = 7$, two deaths coded in ICD-10 and five deaths coded in ICD-9), but the rate of mesothelioma mortality was very similar in the subcohort (24.7 per 100,000 person-years versus 26.8 per 100,000 person-years for the full cohort [18 mesothelioma deaths], a difference of less than 10%).

6.2.3. Modeling of Mesothelioma Exposure Response

A Poisson model is employed for estimating the absolute risk of mesothelioma following exposure to LAA, as the Poisson distribution is an appropriate model to use with data that are counts of a relatively rare outcome, such as observed mesothelioma deaths in the Libby, MT worker cohort. Estimation of the exposure-response relationship for mesothelioma using the Poisson model was performed in WinBUGS software by a MCMC Bayesian approach with an uninformative or diffuse (almost flat) prior. The model was run to fit the mortality data to exposure data for various exposure metrics described above. To comparatively evaluate how much better one model fits than another, the DIC was used. DIC is used in Bayesian analysis and is an analogue of AIC (Burnham and Anderson, 2002). Use of the DIC and AIC is standard practice in comparing the fit of nonnested models to the same data set with the same dependent outcome variable but different independent covariates.

Modeling of mesothelioma mortality included an exposure metric with a cubic function of time (see eq 5-9), originally proposed in Peto et al. (1982) and employed in derivation of the

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1 IUR for asbestos (U.S. EPA, 1988a, 1986a), as well as modifications of Peto model (Peto model
2 with clearance) proposed in the asbestos literature (Berry et al., 2012). See Section 5.4.3 for
3 further details.

4 For the subcohort hired after 1959, two cumulative exposure metrics with decay provided
5 the best model fits. Both metrics had a common 5-year half-life, with lag times of either 10 or
6 15 years. The Peto model and Peto model with clearance did not fit as well. As it is less likely
7 that exposure during the last few years before death were contributory to the development of the
8 cancer and cancer mortality, the zero-lag metrics were dropped from further consideration. The
9 selected metric as well as the Peto model and Peto model with clearance were retained for
10 derivation of the IUR (see Section 6.2.7 below and for additional detail see Section 5.4.5). The
11 selected exposure metric was cumulative exposure with a 5-year half-life and a 10-year lag time
12 with a central estimate for the slope (KM) of 3.11×10^{-4} per fiber/cc-year with a 95% upper
13 confidence limit (UCL) of 5.08×10^{-4} per fiber/cc-year.

14

15 **6.2.4. Unit Risk Estimates for Mesothelioma Mortality**

16 The increased risk of mesothelioma mortality attributable to continuous fiber exposure
17 was estimated using a life-table procedure based on the general U.S. population. The life-table
18 procedure involved the application of the estimated LAA toxicity to a structured representation
19 of the general U.S. population in such a manner as to yield age-specific risk estimates for cancer
20 mortality in the presence or absence of exposure to LAA (see Section 5.4.5; Appendix G).

21 A default linear low-dose extrapolation was used because the mode of action by which
22 LAA causes mesothelioma was not established. The lower limit on the effective concentration
23 (LEC_{01}) yielded a unit risk for mesothelioma mortality of 0.053 per fiber/cc (POD of 1% divided
24 by the LEC_{01}).

25 The value of the effective concentration (EC) that would correspond to the measure of
26 central tendency is the EC_{01}. This value is used in the derivation of a combined risk of
27 mesothelioma and of lung cancer. The EC_{01} yielded a lifetime central estimate value of
28 0.032 per fiber/cc.

29 For mesothelioma, the undercounting of cases (underascertainment) is a particular
30 concern given the limitations of the ICD classification systems used before 1999. In practical
31 terms, this means that some true occurrences of mortality due to mesothelioma are missed on
32 death certificates and in almost all administrative databases such as the National Death Index.
33 Even after introduction of special ICD code for mesothelioma with introduction of ICD-10 in
34 1999, detection rates are still imperfect (Camidge et al., 2006; Pinheiro et al., 2004), and the
35 reported numbers of cases typically reflect an undercount of the true number. Kopylev et al.
36 (2011) reviewed the literature on this underascertainment and developed methods to account for
37 the likely numbers of undocumented mesothelioma deaths.

1   To compensate for mesothelioma underascertainment attributable to ICD coding, the
2   mesothelioma mortality unit risk was further adjusted following the analysis of Kopylev et al.
3   (2011). The adjusted mesothelioma central (i.e., maximum likelihood estimate) risk,
4   corresponding to the best-fit metric, was 0.044 per fiber/cc, and the adjusted mesothelioma
5   mortality unit risk was 0.074 per fiber/cc.
6   The adjusted mesothelioma risks for the Peto model and Peto model with clearance
7   ranged from 2-fold lower (0.035 per fiber/cc) to 3.6-fold higher (0.265 per fiber/cc). Thus, there
8   is uncertainty in mesothelioma risks generated from similar-fitting models from different
9   exposure metrics (see details in Section 5.4.5.3).
10
11   **6.2.5. Modeling of Lung Cancer Exposure Response**
12   All multivariate extended Cox models were fit to the subcohort hired after 1959 with
13   covariates for gender, race, date of birth, and exposure. Exposure for each of the 40 exposure
14   parameterizations was calculated independently, and the fit of these exposure metrics was
15   evaluated one at a time. Of the 40 exposure-response metrics, 14 demonstrated an adequate fit to
16   the data as measured by the overall model fit with the likelihood ratio test ($p < 0.05$) as well as
17   having statistically significant exposure metrics ($p < 0.05$). However, only the nine models that
18   demonstrated adequate model and exposure metric fit and incorporated a lag period to account
19   for cancer latency were considered further in the development of the IUR (see Tables 5-43 and
20   5-50).
21   Lagging exposure by 10 years was a better predictor of lung cancer mortality compared
22   to other lags. As it is less likely that exposure during the last few years before death were
23   contributory to the development of the cancer and cancer mortality, the zero lag metrics were
24   dropped from further consideration. The residence time-weighted cumulative exposure, both
25   with and without decay of the exposure metric, did not fit these lung cancer mortality data well
26   compared to the other models (see Table 5-44); this form of exposure metric does not
27   demonstrate evidence of an empirical fit to these epidemiologic data.
28   The model with the smallest AIC was for cumulative exposure with a 10-year half-life for
29   decay and a 10-year lag for cancer latency. The extended Cox model estimated a beta (the lung
30   cancer slope factor: KL) of 1.26×10^{-2} per fibers/cc-yr based on a 365-day year, and the
31   95th percentile upper bound was 1.88×10^{-2} per fibers/cc-yr. The *p*-value for the LAA regression
32   coefficient beta (slope) was <0.001. The slopes and confidence interval for the other exposure
33   metrics, which had similar fits to these data are reported in Table 5-45. Uncertainty in the choice
34   of the exposure metric is considered in the derivation of the unit risk (see details in
35   Section 5.4.5.2), representing the range of unit risks that are derived from these similarly fitting
36   metrics. The model results that were ultimately selected to reflect the upper bound among the
37   range of results were based on the cumulative exposure with a 10-year lag exposure metric

1 (CE10). The extended Cox model estimated a beta (slope) of 5.28×10^{-3} per fibers/cc-yr based

2 on a 365-day year, and the 95th percentile upper bound was 1.00×10^{-2} per fibers/cc-yr.

3

6.2.5.1. *Analysis of Potential Confounding of Lung Cancer Results by Smoking in the Subcohort*

6 EPA used two approaches to address the confounding issue, including restriction of the

7 cohort and an analytic evaluation of the potential for confounding by smoking including the

8 method described by Richardson (2010). Richardson (2010) describes a method to determine

9 whether an identified exposure relationship with lung cancer is confounded by unmeasured

10 smoking in an occupational cohort study. EPA implemented this methodology to model the

11 potential effects of LAA on the risk of COPD mortality on the subcohort of workers hired after

12 1959 (see Section 5.4.3.8). Summarizing these findings, EPA used the method described by

13 Richardson (2010) to evaluate whether exposures to LAA predicted mortality from COPD as an

14 indication of potential confounding by smoking and found a nonsignificant negative relationship,

15 which was inconsistent with confounding by smoking.

16

6.2.6. Unit Risk Estimates for Lung Cancer Mortality

18 The increased risk of lung cancer mortality attributable to continuous fiber exposure was

19 estimated using a life-table procedure based on the general U.S. population. The life-table

20 procedure involved applying the estimated LAA-specific toxicity to a structured representation

21 of the general U.S. population in such a manner as to yield age-specific risk estimated for cancer

22 mortality in the presence or absence of exposure to LAA (see Section 5.4.5; Appendix G). A

23 default linear low-dose extrapolation was used because the mode of action by which LAA causes

24 lung cancer was not established.

25 The nine exposure-response models retained in Table 5-45 all had reasonably similar

26 goodnesses of fit. No single model stands out as clearly statistically superior; however, there is a

27 range of quality of fit within the set that could be considered to have adequate fit. The lung

28 cancer mortality unit risks are shown in Table 5-52.

29 Using the results of the exposure model based on cumulative exposure with a 10-year lag

30 for cancer latency, the LEC_{01} yielded a lifetime unit risk of 0.0679 per fiber/cc. The value of the

31 risk that would correspond to the measure of central tendency involves the EC_{01} rather than the

32 LEC_{01}. The EC_{01} yielded a lifetime central estimate of 0.0399 per fiber/cc.

33 The resulting unit risks in Table 5-52 ranged from 0.0260 to 0.0679 per fiber/cc, for a

34 lifetime continuous exposure. This shows that the unit risk based on the exposure metric with

35 the lowest AIC value (i.e., cumulative exposure with a 10-year half-life for decay and a 10-year

36 lag for cancer latency) is in the center of this range (i.e., 0.0389 per fiber/cc). This estimate is in

37 the middle of the range of possible unit risks and does not capture the uncertainty across metrics

38 with similar goodness of fit (see details in Section 5.4.6).

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1   The model results selected to represent the upper-bound risk among the range of
2 reasonable results are based on a CE10 metric with a 10-year lag. The model results selected to
3 reflect the upper bound among the range of results are based on the CE10 exposure metric with a
4 10-year lag, providing a unit risk of 0.0679 per fiber/cc.
5

6 **6.2.7. Inhalation Unit Risk (IUR) Derivation Based on Combined Mesothelioma and Lung**
7 **Cancer Mortality from Exposure to Libby Amphibole Asbestos**

8   Once the cancer-specific lifetime unit risks are selected, the two are then combined. It is
9 important to note that this estimate of overall potency describes the risk of mortality from cancer
10 at either of the considered sites and is not just the risk of both cancers simultaneously. Because
11 each of the unit risks is itself an upper-bound estimate, summing such upper-bound estimates
12 across mesothelioma and lung cancer mortality is likely to overpredict the overall risk.
13 Therefore, following the recommendations of the *Guidelines for Carcinogen Risk Assessment*
14 (U.S. EPA, 2005a), a statistically appropriate upper bound on combined risk was derived to gain
15 an understanding of the overall risk of mortality resulting from mesothelioma and from lung
16 cancer. For mesothelioma, the exposure-response models developed by EPA using personal
17 exposure data on the subcohort (see Table 5-50) provided better fit to the subcohort data than the
18 Peto model and the Peto model with clearance that have been proposed in the asbestos literature.
19 For lung cancer, this assessment selected the upper bound among the lung cancer lifetime unit
20 risks from the plausible exposure metrics (regardless of the small residual differences in quality
21 of fit). Because there were few metrics with unit risks higher than the best fitting metric's unit
22 risk for lung cancer mortality endpoint, this method effectively selects the highest lifetime unit
23 risk among those considered for the lung cancer mortality endpoint.
24   Table 6-1 shows cancer-specific unit risks as well as combined risk of mesothelioma and
25 lung cancer. The IUR value of 0.17 per fiber/cc, continuous lifetime exposure, accounts for
26 important quantitative uncertainties in the selection of the specific exposure metric that may have
27 remained in an IUR that might have been based on the best-fitting exposure models alone.
28 Additional uncertainties are discussed in detail in Section 5.4.6.

Table 6-1. Estimates of the combined central estimate of the unit risk for mesothelioma and lung cancer and the combined upper-bound lifetime unit risks for mesothelioma and lung cancer risks (the Inhalation Unit Risk) for different combination of mesothelioma and lung cancer models[a]

Lung cancer	Mesothelioma	Combined central estimate per fiber/cc	Combined upper bound per fiber/cc
Selected IUR based directly on the Libby data			
CE10 subcohort	**CE10 5-yr half-life**	**0.115**	**0.169**
Best models from the epidemiologic literature (Peto model with clearance)			

CE10 subcohort	Peto with clearance
	    Decay rate of 6.8%/yr
	    Power of time = 3.9
	    Subcohort
		0.089	0.135

CE10 subcohort	Peto with clearance
	    Decay rate of 15%/yr
	    Power of time = 5.4
	    Subcohort
		0.061	0.092

Alternative model from the epidemiologic literature (Peto model)			

CE10 subcohort	Peto
	    No decay
	    Power of time = 3
	    Subcohort
		0.203	0.308

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

1   *Age-dependent adjustment factor*

2   As discussed in Section 4.7.1.1, there is no chemical-specific information for LAA, or

3   general asbestos, that would allow for the computation of a chemical-specific age-dependent

4   adjustment factor for assessing the risk of exposure that includes early-life exposures.

5   The review of mode-of-action information in this assessment (see Section 4.6.2.2)

6   concluded that the available information on the mode of action by which LAA causes lung

7   cancer or mesothelioma is complex and a mode of action is not established at this time. Thus, in

8   accordance with EPA's *Supplemental Guidance for Assessing Susceptibility from Early-Life*

9   *Exposure to Carcinogens* (U.S. EPA, 2005b), the application of the age-dependent adjustment

10   factors for substances that act through a mutagenic mode of action is not recommended.

11

1 **6.2.7.1. *Comparison with Other Published Studies of Libby, MT Workers Cohort***

2   Several published studies have previously evaluated risk of mesothelioma and lung

3 cancer (i.e., Larson et al., 2010b; Moolgavkar et al., 2010; Berman and Crump, 2008; Sullivan,

4 2007) in Libby, MT workers cohort. For mesothelioma, only Moolgavkar et al. (2010) provided

5 an exposure-response relationship for absolute risk of mesothelioma mortality that would be

6 comparable with this current assessment. Based on the full cohort, with mortality data through

7 2001 and a modification of the Peto/Nicholson exposure metric, life-table analysis would

8 provide an upper-bound unit risk of approximately 0.13 per fiber/cc continuous lifetime

9 exposure. Therefore, utilization of the exposure response modeling of Moolgavkar et al. (2010),

10 would provide an IUR for excess mesothelioma mortality in close agreement with the IUR

11 derived in this assessment (see Section 5.4.5.3.1 for more details).

12   For lung cancer, all of the studies provide exposure-response relationships in terms of

13 relative risk of lung cancer mortality, and thus, may provide risk estimates comparable to this

14 assessment. However, inclusion criteria, length of mortality follow-up, and analytic methods

15 differ among the analyses—thus, the results are not necessarily interchangeable. For comparison

16 purposes, the lung cancer unit risks from these studies are computed from life-table analyses (see

17 Table 5-54). The lung cancer unit risks calculated based on the published literature, ranged from

18 0.010 to 0.079 per fiber/cc (based on the upper confidence limit). This is in close agreement

19 with this current assessment where an upper-bound estimate of 0.068 per fiber/cc, continuous

20 lifetime exposure is derived (see Section 5.4.5.3.1 for more details).

21

22 **6.2.8. Uncertainty in the Cancer Risk Values**

23   It is important to consider the uncertainties in the derivation of the mesothelioma and

24 lung cancer mortality risks in this assessment in the context of uncertainties in animal-based

25 health assessments. This assessment does not involve extrapolation from high dose in animals to

26 low dose in humans. The current assessment is based on a well-documented and well-studied

27 cohort of workers with adequate years of follow-up to evaluate mesothelioma and lung cancer

28 mortality risks with PODs within the range of the data. The discussions in Section 5.4.6 explore

29 uncertainty in the derivation of the IUR in order to provide a comprehensive and transparent

30 context for the resulting cancer mortality risk estimates.

31   Section 5.4.6.1 details the several sources of uncertainty in the assessment of the cancer

32 exposure-response relationships and the use of those data to derive the inhalation unit risk. The

33 text that follows summarizes the primary sources of uncertainty and, where possible, the

34 expected direction of effect on the exposure-response risk estimates and the inhalation units risk.

1) *Uncertainty in low-dose extrapolation (see Section 5.4.6.1.1)*

- Some uncertainty remains in the extrapolation of risks based on occupational exposure to environmental exposure levels, but this uncertainty is considered to be low as the lower range of occupational exposure overlaps with expected environmental exposure levels.

2) *Uncertainty in exposure assessment, including analytical measurements uncertainty (see Section 5.4.6.1.2)*

- The JEM was based on the "high" exposure estimate for each job according to Amandus et al. (1987b), and to some extent this could be an overestimate of exposure. The associated cancer risk would be somewhat underestimated resulting in a somewhat underestimated IUR.

- The JEM was largely based on estimated fiber concentration using PCM measurement (with some extrapolations in time), and because PCM may count all long and thin objects as fibers, these measurement could overestimate the true LAA fiber concentrations, leading to an overestimate of exposure and a somewhat underestimated cancer risk resulting in a somewhat underestimated IUR.

- PCM measurements in the era of NIOSH measurements in Libby used a lower resolution, and therefore, included only somewhat thicker fibers, thereby counting fewer fibers than would have been counted by later PCM standards. These earlier measurements could underestimate the true LAA fiber concentrations, leading to an underestimate of exposure and an overestimate of cancer risk resulting in a somewhat overestimated IUR.

- The PCM measurement is the available exposure metric for analysis of the Libby worker cohort at the time of this assessment. Currently, there is no optimal choice of the best dose metric for asbestos, in general and in particular, for LAA. Uncertainties related to PCM analytical method are discussed in Section 2, and such uncertainties cannot be related to the IUR at the time of this assessment.

- Random measurement error in the assignment of exposures could have the effect of underestimating the risk of lung cancer mortality because that measure of risk is based on a relative measure. The effect would be to somewhat underestimate the risk of lung cancer, resulting in a somewhat underestimated unit risk for lung cancer. It is unclear what the impact of such measurement error would be on the absolute risk of mesothelioma.

- Exposure to other kinds of asbestos and residential exposure to LAA may have caused workers' actual personal exposures (as the sum of occupational and nonoccupational exposures) to have been underestimated by the use of estimated Libby occupational exposure information alone. This could underestimate the true LAA fiber exposures leading to an overestimate of the associated cancer risk resulting in a somewhat overestimated IUR.

3) *Uncertainty in model form (see Section 5.6.4.1.3)*

- For mesothelioma, the Poisson model is the standard epidemiologic form and considered to be the most appropriate model form for rare health outcomes; therefore, uncertainty is considered to be low. For lung cancer mortality, the Cox proportional hazards model is the standard epidemiologic form. It is considered to be the most appropriate model form for health outcomes with time-varying exposure data and thus uncertainty is considered to be low.

4) *Uncertainty in selection of exposure metric (see Section 5.6.4.1.4)*

- There is uncertainty about what metric should be used for modeling exposures to LAA. Table 5-53 illustrates the uncertainty in the IUR due to exposure metric selection. The quantitative uncertainty is about threefold.

5) *Uncertainty in assessing mortality corresponding to other cancer endpoints (see Section 5.6.4.1.5)*

- The lack of sufficient numbers of workers to estimate the risk of other cancers potentially related to LAA exposure is an uncertainty of unclear direction but is considered to be low due to the rarity of those cancers.

6) *Uncertainty in control of potential confounding in modeling lung cancer mortality (see Section 5.4.6.1.6)*

- The uncertainty in control of potential confounding by smoking is considered to be low as the described sensitivity analysis did not show evidence of potential confounding.

7) *Uncertainty due to potential effect modification (see Section 5.4.6.1.7)*

- Smoking was not considered to be related to LAA exposure, and therefore, smoking is not considered to be a likely effect modifier of cancer risk. Age has been shown to be a potential effect modifier of lung cancer risk but there was no evidence of this relationship in the subcohort.

8) *Uncertainty due to length of follow-up (see Section 5.4.6.1.8)*

- There is uncertainty related to the limited follow-up for cancer mortality, and it is possible that with subsequent mortality follow-up, the IUR could change in a direction that is unknown.

9) *Uncertainty in the use of life-tables to calculate cancer mortality IUR (see Section 5.4.6.1.9)*

- The life-table procedure computes the extra risk of death from birth to 85 years of age. If the life tables were extended from 85 to 90 years to account for longer life spans, the selected lung cancer mortality unit risk (Table 5-53 shows this as 0.068) would be somewhat larger, about 5−10%, and the selected mesothelioma unit risk (Table 5-53 shows this as 0.122) would be slightly less (about 3%).

1 Taking both effects into consideration, the uncertainty in the IUR is considered to
2 be low.

3 *10) Uncertainty in combining mortality risks to derive a composite cancer mortality IUR*
4 *(see Section 5.4.6.1.10)*

5 • EPA assumed that the cancer risks were independent, conducted a bounding
6 analysis, and showed the related uncertainty to be very low.

7 *11) Uncertainty due to extrapolation of findings in adults to children (see*
8 *Section 5.4.6.1.11)*

9 • There is uncertainty in the assumption that risks are independent of age and that
10 children are at the same exposure-related risk as adults. The lack of published
11 information on cancer risks associated with exposures during childhood remains
12 an uncertainty of unclear magnitude.

7. REFERENCES

Adgate, JL; Cho, SJ; Alexander, BH; Ramachandran, G; Raleigh, KK; Johnson, J; Messing, RB; Williams, AL; Kelly, J; Pratt, GC. (2011). Modeling community asbestos exposure near a vermiculite processing facility: Impact of human activities on cumulative exposure. J Expo Sci Environ Epidemiol 21: 529-535. http://dx.doi.org/10.1038/jes.2011.8

Albert, RE; Lippmann, M; Briscoe, W. (1969). The characteristics of bronchial clearance in humans and the effects of cigarette smoking. Arch Environ Occup Health 18: 738-755.

Alexander, BH; Raleigh, KK; Johnson, J; Mandel, JH; Adgate, JL; Ramachandran, G; Messing, RB; Eshenaur, T; Williams, A. (2012). Radiographic evidence of nonoccupational asbestos exposure from processing Libby vermiculite in Minneapolis, Minnesota. Environ Health Perspect 120: 44-49. http://dx.doi.org/10.1289/ehp.1103529

Amandus, HE; Althouse, R; Morgan, WKC; Sargent, EN; Jones, R. (1987a). The morbidity and mortality of vermiculite miners and millers exposed to tremolite-actinolite: Part III. Radiographic findings. Am J Ind Med 11: 27-37.

Amandus, HE; Wheeler, R. (1987). The morbidity and mortality of vermiculite miners and millers exposed to tremolite-actinolite: Part II. Mortality. Am J Ind Med 11: 15-26.

Amandus, HE; Wheeler, R; Armstrong, BG; McDonald, AD; McDonald, JC; Sébastien, P. (1988). Mortality of vermiculite miners exposed to tremolite. Ann Occup Hyg 32: 459465. http://dx.doi.org/10.1093/annhyg/32.inhaled_particles_VI.459

Amandus, HE; Wheeler, R; Janković, J; Tucker, J. (1987b). The morbidity and mortality of vermiculite miners and millers exposed to tremolite-actinolite: Part I. Exposure estimates. Am J Ind Med 11: 1-14.

Anderson, HA; Lilis, R; Daum, SM; Fischbein, AS; Selikoff, IJ. (1976). Household-contact asbestos neoplastic risk. Ann N Y Acad Sci 271: 311-323. http://dx.doi.org/10.1111/j.1749-6632.1976.tb23127.x

Anderson, HA; Lilis, R; Daum, SM; Selikoff, IJ. (1979). Asbestosis among household contacts of asbestos factory workers. Ann N Y Acad Sci 330: 387-399. http://dx.doi.org/10.1111/j.1749-6632.1979.tb18741.x

Andrion, A; Bosia, S; Paoletti, L; Feyles, E; Lanfranco, C; Bellis, D; Mollo, F. (1994). Malignant peritoneal mesothelioma in a 17-year-old boy with evidence of previous exposure to chrysotile and tremolite asbestos. Hum Pathol 25: 617-622. http://dx.doi.org/10.1016/0046-8177(94)90230-5

Armstrong, B. (1998). Effect of measurement error on epidemiological studies of environmental and occupational exposures. Occup Environ Med 55: 651-656. http://dx.doi.org/10.1136/oem.55.10.651

Armstrong, BG; McDonald, JC; Sébastien, P; Althouse, R; Amandus, HE; Wheeler, R. (1988). Radiological changes in vermiculite workers exposed to Tremolite. Ann Occup Hyg 32: 469-474. http://dx.doi.org/10.1093/annhyg/32.inhaled_particles_VI.469

Asgharian, B; Anjilvel, S. (1998). A multiple-path model of fiber deposition in the rat lung. Toxicol Sci 44: 80-86. http://dx.doi.org/10.1006/toxs.1998.2476

Asgharian, B; Menache, MG; Miller, FJ. (2004). Modeling age-related particle deposition in humans. J Aerosol Med Pulm Drug Deliv 17: 213-224. http://dx.doi.org/10.1089/jam.2004.17.213

Athanasiou, K; Constantopoulos, SH; Rivedal, E; Fitzgerald, DJ; Yamasaki, H. (1992). Metsovo-tremolite asbestos fibres: In vitro effects on mutation, chromosome aberration, cell transformation and intercellular communication. Mutagenesis 7: 343-347. http://dx.doi.org/10.1093/mutage/7.5.343

ATS (American Thoracic Society). (2004). Diagnosis and initial management of nonmalignant diseases related to asbestos. Am J Respir Crit Care Med 170: 691-715. http://dx.doi.org/10.1164/rccm.200310-1436ST

ATSDR (Agency for Toxic Substances and Disease Registry). (2000). Health consultation: Mortality from asbestosis in Libby, Montana. Atlanta, GA: U.S. Department of Health and Human Services, Agency for Toxic Substances and Disease Registry. http://www.atsdr.cdc.gov/hac/pha/pha.asp?docid=1225&pg=0

ATSDR (Agency for Toxic Substances and Disease Registry). (2001a). Toxicological profile for asbestos [ATSDR Tox Profile]. Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service. http://www.atsdr.cdc.gov/ToxProfiles/tp61.pdf

ATSDR (Agency for Toxic Substances and Disease Registry). (2001b). Year 2000 medical testing of individuals potentially exposed to asbestiform minerals associated with vermiculite in Libby, Montana: A report to the community. Atlanta, GA: U.S. Department of Health and Human Services, Agency for Toxic Substances & Disease Registry. http://www.atsdr.cdc.gov/asbestos/sites/libby_montana/medical_testing.html

ATSDR (Agency for Toxic Substances and Disease Registry). (2002). Libby tests: Lung abnormality rates high. Atlanta, GA: U.S. Department of Health and Human Services, Agency for Toxic Substances and Disease Registry.

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

ATSDR (Agency for Toxic Substances and Disease Registry). (2003). Report on the expert panel on health effects of asbestos and synthetic vitreous fibers: The influence of fiber length. U.S. Department of Health and Human Services, Agency for Toxic Substances and Disease Registry.

ATSDR (Agency for Toxic Substances and Disease Registry). (2005). Health consultation: Former O.C. Scott and Sons Company, 14111 Scottslawn Road, Marysville, Union County, Ohio. EPA Facility ID: OHD990834483. (PB2008-104070). Atlanta, GA: U.S. Departmento of Health and Human Services, Agency for Toxic Substances and Disease Registry.

ATSDR (Agency for Toxic Substances and Disease Registry). (2008). Summary report: Exposure to asbestos-containing vermiculite from Libby, Montana, at 28 processing sites in the United States. Atlanta, GA: U.S. Department of Health and Human Services, Agency for Toxic Substances and Disease Registry. http://www.atsdr.cdc.gov/asbestos/sites/national_map/Summary_Report_102908.pdf

Aust, AE; Cook, PM; Dodson, RF. (2011). Morphological and chemical mechanisms of elongated mineral particle toxicities [Review]. J Toxicol Environ Health B Crit Rev 14: 40-75. http://dx.doi.org/10.1080/10937404.2011.556046

Bailey, KF; Kelse, J; Wylie, AG; Lee, RJ. (2006). The asbestiform and prismatic mineral growth habit and their relationship to cancer studies: A pictorial presentation. Alexandria, VA: National Stone, Sand & Gravel Association. http://www.regulations.gov/#!documentDetail;D=EPA-HQ-ORD-2003-0016-0076

Baker, EL; Dagg, T; Greene, RE. (1985). Respiratory illness in the construction trades. I. The significance of asbestos-associated pleural disease among sheet metal workers. J Occup Med 27: 483-489.

Bandli, BR; Gunter, ME; Twamley, B; Foit, FF, Jr; Cornelius, SB. (2003). Optical, compositional, morphological, and X-ray data on eleven particles of amphibole from Libby, Montana, USA. Can Mineral 41: 1241-1253.

Banks, DE; Shi, R; McLarty, J; Cowl, CT; Smith, D; Tarlo, SM; Daroowalla, F; Balmes, J; Baumann, M. (2009). American College of Chest Physicians consensus statement on the respiratory health effects of asbestos. Results of a Delphi study. Chest 135: 1619-1627.

Baris, I; Simonato, L; Artvinli, M; Pooley, F; Saracci, R; Skidmore, J; Wagner, C. (1987). Epidemiological and environmental evidence of the health effects of exposure to erionite fibres: A four-year study in the Cappadocian region of Turkey. Int J Cancer 39: 10-17. http://dx.doi.org/10.1002/ijc.2910390104

Baris, YI; Artvinli, M; Sahin, AA. (1979). Environmental mesothelioma in Turkey. Ann N Y Acad Sci 330: 423-432. http://dx.doi.org/10.1111/j.1749-6632.1979.tb18744.x

Barone-Adesi, F; Ferrante, D; Bertolotti, M; Todesco, A; Mirabelli, D; Terracini, B; Magnani, C. (2008). Long-term mortality from pleural and peritoneal cancer after exposure to asbestos: Possible role of asbestos clearance. Int J Cancer 123: 912-916. http://dx.doi.org/10.1002/ijc.23609

Bates, DV; Fish, BR; Hatch, TF; Mercer, TT; Morrow, PE. (1966). Deposition and retention models for internal dosimetry of the human respiratory tract: Task group on lung dynamics. Health Phys 12: 173-207.

Bateson, T; Wright, J. (2010). Regression calibration for classical exposure measurement error in environmental epidemiology studies using multiple local surrogate exposures. Am J Epidemiol 172: 344-352. http://dx.doi.org/10.1093/aje/kwq123

Bateson, TF; Kopylev, L. (2014). Influence of exposure assessment and parameterization on exposure response. Aspects of epidemiologic cohort analysis using the Libby Amphibole asbestos worker cohort. J Expo Sci Environ Epidemiol e-pub. http://dx.doi.org/doi: 10.1038/jes.2014.3

Bazas, T; Oakes, D; Gilson, JC; Bazas, B; Mcdonald, JC. (1985). Pleural calcification in northwest Greece. Environ Res 38: 239-247. http://dx.doi.org/10.1016/0013-9351(85)90088-X

Becquemin, MH; Swift, DL; Bouchikhi, A; Roy, M; Teillac, A. (1991). Particle deposition and resistance in the noses of adults and children. Eur Respir J 4: 694-702.

Bennett, W; Zeman, K; Jarabek, A. (2003). Nasal contribution to breathing with exercise: effect of race and gender. J Appl Physiol 95: 497-503. http://dx.doi.org/10.1152/japplphysiol.00718.2002

Bennett, WD; Zeman, KL. (2004). Effect of body size on breathing pattern and fine-particle deposition in children. J Appl Physiol 97: 821-826. http://dx.doi.org/10.1152/japplphysiol.01403.2003

Bennett, WD; Zeman, KL. (2005). Effect of race on fine particle deposition for oral and nasal breathing. Inhal Toxicol 17: 641-648. http://dx.doi.org/10.1080/08958370500188984

Bennett, WD; Zeman, KL; Jarabek, AM. (2008). Nasal contribution to breathing and fine particle deposition in children versus adults. J Toxicol Environ Health A 71: 227-237. http://dx.doi.org/10.1080/15287390701598200

Bennett, WD; Zeman, KL; Kim, C. (1996). Variability of fine particle deposition in healthy adults: effect of age and gender. Am J Respir Crit Care Med 153: 1641-1647.

Bennett, WD; Zeman, KL; Kim, C; Mascarella, J. (1997). Enhanced deposition of fine particles in COPD patients spontaneously breathing at rest. Inhal Toxicol 9: 1-14. http://dx.doi.org/10.1080/089583797198376

Benson, B. (2014). Email from Bob Benson to James Lockey, cc Timothy Hilbert. Personal communications. Benson, B.

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

Berkson, J. (1950). Are there two regressions? J Am Stat Assoc 45: 164-180.

Berman, DW. (2010). Comparing milled fiber, Quebec ore, and textile factory dust: has another piece of the asbestos puzzle fallen into place [Review]. Crit Rev Toxicol 40: 151-188. http://dx.doi.org/10.3109/10408440903349137

Berman, DW. (2011). Apples to apples: The origin and magnitude of differences in asbestos cancer risk estimates derived using varying protocols. Risk Anal 55: 565-568. http://dx.doi.org/10.1111/j.1539-6924.2010.01581.x

Berman, DW; Crump, KS. (2008). Update of potency factors for asbestos-related lung cancer and mesothelioma. Crit Rev Toxicol 38: 1-47. http://dx.doi.org/10.1080/10408440802276167

Berman, DW; Crump, KS; Chatfield, EJ; Davis, JM; Jones, AD. (1995). The sizes, shapes, and mineralogy of asbestos structures that induce lung tumors or mesothelioma in AF/HAN rats following inhalation. Risk Anal 15: 181-195.

Bernstein, D; Rogers, R; Smith, P. (2005). The biopersistence of Canadian chrysotile asbestos following inhalation: final results through 1 year after cessation of exposure. Inhal Toxicol 17: 1-14. http://dx.doi.org/10.1080/08958370590885663

Bernstein, DM; Chevalier, J; Smith, P. (2003). Comparison of Calidria chrysotile asbestos to pure tremolite: Inhalation biopersistence and histopathology following short-term exposure. Inhal Toxicol 15: 1387-1419. http://dx.doi.org/10.1080/08958370390248888

Bernstein, DM; Mast, R; Anderson, R; Hesterberg, TW; Musselman, R; Kamstrup, O; Hadley, J. (1994). An experimental approach to the evaluation of the biopersistence of respirable synthetic fibers and minerals. Environ Health Perspect 102 Suppl 5: 15-18.

Bernstein, DM; Rogers, R; Smith, P. (2004). The biopersistence of Brazilian chrysotile asbestos following inhalation. Inhal Toxicol 16: 745-761. http://dx.doi.org/10.1080/08958370490490176

Bernstein, DM; Rogers, RA; Sepulveda, R; Donaldson, K; Schuler, D; Gaering, S; Kunzendorf, P; Chevalier, J; Holm, SE. (2011). Quantification of the pathological response and fate in the lung and pleura of chrysotile in combination with fine particles compared to amosite-asbestos following short-term inhalation exposure. Inhal Toxicol 23: 372-391. http://dx.doi.org/10.3109/08958378.2011.575413

Berry, G. (1991). Prediction of mesothelioma, lung cancer, and asbestosis in former Wittenoom asbestos workers. Br J Ind Med 48: 793-802.

Berry, G. (1999). Models for mesothelioma incidence following exposure to fibers in terms of timing and duration of exposure and the biopersistence of the fibers. Inhal Toxicol 11: 111-130. http://dx.doi.org/10.1080/089583799197203

Berry, G; de Klerk, N; Reid, A; Ambrosini, G; Fritschi, L; Olsen, N; Merler, E; Musk, A. (2004). Malignant pleural and peritoneal mesotheliomas in former miners and millers of crocidolite at Wittenoom, Western Australia. Occup Environ Med 61: e14.

Berry, G; Gilson, JC; Holmes, S; Lewinsohn, HC; Roach, SA. (1979). Asbestosis: A study of dose-response relationships in an asbestos textile factory. Occup Environ Med 36: 98-112. http://dx.doi.org/10.1136/oem.36.2.98

Berry, G; Pooley, F; Gibbs, A; Harris, J; McDonald, J. (2009). Lung fiber burden in the Nottingham gas mask cohort. Inhal Toxicol 21: 168-172. http://dx.doi.org/10.1080/08958370802291304

Berry, G; Reid, A; Aboagye-Sarfo, P; de Klerk, NH; Olsen, NJ; Merler, E; Franklin, P; Musk, AW. (2012). Malignant mesotheliomas in former miners and millers of crocidolite at Wittenoom (Western Australia) after more than 50 years follow-up. Br J Cancer 106: 1016-1020. http://dx.doi.org/10.1038/bjc.2012.23

Berry, G; Wagner, JC. (1969). The application of a mathematical model describing the times of occurrence of mesotheliomas in rats following inoculation with asbestos. Br J Cancer 23: 582-586.

Bianchi, AB; Mitsunaga, SI; Cheng, JQ; Klein, WM; Jhanwar, SC; Seizinger, B; Kley, N; Klein-Szanto, AJ; Testa, JR. (1995). High frequency of inactivating mutations in the neurofibromatosis type 2 gene (NF2) in primary malignant mesotheliomas. PNAS 92: 10854-10858.

Bianchi, C; Bianchi, T. (2008). Susceptibility and resistance in the genesis of asbestos-related mesothelioma. Indian J Occup Environ Med 12: 57-60. http://dx.doi.org/10.4103/0019-5278.43261

Bianchi, C; Bianchi, T. (2009). Malignant pleural mesothelioma in Italy. Indian J Occup Environ Med 13: 80-83. http://dx.doi.org/10.4103/0019-5278.55124

Bignon, J; Monchaux, G; Sebastien, P; Hirsch, A; Lafuma, J. (1979). Human and experimental data on translocation of asbestos fibers through the respiratory system. Ann N Y Acad Sci 330: 745-750.

Bignon, J; Sebastien, P; Gaudichet, A. (1978). Measurement of asbestos retention in the human respiratory system related to health effects. In CC Gravatt; PD LaFleur; KFJ Heinrich (Eds.), Proceedings of the workshop on asbestos: definitions and measurement methods (pp. 95-119). Washington, DC: National Bureau of Standards.

Bilgrad, R. (1997). National Death Index users manual. Hyattsville, MD: National Center for Health Statistics.

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

Bilgrad, R. (1999). National Death Index Plus: Coded causes of death: Supplement to the National Death Index user's manual. Hyattsville, MD: National Center for Health Statistics.

Biswas, R; Bunderson-Schelvan, M; Holian, A. (2011). Potential role of the inflammasome-derived inflammatory cytokines in pulmonary fibrosis. Pulm Med 2011: 105707. http://dx.doi.org/10.1155/2011/105707

Blake, D; Bolin, C; Cox, D; Cardozo-Pelaez, F; Pfau, J. (2007). Internalization of Libby amphibole asbestos and induction of oxidative stress in murine macrophages. Toxicol Sci 99: 277-288. http://dx.doi.org/10.1093/toxsci/kfm166

Blake, D; Wetzel, S; Pfau, J. (2008). Autoantibodies from mice exposed to Libby amphibole asbestos bind SSA/Ro52-enriched apoptotic blebs of murine macrophages. Toxicology 246: 172-179. http://dx.doi.org/10.1016/j.tox.2008.01.008

Bocchetta, M; Di Resta, I; Powers, A; Fresco, R; Tosolini, A; Testa, J; Pass, H; Rizzo, P; Carbone, M. (2000). Human mesothelial cells are unusually susceptible to simian virus 40-mediated transformation and asbestos cocarcinogenicity. PNAS 97: 10214-10219. http://dx.doi.org/10.1073/pnas.170207097

Boettcher, AL. (1966). Vermiculite, hydrobiotite, and biotite in the Rainy Creek igneous complex near Libby, Montana. Clay Miner 6: 283-296.

Boettcher, AL. (1967). The Rainy Creek Alkaline-Ultramafic Igneous Complex near Libby, Montana. I: Ultramafic rocks and fenite. J Geol 75: 526-553. http://dx.doi.org/10.1086/627280

Borton, EK; Lemasters, GK; Hilbert, TJ; Lockey, JE; Dunning, KK; Rice, CH. (2012). Exposure estimates for workers in a facility expanding Libby vermiculite: updated values and comparison with original 1980 values. J Occup Environ Med 54: 1350-1358. http://dx.doi.org/10.1097/JOM.0b013e31824fe174

Boutin, C; Dumortier, P; Rey, F; Viallat, JR; De Vuyst, P. (1996). Black spots concentrate oncogenic asbestos fibers in the parietal pleura. Thoracoscopic and mineralogic study. Am J Respir Crit Care Med 153: 444-449. http://dx.doi.org/10.1164/ajrccm.153.1.8542156

Brain, JD; Mensah, GA. (1983). Comparative toxicology of the respiratory tract. Am Rev Respir Dis 128: S87-S90.

Bringardner, BD; Baran, CP; Eubank, TD; Marsh, CB. (2008). The role of inflammation in the pathogenesis of idiopathic pulmonary fibrosis [Review]. Antioxid Redox Signal 10: 287-301. http://dx.doi.org/10.1089/ars.2007.1897

Broaddus, VC; Everitt, JI; Black, B; Kane, AB. (2011). Non-neoplastic and neoplastic pleural endpoints following fiber exposure [Review]. J Toxicol Environ Health B Crit Rev 14: 153-178. http://dx.doi.org/10.1080/10937404.2011.556049

Brody, AR; Hill, LH; Adkins, B, Jr; O'Connor, RW. (1981). Chrysotile asbestos inhalation in rats: deposition pattern and reaction of alveolar epithelium and pulmonary macrophages. Am Rev Respir Dis 123: 670-679.

Brody, AR; Roe, MW. (1983). Deposition pattern of inorganic particles at the alveolar level in the lungs of rats and mice. Am Rev Respir Dis 128: 724-729.

Brown, BM; Gunter, ME. (2003). Morphological and optical characterization of amphiboles from Libby, Montana, USA by spindle stage assisted-polarized light microscopy. Microscope 51: 121-140.

Brown, J; Bennett, W. (2004). Deposition of coarse particles in cystic fibrosis: Model predictions versus experimental results. J Aerosol Med 17: 239-248. http://dx.doi.org/10.1089/jam.2004.17.239

Brown, JS; Wilson, WE; Grant, LD. (2005). Dosimetric comparisons of particle deposition and retention in rats and humans. Inhal Toxicol 17: 355-385. http://dx.doi.org/10.1080/08958370590929475

Brown, JS; Zeman, KL; Bennett, WD. (2001). Regional deposition of coarse particles and ventilation distribution in healthy subjects and patients with cystic fibrosis. J Aerosol Med Pulm Drug Deliv 14: 443-454. http://dx.doi.org/10.1089/08942680152744659

Bunderson-Schelvan, M; Pfau, JC; Crouch, R; Holian, A. (2011). Nonpulmonary outcomes of asbestos exposure [Review]. J Toxicol Environ Health B Crit Rev 14: 122-152. http://dx.doi.org/10.1080/10937404.2011.556048

Burnham, KP; Anderson, DR. (2002). Model selection and multimodel inference: a practical information-theoretic approach (2nd ed.). New York: Springer. http://www.springer.com/statistics/statistical+theory+and+methods/book/978-0-387-95364-9

Burr, D. (1988). On errors-in-variables in binary regression-Berkson case. J Am Stat Assoc 83: 739-743.

Camidge, DR; Stockton, DL; Bain, M. (2006). Factors affecting the mesothelioma detection rate within national and international epidemiological studies: Insights from Scottish linked cancer registry-mortality data. Br J Cancer 95: 649-652. http://dx.doi.org/10.1038/sj.bjc.6603293

Camner, P. (1980). Clearance of particles from the human tracheobronchial tree [Review]. Clin Sci (Lond) 59: 79-84. http://dx.doi.org/10.1042/cs0590079

Carbone, M; Albelda, SM; Broaddus, VC; Flores, RM; Hillerdal, G; Jaurand, MC; Kjaerheim, K; Pass, HI; Robinson, B; Tsao, A. (2007). Eighth International Mesothelioma Interest Group [Review]. Oncogene 26: 6959-6967. http://dx.doi.org/10.1038/sj.onc.1210515

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

Carroll, RJ; Ruppert, D; Stefanski, LA. (2006). Measurement error in nonlinear models: A modern perspective. London, England: Chapman & Hall.

Case, BW; Abraham, JL; Meeker, G; Pooley, FD; Pinkerton, KE. (2011). Applying definitions of "asbestos" to environmental and "low-dose" exposure levels and health effects, particularly malignant mesothelioma [Review]. J Toxicol Environ Health B Crit Rev 14: 3-39. http://dx.doi.org/10.1080/10937404.2011.556045

Case, BW; Dufresne, A; McDonald, AD; McDonald, JC; Sebastien, P. (2000). Asbestos fiber type and length in lungs of chrysotile textile and production workers: Fibers longer than 18 mum. Inhal Toxicol 12: 411-418. http://dx.doi.org/10.1080/08958370050165319

Castellan, RM; Sanderson, WT; Petersen, MR. (1985). Prevalence of radiographic appearance of pneumoconiosis in an unexposed blue collar population. Am Rev Respir Dis 131: 684-686.

Castranova, V; Pailes, W; Judy, D; Blake, T; Schwegler-Berry, D; Jones, W. (1996). In vitro effects of large and small glass fibers on rat alveolar macrophages. J Toxicol Environ Health 49: 357-369.

CDC (Centers for Disease Control and Prevention). (2009). Malignant mesothelioma mortality: United States, 19992005. MMWR Morb Mortal Wkly Rep 58: 393-396.

CEC (Commission of the European Communities). (1996). Guidance on risk assessment at work. Luxembourg: Office for Official Publications of the European Communities. http://osha.europa.eu/en/topics/riskassessment/guidance.pdf

Cerny, FJ. (1987). Breathing pattern during exercise in young Black and Caucasian subjects. J Appl Physiol 62: 2220-2223.

Cheng, JQ; Lee, WC; Klein, MA; Cheng, GZ; Jhanwar, SC; Testa, JR. (1999). Frequent mutations of NF2 and allelic loss from chromosome band 22q12 in malignant mesothelioma: Evidence for a two-hit mechanism of NF2 inactivation. Genes Chromosomes Cancer 24: 238-242. http://dx.doi.org/10.1002/(SICI)1098-2264(199903)24:3<238::AID-GCC9>3.0.CO;2-M

Cheng, YS. (1986). Bivariate lognormal distribution for characterizing asbestos fiber aerosols. Aerosol Sci Technol 5: 359-368. http://dx.doi.org/10.1080/02786828608959100

Chiu, WA; Crump, KS. (2012). Using copulas to introduce dependence in dose-response modeling of multiple binary endpoints. Journal of Agricultural, Biological, and Environmental Statistics 17: 107-127. http://dx.doi.org/10.1007/s13253-011-0078-2

Christensen, KY; Bateson, TF; Kopylev, L. (2013). Low Levels of Exposure to Libby Amphibole Asbestos and Localized Pleural Thickening. J Occup Environ Med 55: 1350-1355. http://dx.doi.org/10.1097/JOM.0b013e3182a3bb25

Christensen, KY; Kopylev, L. (2012). Localized pleural thickening: smoking and exposure to Libby vermiculite. J Expo Sci Environ Epidemiol 22: 320-323. http://dx.doi.org/10.1038/jes.2012.18

Churg, A. (1982). Fiber counting and analysis in the diagnosis of asbestos-related disease. Hum Pathol 13: 381-392. http://dx.doi.org/10.1016/S0046-8177(82)80227-X

Churg, A. (1988). Chrysotile, tremolite, and malignant mesothelioma in man [Review]. Chest 93: 621-628. http://dx.doi.org/10.1378/chest.93.3.621

Churg, A. (1994). Deposition and clearance of chrysotile asbestos. Ann Occup Hyg 38: 625-633. http://dx.doi.org/10.1093/annhyg/38.4.625

Churg, A; Vedal, S. (1994). Fiber burden and patterns of asbestos-related disease in workers with heavy mixed amosite and chrysotile exposure. Am J Respir Crit Care Med 150: 663-669. http://dx.doi.org/10.1164/ajrccm.150.3.8087335

Churg, A; Wright, J; Gilks, B; DePaoli, L. (1989). Rapid short-term clearance of chrysotile compared with amosite asbestos in the guinea pig. Am Rev Respir Dis 139: 885-890.

Churg, A; Wright, JL; Vedal, S. (1993). Fiber burden and patterns of asbestos-related disease in chrysotile miners and millers. Am Rev Respir Dis 148: 25-31.

Churg, AM; Warnock, ML. (1981). Asbestos and other ferruginous bodies: their formation and clinical significance [Review]. Am J Pathol 102: 447-456.

Claeskens, G; Hjort, NL. (2008). Model selection and model averaging. Cambridge, England: Cambridge University Press.

Clements, M; Berry, G; Shi, J; Ware, S; Yates, D; Johnson, A. (2007). Projected mesothelioma incidence in men in New South Wales. Occup Environ Med 64: 747-752. http://dx.doi.org/10.1136/oem.2006.031823

Clin, B; Paris, C; Ameille, J; Brochard, P; Conso, F; Gislard, A; Laurent, F; Letourneux, M; Luc, A; Schorle, E; Pairon, JC. (2011). Do asbestos-related pleural plaques on HRCT scans cause restrictive impairment in the absence of pulmonary fibrosis. Thorax 66: 985-991. http://dx.doi.org/10.1136/thoraxjnl-2011-200172

Cohen, D; Arai, SF; Brain, JD. (1979). Smoking impairs long-term dust clearance from the lung. Science 204: 514-517.

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

Coin, PG; Roggli, VL; Brody, AR. (1992). Deposition, clearance, and translocation of chrysotile asbestos from peripheral and central regions of the rat lung. Environ Res 58: 97-116. http://dx.doi.org/10.1016/S0013-9351(05)80207-5

Coin, PG; Roggli, VL; Brody, AR. (1994). Persistence of long, thin chrysotile asbestos fibers in the lungs of rats [Review]. Environ Health Perspect 102: 197-199.

Condie, LW. (1983). Review of published studies of orally administered asbestos. Environ Health Perspect 53: 3-9.

Constantopoulos, SH; Goudevenos, JA; Saratzis, N; Langer, AM; Selikoff, IJ; Moutsopoulos, HM. (1985). Metsovo lung: Pleural calcification and restrictive lung function in northwestern Greece: Environmental exposure to mineral fiber as etiology. Environ Res 38: 319-331. http://dx.doi.org/10.1016/0013-9351(85)90096-9

Constantopoulos, SH; Saratzis, NA; Kontogiannis, D; Karantanas, A; Goudevenos, JA; Katsiotis, P. (1987). Tremolite whitewashing and pleural calcifications. Chest 92: 709-712. http://dx.doi.org/10.1378/chest.92.4.709

Cook, PJ; Doll, R; Fellingham, SA. (1969). A mathematical model for the age distribution of cancer in man. Int J Cancer 4: 93-112. http://dx.doi.org/10.1002/ijc.2910040113

Cooper, SP; Fraire, AE; Buffler, PA; Greenberg, SD; Langston, C. (1989). Epidemiologic aspects of childhood mesothelioma. Pathol Immunopathol Res 8: 276-286. http://dx.doi.org/10.1159/000157156

Cordier, S; Lazar, P; Brochard, P; Bignon, J; Ameille, J; Proteau, J. (1987). Epidemiologic investigation of respiratory effects related to environmental exposure to asbestos inside insulated buildings. Arch Environ Health 42: 303-309. http://dx.doi.org/10.1080/00039896.1987.9935825

Correa, P. (1996). Helicobacter pylori and gastric cancer: state of the art. Cancer Epidemiol Biomarkers Prev 5: 477-481.

Cox, DR. (1972). Regression models and life-tables. J Roy Stat Soc B 34: 187-220.

Cristaudo, A; Foddis, R; Vivaldi, A; Buselli, R; Gattini, V; Guglielmi, G; Cosentino, F; Ottenga, F; Ciancia, E; Libener, R; Filiberti, R; Neri, M; Betta, P; Tognon, M; Mutti, L; Puntoni, R. (2005). SV40 enhances the risk of malignant mesothelioma among people exposed to asbestos: A molecular epidemiologic case-control study. Cancer Res 65: 3049-3052. http://dx.doi.org/10.1158/0008-5472.CAN-04-2219

Crump, KS; Howe, RB. (1985). A review of methods for calculating statistical confidence limits in low dose extrapolation. In DB Clayson; D Krewski; I Munro (Eds.), Toxicological risk assessment: Vol 1 Biological and statistical criteria (pp. 187-203). Boca Raton, FL: CRC Press, Inc.

Cullen, MR; Barnett, MJ; Balmes, JR; Cartmel, B; Redlich, CA; Brodkin, CA; Barnhart, S; Rosenstock, L; Goodman, GE; Hammar, SP; Thornquist, MD; Omenn, GS. (2005). Predictors of lung cancer among asbestos-exposed men in the beta-carotene and retinol efficacy trial. Am J Epidemiol 161: 260-270. http://dx.doi.org/10.1093/aje/kwi034

Cunningham, HM; Pontefract, RD. (1974). Placental transfer of asbestos. Nature 249: 177-178. http://dx.doi.org/10.1038/249177a0

Cyphert, JM; Nyska, A; Mahoney, RK; Schladweiler, MC; Kodavanti, UP; Gavett, SH. (2012a). Sumas Mountain chrysotile induces greater lung fibrosis in Fischer344 rats than Libby amphibole, El Dorado tremolite, and Ontario ferroactinolite. Toxicol Sci 130: 405-415. http://dx.doi.org/10.1093/toxsci/kfs249

Cyphert, JM; Padilla-Carlin, DJ; Schladweiler, MC; Shannahan, JH; Nyska, A; Kodavanti, UP; Gavett, SH. (2012b). Long-term response of rats to single intratracheal exposure of libby amphibole or amosite. J Toxicol Environ Health A 75: 183-200. http://dx.doi.org/10.1080/15287394.2012.641203

Dai, YT; Yu, CP. (1998). Alveolar deposition of fibers in rodents and humans. J Aerosol Med 11: 247-258. http://dx.doi.org/10.1089/jam.1998.11.247

Davis, JM. (1989). Mineral fibre carcinogenesis: Experimental data relating to the importance of fibre type, size, deposition, dissolution and migration. In Non-occupational exposure to mineral fibres. Lyon, France: International Agency for Research on Cancer. http://apps.who.int/bookorders/anglais/detart1.jsp?sesslan=1&codlan=1&codcol=73&codcch=90

Davis, JM. (1994). The role of clearance and dissolution in determining the durability or biopersistence of mineral fibers. Environ Health Perspect 102: 113-117.

Davis, JMG; Addison, J; Bolton, RE; Donaldson, K; Jones, AD; Miller, BG. (1985). Inhalation studies on the effects of tremolite and brucite dust in rats. Carcinogenesis 6: 667-674. http://dx.doi.org/10.1093/carcin/6.5.667

Davis, JMG; Addison, J; McIntosh, C; Miller, BG; Niven, K. (1991). Variations in the carcinogenicity of tremolite dust samples of differing morphology. Ann N Y Acad Sci 643: 473-490. http://dx.doi.org/10.1111/j.1749-6632.1991.tb24497.x

de Klerk, NH; Armstrong, BK; Musk, AW; Hobbs, MST. (1989). Cancer mortality in relation to measures of occupational exposure to crocidolite at Wittenoom Gorge in Western Australia. Br J Ind Med 46: 529-536. http://dx.doi.org/10.1136/oem.46.8.529

Deer, WA, Howie, R. A.; Zussman, J. (1997). Rock forming minerals: Double chain silicates. In WAHRA Deer; J Zussman (Eds.), (2 ed.). London: The Geological Society.

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

Delclos, GL; Wilson, RK; Bradley, BL. (1990). Influence of smoking on radiographic profusion and pleural changes in asbestos-exposed subjects. J Occup Med 32: 577-581.

Dement JM, K, uempel ED, Z.,umwalde RD, S.,mith RJ, S.,tayner LT, L.,oomis D. (2008). Development of a fibre size-specific job-exposure matrix for airborne asbestos fibres. Occup Environ Med 65: 605-612.

Dement, JM; Welch, L; Bingham, E; Cameron, B; Rice, C; Quinn, P; Ringen, K. (2003). Surveillance of respiratory diseases among construction and trade workers at Department of Energy nuclear sites. Am J Ind Med 43: 559-573. http://dx.doi.org/10.1002/ajim.10226

Dianzani, I; Gibello, L; Biava, A; Giordano, M; Bertolotti, M; Betti, M; Ferrante, D; Guarrera, S; Betta, GP; Mirabelli, D; Matullo, G; Magnani, C. (2006). Polymorphisms in DNA repair genes as risk factors for asbestos-related malignant mesothelioma in a general population study. Mutat Res-Fundam Mol Mech Mutagen 599: 124-134. http://dx.doi.org/10.1016/j.mrfmmm.2006.02.005

Ding, M; Dong, Z; Chen, F; Pack, D; Ma, W; Ye, J; Shi, X; Castranova, V; Vallyathan, V. (1999). Asbestos induces activator protein-1 transactivation in transgenic mice. Cancer Res 59: 1884-1889.

DiPaolo, JA; DeMarinis, AJ; Doniger, J. (1983). Asbestos and benzo(a)pyrene synergism in the transformation of Syrian hamster embryo cells. Pharmacology 27: 65-73. http://dx.doi.org/10.1159/000137837

Dodson, R; O'Sullivan, M; Brooks, D; Bruce, J. (2001). Asbestos content of omentum and mesentery in nonoccupationally exposed individuals. Toxicol Ind Health 17: 138-143.

Dodson, R; O'Sullivan, M; Brooks, D; Hammar, S. (2003). Quantitative analysis of asbestos burden in women with mesothelioma. Am J Ind Med 43: 188-195. http://dx.doi.org/10.1002/ajim.10164

Dodson, R; O'Sullivan, M; Huang, J; Holiday, D; Hammar, S. (2000a). Asbestos in extrapulmonary sites: Omentum and mesentery. Chest 117: 486-493. http://dx.doi.org/10.1002/ajim.10164

Dodson, R; Williams, M; Corn, C; Brollo, A; Bianchi, C. (1990). Asbestos content of lung tissue, lymph nodes, and pleural plaques from former shipyard workers. Am Rev Respir Dis 142: 843-847.

Dodson, RF; Atkinson, MA. (2006). Measurements of asbestos burden in tissues. Ann N Y Acad Sci 1076: 281-291. http://dx.doi.org/10.1196/annals.1371.015

Dodson, RF; Graef, R; Shepherd, S; O'Sullivan, M; Levin, J. (2005). Asbestos burden in cases of mesothelioma from individuals from various regions of the United States. Ultrastruct Pathol 29: 415-433. http://dx.doi.org/10.1080/019131290945682

Dodson, RF; Huang, J; Bruce, JR. (2000b). Asbestos content in the lymph nodes of nonoccupationally exposed individuals. Am J Ind Med 37: 169-174. http://dx.doi.org/10.1002/(SICI)1097-0274(200002)37:2<169::AID-AJIM2>3.0.CO;2-V

Dodson, RF; O'Sullivan, M; Corn, CJ. (1996). Relationships between ferruginous bodies and uncoated asbestos fibers in lung tissue. Arch Environ Health 51: 462-466. http://dx.doi.org/10.1080/00039896.1996.9936047

Dodson, RF; O'Sullivan, M; Corn, CJ; Garcia, JG; Stocks, JM; Griffith, DE. (1993). Analysis of ferruginous bodies in bronchoalveolar lavage from foundry workers. Br J Ind Med 50: 1032-1038.

Dodson, RF; O'Sullivan, M; Corn, CJ; Mclarty, JW; Hammar, SP. (1997). Analysis of asbestos fiber burden in lung tissue from mesothelioma patients. Ultrastruct Pathol 21: 321-336.

Donaldson, K; Murphy, FA; Duffin, R; Poland, CA. (2010). Asbestos, carbon nanotubes and the pleural mesothelium: A review and the hypothesis regarding the role of long fibre retention in the parietal pleura, inflammation and mesothelioma [Review]. Part Fibre Toxicol 7: 42. http://dx.doi.org/10.1186/1743-8977-7-5

Dopp, E; Yadav, S; Ansari, FA; Bhattacharya, K; von Recklinghausen, U; Rauen, U; Rödelsperger, K; Shokouhi, B; Geh, S; Rahman, Q. (2005). ROS-mediated genotoxicity of asbestos-cement in mammalian lung cells in vitro. Part Fibre Toxicol 2: 9. http://dx.doi.org/10.1186/1743-8977-2-9

Dostert, C; Pétrilli, V; Van Bruggen, R; Steele, C; Mossman, BT; Tschopp, J. (2008). Innate immune activation through Nalp3 inflammasome sensing of asbestos and silica. Science 320: 674-677. http://dx.doi.org/10.1126/science.1156995

Driscoll, KE; Carter, JM; Howard, BW; Hassenbein, DG; Pepelko, W; Baggs, RB; Oberdorster, G. (1996). Pulmonary inflammatory, chemokine, and mutagenic responses in rats after subchronic inhalation of carbon black. Toxicol Appl Pharmacol 136: 372-380. http://dx.doi.org/10.1006/taap.1996.0045

Driscoll, KE; Deyo, LC; Carter, JM; Howard, BW; Hassenbein, DG; Bertram, TA. (1997). Effects of particle exposure and particle-elicited inflammatory cells on mutation in rat alveolar epithelial cells. Carcinogenesis 18: 423-430.

Driscoll, KE; Maurer, JK; Higgins, J; Poynter, J. (1995). Alveolar macrophage cytokine and growth factor production in a rat model of crocidolite-induced pulmonary inflammation and fibrosis. J Toxicol Environ Health 46: 155-169. http://dx.doi.org/10.1080/15287399509532026

Dumortier, P; Coplu, L; De Maertelaer, V; Emri, S; Baris, I; De Vuyst, P. (1998). Assessment of environmental asbestos exposure in Turkey by bronchoalveolar lavage. Am J Respir Crit Care Med 158: 1815-1824.

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

Duncan, K; Ghio, A; Dailey, L; Bern, A; Gibbs-Flournoy, E; Padilla-Carlin, D; Roggli, V; Devlin, R. (2010). Effect of size fractionation on the toxicity of amosite and Libby amphibole asbestos. Toxicol Sci 118: 420-434. http://dx.doi.org/10.1093/toxsci/kfq281

Duncan, KE; Cook, PM; Gavett, SH; Dailey, LA; Mahoney, RK; Ghio, AJ; Roggli, VL; Devlin, RB. (2014). In vitro determinants of asbestos fiber toxicity: effect on the relative toxicity of Libby amphibole in primary human airway epithelial cells. Part Fibre Toxicol 11. http://dx.doi.org/10.1186/1743-8977-11-2

Dunning, KK; Adjei, S; Levin, L; Rohs, AM; Hilbert, T; Borton, E; Kapil, V; Rice, C; Lemasters, GK; Lockey, JE. (2012). Mesothelioma associated with commercial use of vermiculite containing Libby amphibole. J Occup Environ Med 54: 1359-1363. http://dx.doi.org/10.1097/JOM.0b013e318250b5f5

Eastmond, DA; Hartwig, A; Anderson, D; Anwar, WA; Cimino, MC; Dobrev, I; Douglas, GR; Nohmi, T; Phillips, DH; Vickers, C. (2009). Mutagenicity testing for chemical risk assessment: Update of the WHO/IPCS harmonized scheme. Mutagenesis 24: 341-349. http://dx.doi.org/10.1093/mutage/gep014

Edwards, GH; Lynch, JR. (1968). The method used by the U.S. public health service for enumeration of asbestos dust on membrane filters. Ann Occup Hyg 11: 1-6. http://dx.doi.org/10.1093/annhyg/11.1.1

Ehrlich, R; Lilis, R; Chan, E; Nicholson, WJ; Selikoff, IJ. (1992). Long term radiological effects of short term exposure to amosite asbestos among factory workers. Br J Ind Med 49: 268-275.

Epler, GR; Fitz Gerald, MX; Gaensler, EA; Carrington, CB. (1980). Asbestos-related disease from household exposure. Respiration 39: 229-240. http://dx.doi.org/10.1159/000194221

Ewing, WM; Hays, SM; Hatfield, R; Longo, WE; Millette, JR. (2010). Zonolite attic insulation exposure studies. Int J Occup Environ Health 16: 279-290.

Fattman, CL; Tan, RJ; Tobolewski, JM; Oury, TD. (2006). Increased sensitivity to asbestos-induced lung injury in mice lacking extracellular superoxide dismutase. Free Radic Biol Med 40: 601-607. http://dx.doi.org/10.1016/j.freeradbiomed.2005.09.030

Finkelstein, MM. (1985). A study of dose-response relationships for asbestos associated disease. Br J Ind Med 42: 319-325.

Finkelstein, MM; Dufresne, A. (1999). Inferences on the kinetics of asbestos deposition and clearance among chrysotile miners and millers. Am J Ind Med 35: 401-412. http://dx.doi.org/10.1002/(SICI)1097-0274(199904)35:4<401::AID-AJIM12>3.0.CO;2-4

Foddis, R; De Rienzo, A; Broccoli, D; Bocchetta, M; Stekala, E; Rizzo, P; Tosolini, A; Grobelny, JV; Jhanwar, SC; Pass, HI; Testa, JR; Carbone, M. (2002). SV40 infection induces telomerase activity in human mesothelial cells. Oncogene 21: 1434-1442. http://dx.doi.org/10.1038/sj.onc.1205203

Gao, F; Koenitzer, JR; Tobolewski, JM; Jiang, D; Liang, J; Noble, PW; Oury, TD. (2008). Extracellular superoxide dismutase inhibits inflammation by preventing oxidative fragmentation of hyaluronan. J Biol Chem 283: 6058-6066. http://dx.doi.org/10.1074/jbc.M709273200

Gasparrini, A; Pizzo, AM; Gorini, G; Costantini, AS; Silvestri, S; Ciapini, C; Innocenti, A; Berry, G. (2008). Prediction of mesothelioma and lung cancer in a cohort of asbestos exposed workers. Eur J Epidemiol 23: 541-546. http://dx.doi.org/10.1007/s10654-008-9257-z

Ghio, AJ; Kennedy, TP; Whorton, AR; Crumbliss, AL; Hatch, GE; Hoidal, JR. (1992). Role of surface complexed iron in oxidant generation and lung inflammation induced by silicates. Am J Physiol 263: L511-L518.

Gibbs, AR; Stephens, M; Griffiths, DM; Blight, BJ; Pooley, FD. (1991). Fibre distribution in the lungs and pleura of subjects with asbestos related diffuse pleural fibrosis. Br J Ind Med 48: 762-770. http://dx.doi.org/10.1136/oem.48.11.762

Gilmartin, D. (1979). The serratus anterior muscle on chest radiographs. Radiology 131: 629-635. http://dx.doi.org/10.1148/131.3.629

Graham, DR; Chamberlain, MJ; Hutton, L; King, M; Morgan, WK. (1990). Inhaled particle deposition and body habitus. Br J Ind Med 47: 38-43.

Green, GM. (1973). Alveolobronchiolar transport mechanisms. Arch Intern Med 131: 109-114.

Griffis, LC; Pickrell, JA; Carpenter, RL; Wolff, RK; McAllen, SJ; Yerkes, KL. (1983). Deposition of crocidolite asbestos and glass microfibers inhaled by the beagle dog. Am Ind Hyg Assoc J 44: 216-222. http://dx.doi.org/10.1080/15298668391404671

Gunter, ME; Belluso, E; Mottana, A. (2007). Amphiboles: environmental and health concerns. Rev Mineral Geochem 67: 453-516. http://dx.doi.org/10.2138/rmg.2007.67.12

Gunter, ME; Sanchez, MS. (2009). Amphibole forensics: Using the composition of amphiboles to determine their source, the Libby, Montana, example. Am Mineral 94: 837-840. http://dx.doi.org/10.2138/am.2009.3224

Guzelian, PS; Henry, CJ; Olin, SS. (1992). Similarities and differences between children and adults: Implications for risk assessment. In PS Guzelian; CJ Henry; SS Olin (Eds.). Washington, DC: ILSI Press.

Hamilton, R; Holian, A; Morandi, M. (2004). A comparison of asbestos and urban particulate matter in the in vitro modification of human alveolar macrophage antigen-presenting cell function. Exp Lung Res 30: 147-162. http://dx.doi.org/10.1080/01902140490266439

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

Hammond, EC; Selikoff, IJ; Seidman, H. (1979). Asbestos exposure, cigarette smoking and death rates. Ann N Y Acad Sci 330: 473-490.

Hanahan, D; Weinberg, RA. (2011). Hallmarks of cancer: The next generation. Cell 144: 646-674. http://dx.doi.org/10.1016/j.cell.2011.02.013

Hankinson, JL; Odencrantz, JR; Fedan, KB. (1999). Spirometric reference values from a sample of the general US population. Am J Respir Crit Care Med 159: 179-187.

Hansen, J; de Klerk, NH; Eccles, JL; Musk, AW; Hobbs, MS. (1993). Malignant mesothelioma after environmental exposure to blue asbestos. Int J Cancer 54: 578-581. http://dx.doi.org/10.1002/ijc.2910540410

Hansen, J; de Klerk, NH; Musk, AW; Hobbs, MST. (1998). Environmental exposure to crocidolite and mesothelioma: Exposure-response relationships. Am J Respir Crit Care Med 157: 69-75.

Hansen, J; de Klerk, NH; Musk, W; Hobbs, MST. (1997). Individual exposure levels in people environmentally exposed to crocidolite. Appl Occup Environ Hyg 12: 485-490. http://dx.doi.org/10.1080/1047322X.1997.10390032

Haque, A; Kanz, M; Mancuso, M; Williams, G; Dodson, R. (1991). Asbestos in the lungs of children. Ann N Y Acad Sci 643: 419-429.

Haque, AK; Ali, I; Vrazel, DM; Uchida, T. (2001). Chrysotile asbestos fibers detected in the newborn pups following gavage feeding of pregnant mice. J Toxicol Environ Health A 62: 23-31.

Haque, AK; Kanz, ME. (1988). Asbestos bodies in children's lungs: An association with sudden infant death syndrome and bronchopulmonary dysplasia. Arch Pathol Lab Med 112: 514-518.

Haque, AK; Mancuso, MG; Williams, MG; Dodson, RF. (1992). Asbestos in organs and placenta of five stillborn infants suggests transplacental transfer. Environ Res 58: 163-175.

Haque, AK; Vrazel, DM. (1998). Transplacental transfer of asbestos in pregnant mice. Bull Environ Contam Toxicol 60: 620-625. http://dx.doi.org/10.1007/s001289900671

Haque, AK; Vrazel, DM; Burau, KD; Cooper, SP; Downs, T. (1996). Is there transplacental transfer of asbestos? A study of 40 stillborn infants. Pediatr Pathol Lab Med 16: 877-892.

Haque, AK; Vrazel, DM; Uchida, T. (1998). Assessment of asbestos burden in the placenta and tissue digests of stillborn infants in South Texas. Arch Environ Contam Toxicol 35: 532-538. http://dx.doi.org/10.1007/s002449900413

Harris, RL, Jr; Fraser, DA. (1976). A model for deposition of fibers in the human respiratory system. Am Ind Hyg Assoc J 37: 73-89. http://dx.doi.org/10.1080/0002889768507416

Harris, RL, Jr; Timbrell, V. (1975). The influence of fibre shape in lung deposition-mathematical estimates. Inhaled Particles 4: 75-89.

Hasanoglu, HC; Yildirim, Z; Ermis, H; Kilic, T; Koksal, N. (2006). Lung cancer and mesothelioma in towns with environmental exposure to asbestos in Eastern Anatolia. Int Arch Occup Environ Health 79: 89-91. http://dx.doi.org/10.1007/s00420-005-0010-6

Hauptmann, M; Pohlabeln, H; Lubin, JH; Jöckel, KH; Ahrens, W; Brüske-Hohlfeld, I; Wichmann, HE. (2002). The exposure-time-response relationship between occupational asbestos exposure and lung cancer in two German case-control studies. Am J Ind Med 41: 89-97.

Hawthorne, FC. (1981). Amphibole spectoscopy. Rev Mineral Geochem 9: 103-139.

HEI (Health Effects Institute). (1991). Asbestos in public and commercial buildings: a literature review and synthesis of current knowledge.

Hei, TK; Piao, CQ; He, ZY; Vannais, D; Waldren, CA. (1992). Chrysotile fiber is a strong mutagen in mammalian cells. Cancer Res 52: 6305-6309.

Hei, TK; Xu, A; Huang, SX; Zhao, Y. (2006). Mechanism of fiber carcinogenesis: From reactive radical species to silencing of the beta igH3 gene. Inhal Toxicol 18: 985-990. http://dx.doi.org/10.1080/08958370600835310

Heid, IM; Küchenhoff, H; Miles, J; Kreienbrock, L; Wichmann, HE. (2004). Two dimensions of measurement error: Classical and Berkson error in residential radon exposure assessment. J Expo Anal Environ Epidemiol 14: 365-377. http://dx.doi.org/10.1038/sj.jea.7500332

Hein, MJ; Stayner, LT; Lehman, E; Dement, JM. (2007). Follow-up study of chrysotile textile workers: Cohort mortality and exposure-response. Occup Environ Med 64: 616-625. http://dx.doi.org/10.1136/oem.2006.031005

Henderson, VL; Enterline, PE. (1979). Asbestos exposure: Factors associated with excess cancer and respiratory disease mortality. Ann N Y Acad Sci 330: 117-126. http://dx.doi.org/10.1111/j.1749-6632.1979.tb18712.x

Hesterberg, T; Hart, G; Chevalier, J; Miiller, W; Hamilton, R; Bauer, J; Thevenaz, P. (1998a). The importance of fiber biopersistence and lung dose in determining the chronic inhalation effects of X607, RCF1, and chrysotile asbestos in rats. Toxicol Appl Pharmacol 153: 68-82. http://dx.doi.org/10.1006/taap.1998.8522

Hesterberg, TW; Chase, G; Axten, C; Miller, WC; Musselman, RP; Kamstrup, O; Hadley, J; Morscheidt, C; Bernstein, DM; Thevenaz, P. (1998b). Biopersistence of synthetic vitreous fibers and amosite asbestos in

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

the rat lung following inhalation. Toxicol Appl Pharmacol 151: 262-275. http://dx.doi.org/10.1006/taap.1998.8472

HHS (U.S. Department of Health and Human Services). (1990). The health benefits of smoking cessation: A report of the surgeon general. Rockville, MD: U.S. Department of Health and Human Services, Public Health Service. http://profiles.nlm.nih.gov/ps/access/NNBBCV.pdf

Hilbert, TJ; Franzblau, A; Dunning, KK; Borton, EK; Rohs, AM; Lockey, JE. (2013). Asbestos-related radiographic findings among household contacts of workers exposed to Libby vermiculite: impact of workers' personal hygiene practices. J Occup Environ Med 55: 1300-1304. http://dx.doi.org/10.1097/JOM.0b013e31829fcf1a

Hillegass, JM; Miller, JM; MacPherson, MB; Westbom, CM; Sayan, M; Thompson, JK; Macura, SL; Perkins, TN; Beuschel, SL; Alexeeva, V; Pass, HI; Steele, C; Mossman, BT; Shukla, A. (2013). Asbestos and erionite prime and activate the NLRP3 inflammasome that stimulates autocrine cytokine release in human mesothelial cells. Part Fibre Toxicol 10: 39. http://dx.doi.org/10.1186/1743-8977-10-39

Hillegass, JM; Shukla, A; MacPherson, MB; Lathrop, SA; Alexeeva, V; Perkins, TN; van der Vliet, A; Vacek, PM; Gunter, ME; Mossman, BT. (2010). Mechanisms of oxidative stress and alterations in gene expression by Libby six-mix in human mesothelial cells. Part Fibre Toxicol 7: 26. http://dx.doi.org/10.1186/1743-8977-7-26

Hillerdal, G. (1983). Malignant mesothelioma 1982: Review of 4710 published cases. Br J Dis Chest 77: 321-343. http://dx.doi.org/10.1016/0007-0971(83)90068-2

Hillerdal, G. (1994a). The human evidence: Parenchymal and pleural changes. Ann Occup Hyg 38: 561-567. http://dx.doi.org/10.1093/annhyg/38.4.561

Hillerdal, G. (1994b). Pleural plaques and risk for bronchial carcinoma and mesothelioma. A prospective study. Chest 105: 144-150.

Hillerdal, G; Henderson, DW. (1997). Asbestos, asbestosis, pleural plaques and lung cancer [Review]. Scand J Work Environ Health 23: 93-103.

Hirvonen, A; Tuimala, J; Ollikainen, T; Linnainmaa, K; Kinnula, V. (2002). Manganese superoxide dismutase genotypes and asbestos-associated pulmonary disorders. Cancer Lett 178: 71-74. http://dx.doi.org/10.1016/S0304-3835(01)00819-9

Hodgson, J; McElvenny, D; Darnton, A; Price, M; Peto, J. (2005). The expected burden of mesothelioma mortality in Great Britain from 2002 to 2050. Br J Cancer 92: 587-593. http://dx.doi.org/10.1038/sj.bjc.6602307

Horton, K; Kapil, V; Larson, T; Muravov, O; Melnikova, N; Anderson, B. (2006). A review of the federal government's health activities in response to asbestos-contaminated ore found in Libby, Montana. Inhal Toxicol 18: 925-940. http://dx.doi.org/10.1080/08958370600835161

Hosmer, DW, Jr; Lemeshow, S. (2000). Applied logistic regression. In WA Shewhart; SS Wilks (Eds.), (2nd ed.). New York, NY: John Wiley & Sons. http://dx.doi.org/10.1002/0471722146

Howlader, N; Noone, AM; Krapcho, M; Garshell, J; Neyman, N; Altekruse, SF; Kosary, CL; Yu, M; Ruhl, J; Tatalovich, Z; Cho; Mariotto, A; Lewis, DR; Chen, HS, : Feuer, E. J.; Cronin, KA; (eds). (2013). SEER cancer statistics review, 1975-2010. Bethesda, MD: National Cancer Institute. http://seer.cancer.gov/csr/1975_2010/

Huang, SX; Jaurand, MC; Kamp, DW; Whysner, J; Hei, TK. (2011). Role of mutagenicity in asbestos fiber-induced carcinogenicity and other diseases. J Toxicol Environ Health B Crit Rev 14: 179-245. http://dx.doi.org/10.1080/10937404.2011.556051

Huncharek, M. (2002). Non-asbestos related diffuse malignant mesothelioma. Tumori 88: 1-9.

IARC (International Agency for Research on Cancer). (2012). Asbestos (chrysotile, amosite, crocidolite, tremolite, actinolite and anthophyllite). In A review of human carcinogens: arsenic, metals, fibres, and dusts (pp. 219-309). Lyon, France. http://monographs.iarc.fr/ENG/Monographs/vol100C/

ICRP (International Commission on Radiological Protection). (1994). Human respiratory tract model for radiological protection: A report of a task group of the International Commission on Radiological Protection. ICRP Publication 66. Ann ICRP 24: 1-482.

ILO (International Labour Organization). (1971). International classification of radiographs of pneumoconioses (revised, 1968) (Red. Ed. 1968 ed.). Geneva, Switzerland: International Labour Office.

ILO (International Labour Organization). (1980). Guidelines for the use of the ILO international classification of radiographs of pneumoconioses. Geneva, Switzerland: International Labour Office.

ILO (International Labour Organization). (2002). International classification of radiographs of pneumoconioses. (Occupational Safety and Health Series No. 22 (Rev. 2000)). Geneva, Switzerland: International Labour Office. http://www.ilo.org/wcmsp5/groups/public/---ed_protect/---protrav/---safework/documents/publication/wcms_108568.pdf

ILSI (International Life Sciences Institute). (2005). Testing of of fibrous particles: short-term assays and strategies. Inhal Toxicol 17: 497-537.

IOM (Institute of Medicine). (2006). Asbestos: Selected cancers. Washington, DC: National Academies Press.

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

IPCS (International Programme on Chemical Safety). (1986). Asbestos and other natural mineral fibres (pp. 112). (Environmental Health Criteria 53). Geneva, Switzerland: World Health Organization. http://www.inchem.org/documents/ehc/ehc/ehc53.htm

Isaacs, KK; Martonen, TB. (2005). Particle deposition in children's lungs: Theory and experiment. J Aerosol Med 18: 337-353. http://dx.doi.org/10.1089/jam.2005.18.337

Jahr, J, . (1974). Dose-response basis for setting a quartz threshold limit value. Arch Environ Health 29: 338-340.

Jakobsson, K; Strömberg, U; Albin, M; Welinder, H; Hagmar, L. (1995). Radiological changes in asbestos cement workers. Occup Environ Med 52: 20-27.

Janković, S; Šimundić, I; Tocilj, J; Miše, K; Čapkun, V; Tadić, T. (2002). Clincal and radiological manifestations of asbestosis depending on the mineralogic characteristics of asbestos. Acta Clin Croat 41: 79-85.

Jarabek, AM; Asgharian, B; Miller, FJ. (2005). Dosimetric adjustments for interspecies extrapolation of inhaled poorly soluble particles (PSP). Inhal Toxicol 17: 317-334. http://dx.doi.org/10.1080/08958370590929394

Järvholm, B. (1992). Pleural plaques and exposure to asbestos: a mathematical model. Int J Epidemiol 21: 1180-1184.

Jaurand, MC. (1997). Mechanisms of fiber-induced genotoxicity. Environ Health Perspect 105: 1073-1084.

Jones, AD; McMillan, CH; Johnston, AM; McIntosh, C; Cowie, H; Bolton, RE; Borzucki, G; Vincent, JH. (1988). Pulmonary clearance of UICC amosite fibres inhaled by rats during chronic exposure at low concentration. Br J Ind Med 45: 300-304.

Kamp, DW; Graceffa, P; Pryor, WA; Weitzman, SA. (1992). The role of free radicals in asbestos-induced diseases. Free Radic Biol Med 12: 293-315. http://dx.doi.org/10.1016/0891-5849(92)90117-Y

Kamp, DW; Weitzman, SA. (1999). The molecular basis of asbestos induced lung injury. Thorax 54: 638-652. http://dx.doi.org/10.1136/thx.54.7.638

Karlson, EW; Mandl, LA; Aweh, GN; Grodstein, F. (2003). Coffee consumption and risk of rheumatoid arthritis. Arthritis Rheum 48: 3055-3060. http://dx.doi.org/10.1002/art.11306

Kelly, J; Pratt, G; Johnson, J; Messing, R. (2006). Community exposure to asbestos from a vermiculite exfoliation plant in NE Minneapolis. Inhal Toxicol 18: 941-947. http://dx.doi.org/10.1080/08958370600834883

Kim, CS; Kang, TC. (1997). Comparative measurement of lung deposition of inhaled fine particles in normal subjects and patients with obstructive airway disease. Am J Respir Crit Care Med 155: 899-905.

Kim, H; Yasui, Y; Burstyn, I. (2006). Attenuation in risk estimates in logistic and Cox proportional-hazards models due to group-based exposure assessment strategy. Ann Occup Hyg 50: 623-635. http://dx.doi.org/10.1093/annhyg/mel021

Kimizuka, G; Ohwada, H; Hayashi, Y. (1987). Co-carcinogenic effect of asbestos and benzo(a)pyrene in the lung of hamster. Acta Pathol Jpn 37: 465-474. http://dx.doi.org/10.1111/j.1440-1827.1987.tb00380.x

Kleinbaum, DG; Klein, M. (1996). Survival analysis: A self-learning text. New York: Springer-Verlag.

Kleymenova, EV; Bianchi, AA; Kley, N; Pylev, LN; Walker, CL. (1997). Characterization of the rat neurofibromatosis 2 gene and its involvement in asbestos-induced mesothelioma. Mol Carcinog 18: 54-60. http://dx.doi.org/10.1002/(SICI)1098-2744(199701)18:1<54::AID-MC7>3.0.CO;2-R

Kliment, CR; Englert, JM; Gochuico, BR; Yu, G; Kaminski, N; Rosas, I; Oury, TD. (2009). Oxidative stress alters syndecan-1 distribution in lungs with pulmonary fibrosis. J Biol Chem 284: 3537-3545. http://dx.doi.org/10.1074/jbc.M807001200

Kohyama, N; Suzuki, Y. (1991). Analysis of asbestos fibers in lung parenchyma, pleural plaques, and mesothelioma tissues of North American insulation workers. Ann N Y Acad Sci 643: 27-52. http://dx.doi.org/10.1111/j.1749-6632.1991.tb24442.x

Kopylev, L; Sullivan, PA; Vinikoor, LC; Bateson, TF. (2011). Monte Carlo analysis of impact of underascertainment of Mesothelioma cases on underestimation of risk. Open Epidemiol J 4: 45-53.

Koskinen, K; Zitting, A; Tossavainen, A; Rinne, JP; Roto, P; Kivekäs, J; Reijula, K; Huuskonen, MS. (1998). Radiographic abnormalities among Finnish construction, shipyard and asbestos industry workers. Scand J Work Environ Health 24: 109-117.

Kroczynska, B; Cutrone, R; Bocchetta, M; Yang, H; Elmishad, AG; Vacek, P; Ramos-Nino, M; Mossman, BT; Pass, HI; Carbone, M. (2006). Crocidolite asbestos and SV40 are cocarcinogens in human mesothelial cells and in causing mesothelioma in hamsters. PNAS 103: 14128-14133. http://dx.doi.org/10.1073/pnas.0604544103

Kroschwitz, JI; Seidel, A; Eds. (2007). Kirk-Othmer concise encyclopedia of chemical technology (5th ed.). New York, NY: John Wiley and Sons.

Krowke, R; Bluth, V; Merker, JH; Neubert, D. (1983). Placental transfer and possible teratogenic potential of asbestos in mice [Abstract]. Teratology 32: 26A-27A.

Landi, M; Dracheva, T; Rotunno, M; Figueroa, J; Liu, H; Dasgupta, A; Mann, F; Fukuoka, J; Hames, M; Bergen, A; Murphy, S; Yang, P; Pesatori, A; Consonni, D; Bertazzi, P; Wacholder, S; Shih, J; Caporaso, N; Jen, J.

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

(2008). Gene expression signature of cigarette smoking and its role in lung adenocarcinoma development and survival. PLoS ONE 3: e1651. http://dx.doi.org/10.1371/journal.pone.0001651

Langer, AM; Nolan, RP; Constantopoulos, SH; Moutsopoulos, HM. (1987). Association of Metsovo lung and pleural mesothelioma with exposure to tremolite-containing whitewash. Lancet 329: 965-967. http://dx.doi.org/10.1016/S0140-6736(87)90305-9

Langseth, H; Johansen, BV; Nesland, JM; Kjaerheim, K. (2007). Asbestos fibers in ovarian tissue from Norwegian pulp and paper workers. Int J Gynecol Cancer 17: 44-49. http://dx.doi.org/10.1111/j.1525-1438.2006.00768.x

Larsen, ES. (1942). Alkalic rocks of Iron Hill, Gunnison County, Colorado. Geological Survey professional paper 197-A. Washington, DC: U.S. Geological Survey. http://pubs.usgs.gov/pp/0197a/report.pdf

Larson, T; Meyer, C; Kapil, V; Gurney, J; Tarver, R; Black, C; Lockey, J. (2010a). Workers with Libby amphibole exposure: retrospective identification and progression of radiographic changes. Radiology 255: 924-933. http://dx.doi.org/10.1148/radiol.10091447

Larson, TC; Antao, VC; Bove, FJ. (2010b). Vermiculite worker mortality: Estimated effects of occupational exposure to Libby amphibole. J Occup Environ Med 52: 555-560. http://dx.doi.org/10.1097/JOM.0b013e3181dc6d45

Larson, TC; Antao, VC; Bove, FJ; Cusack, C. (2012a). Association between cumulative fiber exposure and respiratory outcomes among Libby vermiculite workers. J Occup Environ Med 54: 56-63. http://dx.doi.org/10.1097/JOM.0b013e31823c141c

Larson, TC; Lewin, M; Gottschall, EB; Antao, VC; Kapil, V; Rose, CS. (2012b). Associations between radiographic findings and spirometry in a community exposed to Libby amphibole. Occup Environ Med 69: 361-366. http://dx.doi.org/10.1136/oemed-2011-100316

Leake, BE. (1978). Nomenclature of amphiboles. Mineral Mag 42: 533-563.

Leake, BE; Woolley, AR; Arps, CES; Birch, WD; Gilbert, MC; Grice, JD; Hawthorne, FC; Kato, A; Kisch, HJ; Krivovichev, VG; Linthout, K; Laird, J; Mandarino, J; Maresch, WV; Nickel, EH; Rock, NMS; Schumacher, JC; Smith, DC; Shephenson, NCN; Ungaretti, L; Whittake, EJW; Youzhi, G. (1997). Nomenclature of amphiboles: report of the Subcommittee on Amphiboles of the International Mineralogical Association Commission on New Minerals and Mineral Names. Can Mineral 35: 219-246.

Leanderson, P; Soderkvist, P; Tagesson, C; Axelson, O. (1988). Formation of 8-hydroxydeoxyguanosine by asbestos and man made mineral fibres. Occup Environ Med 45: 309-311.

Lebedova, J; Dlouha, B; Rychla, L; Neuwirth, J; Brabec, M; Pelclova, D; Fenclova, Z. (2003). Lung function impairment in relation to asbestos-induced pleural lesions with reference to the extent of the lesions and the initial parenchymal fibrosis. Scand J Work Environ Health 29: 388-395. http://dx.doi.org/10.5271/sjweh.745

Lenters, V; Burdorf, A; Vermeulen, R; Stayner, L; Heederik, D. (2012). Quality of evidence must guide risk assessment of asbestos. Ann Occup Hyg 56: 879-887.

Lenters, V; Vermeulen, R; Dogger, S; Stayner, L; Portengen, L; Burdorf, A; Heederik, D. (2011). A meta-analysis of asbestos and lung cancer: is better quality exposure assessment associated with steeper slopes of the exposure-response relationships? [Review]. Environ Health Perspect 119: 1547-1555. http://dx.doi.org/10.1289/ehp.1002879

Lentz, TJ; Rice, CH; Succop, PA; Lockey, JE; Dement, JM; LeMasters, GK. (2003). Pulmonary deposition modeling with airborne fiber exposure data: a study of workers manufacturing refractory ceramic fibers. Appl Occup Environ Hyg 18: 278-288. http://dx.doi.org/10.1080/10473220301404

Levin, JL; Mclarty, JW; Hurst, GA; Smith, AN; Frank, AL. (1998). Tyler asbestos workers: mortality experience in a cohort exposed to amosite. Occup Environ Med 55: 155-160.

Li, M; Gunter, ME; Fukagawa, NK. (2012). Differential activation of the inflammasome in THP-1 cells exposed to chrysotile asbestos and Libby "six-mix" amphiboles and subsequent activation of BEAS-2B cells. Cytokine 60: 718-730. http://dx.doi.org/10.1016/j.cyto.2012.08.025

Lieben, J; Pistawka, H. (1967). Mesothelioma and asbestos exposure. Arch Environ Health 14: 559-563.

Lilis, R; Miller, A; Godbold, J; Chan, E; Selikoff, IJ. (1991). Radiographic abnormalities in asbestos insulators: Effects of duration from onset of exposure and smoking. Relationships of dyspnea with parenchymal and pleural fibrosis. Am J Ind Med 20: 1-15. http://dx.doi.org/10.1002/ajim.4700200102

Lin, F; Liu, Y; Liu, Y; Keshava, N; Li, S. (2000). Crocidolite induces cell transformation and p53 gene mutation in BALB/c-3T3 cells. Teratog Carcinog Mutagen 20: 273-281. http://dx.doi.org/10.1002/1520-6866(2000)20:5<273::AID-TCM3>3.0.CO;2-1

Ling, S; Fried, L; Garrett, E; Hirsch, R; Guralnik, J; Hochberg, M. (2000). The accuracy of self-report of physician diagnosed rheumatoid arthritis in moderately to severely disabled older women. Women's Health and Aging Collaborative Research Group. J Rheumatol 27: 1390-1394.

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

Lippmann, M. (1990). Effects of fiber characteristics on lung deposition, retention, and disease. Environ Health Perspect 88: 311-317. http://dx.doi.org/10.1289/ehp.9088311

Lockey, JE. (1985) Pulmonary hazards associated with vermiculite exposure. (Master's Thesis). University of Cincinnati, Cincinnati, OH.

Lockey, JE; Brooks, SM; Jarabek, AM; Khoury, PR; Mckay, RT; Carson, A; Morrison, JA; Wiot, JF; Spitz, HB. (1984). Pulmonary changes after exposure to vermiculite contaminated with fibrous tremolite. Am Rev Respir Dis 129: 952-958.

Loli, P; Topinka, J; Georgiadis, P; Dusinská, M; Hurbánková, M; Kovácíková, Z; Volkovová, K; Wolff, T; Oesterle, D; Kyrtopoulos, S. (2004). Benzo[a]pyrene-enhanced mutagenesis by asbestos in the lung of lambda-lacI transgenic rats. Mutat Res 553: 79-90. http://dx.doi.org/10.1016/j.mrfmmm.2004.06.025

Loomis D, D, ement J, R.,ichardson D, W.,olf S. (2009). Asbestos fibre dimensions and lung cancer mortality among workers exposed to chrysotile. Occup Environ Med 67: 580-584.

Lowers, H; Meeker, G. (2002). Tabulation of asbestos-related terminology. (Report 02-458). U.S. Geological Survey. http://pubs.usgs.gov/of/2002/ofr-02-458/OFR-02-458-508.pdf

Lowers, HA; Wilson, SA; Hoefen, TM; Benzel, WM; Meeker, GP. (2012). Preparation and characterization of Libby Amphibole toxicological testing material: U.S. Geological Survey Open-File Report 20121012. (Open-File Report 20121012). Reston, Virginia: U.S. Geological Survey.

Luce, D; Bugel, I; Goldberg, P; Goldberg, M; Salomon, C; Billon-Galland, MA; Nicolau, J; Quénel, P; Fevotte, J; Brochard, P. (2000). Environmental exposure to tremolite and respiratory cancer in New Caledonia: a case-control study. Am J Epidemiol 151: 259-265.

Lund, LG; Williams, MG; Dodson, RF; Aust, AE. (1994). Iron associated with asbestos bodies is responsible for the formation of single strand breaks in phi X174 RFI DNA. Occup Environ Med 51: 200-204.

Magnani, C; Ferrante, D; Barone-Adesi, F; Bertolotti, M; Todesco, A; Mirabelli, D; Terracini, B. (2008). Cancer risk after cessation of asbestos exposure: A cohort study of Italian asbestos cement workers. Occup Environ Med 65: 164-170. http://dx.doi.org/10.1136/oem.2007.032847

Marchand, LS; St-Hilaire, S; Putnam, EA; Serve, KM; Pfau, JC. (2012). Mesothelial cell and anti-nuclear autoantibodies associated with pleural abnormalities in an asbestos exposed population of Libby MT. Toxicol Lett 208: 168-173. http://dx.doi.org/10.1016/j.toxlet.2011.10.024

Marsella, JM; Liu, BL; Vaslet, CA; Kane, AB. (1997). Susceptibility of p53-deficient mice to induction of mesothelioma by crocidolite asbestos fibers. Environ Health Perspect 105: 1069-1072.

Marsh, GM; Gula, MJ; Youk, AO; Buchanich, JM; Churg, A; Colby, TV. (2001). Historical cohort study of US man-made vitreous fiber production workers: II. Mortality from mesothelioma. J Occup Environ Med 43: 757-766.

Mastrangelo, G; Ballarin, MN; Bellini, E; Bicciato, F; Zannol, F; Gioffrè, F; Zedde, A; Tessadri, G; Fedeli, U; Valentini, F; Scoizzato, L; Marangi, G; Lange, JH. (2009). Asbestos exposure and benign asbestos diseases in 772 formerly exposed workers: dose-response relationships. Am J Ind Med 52: 596-602. http://dx.doi.org/10.1002/ajim.20713

Maxim, LD; Hadley, JG; Potter, RM; Niebo, R. (2006). The role of fiber durability/biopersistence of silica-based synthetic vitreous fibers and their influence on toxicology. Regul Toxicol Pharmacol 46: 42-62. http://dx.doi.org/10.1016/j.yrtph.2006.05.003

Mayall, FG; Jacobson, G; Wilkins, R. (1999). Mutations of p53 gene and SV40 sequences in asbestos associated and non-asbestos-associated mesotheliomas. J Clin Pathol 52: 291-293.

McConnell, EE; Rutter, HA; Ulland, BM; Moore, JA. (1983a). Chronic effects of dietary exposure to amosite asbestos and tremolite in F344 rats. Environ Health Perspect 53: 27-44.

McConnell, EE; Shefner, AM; Rust, JH; Moore, JA. (1983b). Chronic effects of dietary exposure to amosite and chrysotile asbestos in Syrian golden hamsters. Environ Health Perspect 53: 11-25.

McDonald, JC; Edwards, CW; Gibbs, AR; Lloyd, HM; Pooley, FD; Ross, DJ; Rudd, RM. (2001). Case-referent survey of young adults with mesothelioma: II. Occupational analyses. Ann Occup Hyg 45: 519-523. http://dx.doi.org/10.1093/annhyg/45.7.519

McDonald, JC; Harris, J; Armstrong, B. (2002). Cohort mortality study of vermiculite miners exposed to fibrous tremolite: an update. Ann Occup Hyg 46: 93-94. http://dx.doi.org/10.1093/annhyg/46.suppl_1.93

McDonald, JC; Harris, J; Armstrong, B. (2004). Mortality in a cohort of vermiculite miners exposed to fibrous amphibole in Libby, Montana. Occup Environ Med 61: 363-366. http://dx.doi.org/10.1136/oem.2003.008649

McDonald, JC; McDonald, AD; Armstrong, B; Sebastien, P. (1986a). Cohort study of mortality of vermiculite miners exposed to tremolite. Occup Environ Med 43: 436-444. http://dx.doi.org/10.1136/oem.43.7.436

McDonald, JC; Sebastien, P; Armstrong, B. (1986b). Radiological survey of past and present vermiculite miners exposed to tremolite. Br J Ind Med 43: 445-449. http://dx.doi.org/10.1136/oem.43.7.445

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

McFadden, D; Wright, J; Wiggs, B; Churg, A. (1986). Cigarette smoke increases the penetration of asbestos fibers into airway walls. Am J Pathol 123: 95-99.

McMillan, GH; Pethybridge, RJ; Sheers, G. (1980). Effect of smoking on attack rates of pulmonary and pleural lesions related to exposure to asbestos dust. Br J Ind Med 37: 268-272. http://dx.doi.org/10.1136/oem.37.3.268

Meek, ME; Grasso, P. (1983). An investigation of the penetration of ingested asbestos into the normal and abnormal intestinal mucosa of the rat. Food Chem Toxicol 21: 193-200. http://dx.doi.org/10.1016/0278-6915(83)90236-3

Meeker, G. (2007). Photo of raw vermiculite ore taken on the mine site at Vermiculite Mountain near Libby, MT. USGS field collection. Reston, VA: U.S. Geological Survey.

Meeker, GP; Bern, AM; Brownfield, IK; Lowers, HA; Sutley, SJ; Hoefen, TM; Vance, JS. (2003). The composition and morphology of amphiboles from the Rainy Creek Complex, near Libby, Montana. Am Mineral 88: 1955-1969.

Merchant, JA. (1990). Human epidemiology: A review of fiber type and characteristics in the development of malignant and nonmalignant disease. Environ Health Perspect 88: 287-293.

Metintas, M; Metintas, S; Hillerdal, G; Ucgun, I; Erginel, S; Alatas, F; Yildirim, H. (2005). Nonmalignant pleural lesions due to environmental exposure to asbestos: a field-based, cross-sectional study. Eur Respir J 26: 875-880. http://dx.doi.org/10.1183/09031936.05.00136404

Metintas, S; Metintas, M; Ucgun, I; Oner, U. (2002). Malignant mesothelioma due to environmental exposure to asbestos: Follow-up of a Turkish cohort living in a rural area. Chest 122: 2224-2229.

Miller, BG; Searl, A; Davis, JM; Donaldson, K; Cullen, RT; Bolton, RE; Buchanan, D; Soutar, CA. (1999). Influence of fibre length, dissolution and biopersistence on the production of mesothelioma in the rat peritoneal cavity. Ann Occup Hyg 43: 155-166.

Miserocchi, G; Sancini, G; Mantegazza, F; Chiappino, G. (2008). Translocation pathways for inhaled asbestos fibers. Environ Health 7: 4. http://dx.doi.org/10.1186/1476-069X-7-4

Moatamed, F; Lockey, JE; Parry, WT. (1986). Fiber contamination of vermiculites: A potential occupational and environmental health hazard. Environ Res 41: 207-218. http://dx.doi.org/10.1016/S0013-9351(86)80183-9

Moolgavkar, SH; Turim, J; Alexander, DD; Lau, EC; Cushing, CA. (2010). Potency factors for risk assessment at Libby, Montana. Risk Anal 30: 1240-1248. http://dx.doi.org/10.1111/j.1539-6924.2010.01411.x

Morgan, A; Talbot, RJ; Holmes, A. (1978). Significance of fibre length in the clearance of asbestos fibres from the lung. Br J Ind Med 35: 146-153. http://dx.doi.org/10.1136/oem.35.2.146

Moss, OR; Wong, BA; Asgharian, B. (1994). Bimodal bivariate log-normal distributions in the application of inhalation toxicology specific to the measurement of fiber and particle dosimetry. In U Mohr; DL Dungworth; JL Mauderly; G Oberdorster (Eds.), Toxic and carcinogenic effects of solid particles in the respiratory tract (pp. 623 628). Washington, DC: ILSI Press.

Mossman, BT; Borm, PJ; Castranova, V; Costa, DL; Donaldson, K; Kleeberger, SR. (2007). Mechanisms of action of inhaled fibers, particles and nanoparticles in lung and cardiovascular diseases [Editorial]. Part Fibre Toxicol 4: 4. http://dx.doi.org/10.1186/1743-8977-4-4

Mossman, BT; Cameron, GS; Yotti, LP. (1985). Cocarcinogenic and tumor promoting properties of asbestos and other minerals in tracheobronchial epithelium. In Carcinogenesis - a comprehensive survey volume 8: cancer of the respiratory tract predisposing factors. New York, NY: Raven Press.

Mossman, BT; Churg, A. (1998). Mechanisms in the pathogenesis of asbestosis and silicosis [Review]. Am J Respir Crit Care Med 157: 1666-1680. http://dx.doi.org/10.1164/ajrccm.157.5.9707141

Mossman, BT; Eastman, A; Bresnick, E. (1984). Asbestos and benzo[a]pyrene act synergistically to induce squamous metaplasia and incorporation of [3H]thymidine in hamster tracheal epithelium. Carcinogenesis 5: 1401-1404. http://dx.doi.org/10.1093/carcin/5.11.1401

Mossman, BT; Eastman, A; Landesman, JM; Bresnick, E. (1983). Effects of crocidolite and chrysotile asbestos on cellular uptake and metabolism of benzo(a)pyrene in hamster tracheal epithelial cells. Environ Health Perspect 51: 331-335.

Mossman, BT; Lippmann, M; Hesterberg, TW; Kelsey, KT; Barchowsky, A; Bonner, JC. (2011). Pulmonary endpoints (lung carcinomas and asbestosis) following inhalation exposure to asbestos. J Toxicol Environ Health B Crit Rev 14: 76-121. http://dx.doi.org/10.1080/10937404.2011.556047

Mossman, BT; Shukla, A; Heintz, NH; Verschraegen, CF; Thomas, A; Hassan, R. (2013). New insights into understanding the mechanisms, pathogenesis, and management of malignant mesotheliomas. Am J Pathol 182: 1065-1077. http://dx.doi.org/10.1016/j.ajpath.2012.12.028

Muravov, OI; Kaye, WE; Lewin, M; Berkowitz, Z; Lybarger, JA; Campolucci, SS; Parker, JE. (2005). The usefulness of computed tomography in detecting asbestos-related pleural abnormalities in people who had indeterminate chest radiographs: the Libby, MT, experience. Int J Hyg Environ Health 208: 87-99.

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

Musk, AW; de Klerk, NH; Reid, A; Ambrosini, GL; Fritschi, L; Olsen, NJ; Merler, E; Hobbs, MST; Berry, G. (2008). Mortality of former crocidolite (blue asbestos) miners and millers at Wittenoom. Occup Environ Med 65: 541-543. http://dx.doi.org/10.1136/oem.2007.034280

Myojo, T; Takaya, M. (2001). Estimation of fibrous aerosol deposition in upper bronchi based on experimental data with model bifurcation. Ind Health 39: 141-149.

NCI (National Cancer Institute). (2011). Fast Stats: an interactive tool for access to SEER cancer statistics: Surveillance Research Program, National Cancer Institute. Retrieved from http://seer.cancer.gov/faststats

NCI (National Cancer Institute). (2012). Mortality - All cause of death, total U.S. (1969-2010), from the surveillance, epidemiology, and end results program. Available online at http://seer.cancer.gov/mortality/

Nelson, HH; Kelsey, KT. (2002). The molecular epidemiology of asbestos and tobacco in lung cancer. Oncogene 21: 7284-7288. http://dx.doi.org/10.1038/sj.onc.1205804

Neri, M; Ugolini, D; Dianzani, I; Gemignani, F; Landi, S; Cesario, A; Magnani, C; Mutti, L; Puntoni, R; Bonassi, S. (2008). Genetic susceptibility to malignant pleural mesothelioma and other asbestos-associated diseases [Review]. Mutat Res 659: 126-136. http://dx.doi.org/10.1016/j.mrrev.2008.02.002

Neri, S; Boraschi, P; Antonelli, A; Falaschi, F; Baschieri, L. (1996). Pulmonary function, smoking habits, and high resolution computed tomography (HRCT) early abnormalities of lung and pleural fibrosis in shipyard workers exposed to asbestos. Am J Ind Med 30: 588-595. http://dx.doi.org/10.1002/(SICI)1097-0274(199611)30:5<588::AID-AJIM6>3.0.CO;2-P

Newhouse, ML; Berry, G. (1976). Predictions of mortality from mesothelial tumours in asbestos factory workers. Br J Ind Med 33: 147-151.

Newhouse, ML; Berry, G; Wagner, JC; Turok, ME. (1972). A study of the mortality of female asbestos workers. Br J Ind Med 29: 134-141.

Ni, Z; Liu, Y; Keshava, N; Zhou, G; Whong, W; Ong, T. (2000). Analysis of K-ras and p53 mutations in mesotheliomas from humans and rats exposed to asbestos. Mutat Res 468: 87-92. http://dx.doi.org/10.1016/S1383-5718(00)00043-7

NIOSH (National Institute for Occupational Safety and Health). (1994). Method 7400: asbestos and other fibers by PCM (4 ed., pp. N/A). Cincinnati, OH: Department of Health and Human Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health (NIOSH). http://www.cdc.gov/niosh/docs/2003-154/pdfs/7400.pdf

NIOSH (National Institute for Occupational Safety and Health). (2011). Asbestos fibers and other elongate mineral particles: State of the science and roadmap for research. (2011-159). Atlanta, GA: National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention. http://www.cdc.gov/niosh/docs/2011-159/

Noonan, C; Pfau, J; Larson, T; Spence, M. (2006). Nested case-control study of autoimmune disease in an asbestos-exposed population. Environ Health Perspect 114: 1243-1247.

Noonan, CW. (2006). Exposure matrix development for the Libby cohort. Inhal Toxicol 18: 963-967. http://dx.doi.org/10.1080/08958370600835021

NRC (National Research Council). (1983). Risk assessment in the federal government: Managing the process. Washington, DC: National Academies Press. http://www.nap.edu/openbook.php?record_id=366&page=R1

NRC (National Research Council). (1993). Pesticides in the diets of infants and children. Washington, DC: National Academy Press. http://www.nap.edu/openbook.php?isbn=0309048753

NRC (National Research Council). (1994). Science and judgement in risk assessment (pp. 908-909). Washington, DC: National Academy Press.

NTP (National Toxicology Program). (1983). NTP lifetime carcinogenesis studies of amosite asbestos (CAS no. 12172-73-5) in Syrian golden hamsters (feed studies). (TR 249). Research Triangle Park, NC: U.S. Department of Health and Human Services, National Toxicology Program. http://ntp.niehs.nih.gov/ntp/htdocs/LT_rpts/tr249.pdf

NTP (National Toxicology Program). (1985). NTP toxicology and carcinogenesis studies of chrysotile asbestos (CAS no. 12001-29-5) in F344/N rats (feed studies) (pp. 1-390). Research Triangle Park, NC: U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health. http://ntp.niehs.nih.gov/ntp/htdocs/LT_rpts/tr279.pdf#search=Toxicology%20and%20carcinogenesis%20studies%20of%20chrysotile%20asbestos

NTP (National Toxicology Program). (1988). NTP technical report on the toxicology and carcinogenesis studies of crocidolite asbestos (CAS No. 12001-28-4) in F344/N rats (feed studies). (TR 280). Research Triangle Park, NC: U.S. Department of Health and Human Services, National Toxicology Program. http://ntp.niehs.nih.gov/ntp/htdocs/LT_rpts/tr280.pdf

NTP (National Toxicology Program). (1990a). NTP technical report on the toxicology and carcinogenesis studies of amosite asbestos (CAS no. 12172-73-5) in F344/N rats (feed studies). (TR 279). Research Triangle Park,

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

NC: U.S. Department of Health and Human Services, National Toxicology Program. http://ntp.niehs.nih.gov/ntp/htdocs/LT_rpts/tr279.pdf

NTP (National Toxicology Program). (1990b). NTP technical report on the toxicology and carcinogenesis studies of tremolite (CAS no. 14567-73-8) in F344/N rats (feed studies). (TR 277). Research Triangle Park, NC: U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health. http://ntp.niehs.nih.gov/ntp/htdocs/LT_rpts/tr277.pdf

Oberdorster, G. (1991). Lung dosimetry and extrapolation of results from animal inhalation studies to man. J Aerosol Med Pulm Drug Deliv 4: 335-347.

Oberdorster, G; Sharp, Z; Atudorei, V; Elder, A; Gelein, R; Lunts, A; Kreyling, W; Cox, C. (2002). Extrapulmonary translocation of ultrafine carbon particles following whole-body inhalation exposure of rats. J Toxicol Environ Health A 65: 1531-1543. http://dx.doi.org/10.1080/00984100290071658

Okayasu, R; Wu, L; Hei, TK. (1999). Biological effects of naturally occurring and man-made fibres: in vitro cytotoxicity and mutagenesis in mammalian cells. Br J Cancer 79: 1319-1324. http://dx.doi.org/10.1038/sj.bjc.6690213

Oldham, MJ; Mannix, RC; Phalen, RF. (1997). Deposition of monodisperse particles in hollow models representing adult and child-size tracheobronchial airways. Health Phys 72: 827-834.

OSHA (Occupational Safety & Health Administration). (1994). Toxic and hazardous substances - asbestos. (Standard No. 1910.1001). Washington, DC: United States Department of Labor.

OSHA. Occupational safety and health standards: Toxic and hazardous substances: Asbestos, 29 CFR § 1910.1001 (2006).

Padilla-Carlin, DJ; Schladweiler, MCJ; Shannahan, JH; Kodavanti, UP; Nyska, A; Burgoon, LD; Gavett, SH. (2011). Pulmonary inflammatory and fibrotic responses in Fischer 344 rats after intratracheal instillation exposure to Libby amphibole. J Toxicol Environ Health A 74: 1111-1132. http://dx.doi.org/10.1080/15287394.2011.586940

Pairon, JC; Laurent, F; Rinaldo, M; Clin, B; Andujar, P; Ameille, J; Brochard, P; Chammings, S; Ferretti, G; Galateau-Sallé, F; Gislard, A; Letourneux, M; Luc, A; Schorlé, E; Paris, C. (2013). Pleural plaques and the risk of pleural mesothelioma. National Cancer Institute Journal (Online) 105: 293-301. http://dx.doi.org/10.1093/jnci/djs513

Pardee, JT; Larsen, ES. (1928). Deposits of vermiculite and other minerals in the Rainy Creek district, near Libby, Montana. Washington, DC: Contributions to Economic Geology.

Paris, C; Martin, A; Letourneux, M; Wild, P. (2008). Modelling prevalence and incidence of fibrosis and pleural plaques in asbestos-exposed populations for screening and follow-up: a cross-sectional study. Environ Health 7: 30. http://dx.doi.org/10.1186/1476-069X-7-30

Paris, C; Thierry, S; Brochard, P; Letourneux, M; Schorle, E; Stoufflet, A; Ameille, J; Conso, F; Pairon, JC. (2009). Pleural plaques and asbestosis: dose- and time-response relationships based on HRCT data. Eur Respir J 34: 72-79. http://dx.doi.org/10.1183/09031936.00094008

Peacock, A. (2003). Libby, Montana: Asbestos and the deadly silence of an American corporation. Neenah, WI: Big Earth Publishing.

Peacock, C; Copley, SJ; Hansell, DM. (2000). Asbestos-related benign pleural disease. Clin Radiol 55: 422-432. http://dx.doi.org/10.1053/crad.2000.0450

Peipins, LA; Lewin, M; Campolucci, S; Lybarger, JA; Kapil, V; Middleton, D; Miller, A; Weis, C; Spence, M; Black, B. (2004a). Overstating the consequences: Peipins et al.'s response. Environ Health Perspect 112: A84-A85. http://dx.doi.org/10.1289/ehp.112-a84b

Peipins, LA; Lewin, M; Campolucci, S; Lybarger, JA; Kapil, V; Middleton, D; Miller, A; Weis, C; Spence, M; Black, B. (2004b). Radiographic abnormalities: Response from Peipins et al. Environ Health Perspect 112: A83. http://dx.doi.org/10.1289/ehp.112-a83

Peipins, LA; Lewin, M; Campolucci, S; Lybarger, JA; Miller, A; Middleton, D; Weis, C; Spence, M; Black, B; Kapil, V. (2003). Radiographic abnormalities and exposure to asbestos-contaminated vermiculite in the community of Libby, Montana, USA. Environ Health Perspect 111: 1753-1759.

Pellegrino, R; Viegi, G; Brusasco, V; Crapo, RO; Burgos, F; Casaburi, R; Coates, A; van Der Grinten, CP; Gustafsson, P; Hankinson, J; Jensen, R; Johnson, DC; Macintyre, N; Mckay, R; Miller, MR; Navajas, D; Pedersen, OF; Wanger, J. (2005). Interpretative strategies for lung function tests. Eur Respir J 26: 948-968. http://dx.doi.org/10.1183/09031936.05.00035205

Percy, C; Stanek, E, III; Gloeckler, L. (1981). Accuracy of cancer death certificates and its effect on cancer mortality statistics. Am J Public Health 71: 242-250. http://dx.doi.org/10.2105/AJPH.71.3.242

Peto, J. (1978). The hygiene standard for chrysotile asbestos. Lancet 1: 484-489.

Peto, J. (1979). Dose-response relationships for asbestos-related disease: Implications for hygiene standards: Part II. Mortality. Ann N Y Acad Sci 330: 195-203. http://dx.doi.org/10.1111/j.1749-6632.1979.tb18720.x

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

Peto, J; Seidman, H; Selikoff, IJ. (1982). Mesothelioma mortality in asbestos workers: implications for models of carcinogenesis and risk assessment. Br J Cancer 45: 124-135. http://dx.doi.org/10.1038/bjc.1982.15

Pezerat, H. (2009). Chrysotile biopersistence: the misuse of biased studies. Int J Occup Environ Health 15: 102-106. http://dx.doi.org/10.1179/107735209799449770

Pfau, JC; Seib, T; Overocker, JJ; Roe, J; Ferro, AS. (2012). Functional expression of system x(c)(-) is upregulated by asbestos but not crystalline silica in murine macrophages. Inhal Toxicol 24: 476-485. http://dx.doi.org/10.3109/08958378.2012.689782

Pfau, JC; Sentissi, JJ; Li, S; Calderon-Garciduenas, L; Brown, JM; Blake, DJ. (2008). Asbestos-induced autoimmunity in C57Bl/6 mice. J Immunotoxicol 5: 129-137. http://dx.doi.org/10.1080/15476910802085756

Pfau, JC; Sentissi, JJ; Weller, G; Putnam, EA. (2005). Assessment of autoimmune responses associated with asbestos exposure in Libby, Montana, USA. Environ Health Perspect 113: 25-30. http://dx.doi.org/10.1289/ehp.7431

Phalen, RF; Oldham, MJ. (2001). Methods for modeling particle deposition as a function of age. Respir Physiol Neurobiol 128: 119-130. http://dx.doi.org/10.1016/S0034-5687(01)00270-5

Phalen, RF; Oldham, MJ; Beaucage, CB; Crocker, TT; Mortensen, JD. (1985). Postnatal enlargement of human tracheobronchial airways and implications for particle deposition. Anat Rec 212: 368-380. http://dx.doi.org/10.1002/ar.1092120408

Phalen, RF; Oldham, MJ; Nel, AE. (2006). Tracheobronchial particle dose considerations for in vitro toxicology studies. Toxicol Sci 92: 126-132. http://dx.doi.org/10.1093/toxsci/kfj182

Pietruska, JR; Johnston, T; Zhitkovich, A; Kane, AB. (2010). XRCC1 deficiency sensitizes human lung epithelial cells to genotoxicity by crocidolite asbestos and Libby amphibole. Environ Health Perspect 118: 1707-1713. http://dx.doi.org/10.1289/ehp.1002312

Pinheiro, GA; Antao, VC; Bang, KM; Attfield, MD. (2004). Malignant mesothelioma surveillance: a comparison of ICD 10 mortality data with SEER incidence data in nine areas of the United States. Int J Occup Environ Health 10: 251-255.

Pinsky, PF; Freedman, M; Kvale, P; Oken, M; Caporaso, N; Gohagan, J. (2006). Abnormalities on chest radiograph reported in subjects in a cancer screening trial. Chest 130: 688-693. http://dx.doi.org/10.1378/chest.130.3.688

Poser, I; Rahman, Q; Lohani, M; Yadav, S; Becker, HH; Weiss, DG; Schiffmann, D; Dopp, E. (2004). Modulation of genotoxic effects in asbestos-exposed primary human mesothelial cells by radical scavengers, metal chelators and a glutathione precursor. Mutat Res 559: 19-27. http://dx.doi.org/10.1016/j.mrgentox.2003.12.006

Pott, F; Huth, F; Friedrichs, KH. (1974). Tumorigenic effect of fibrous dusts in experimental animals. Environ Health Perspect 9: 313-315.

Pott, F; Ziem, U; Reiffer, FJ; Huth, F; Ernst, H; Mohr, U. (1987). Carcinogenicity studies on fibres, metal compounds, and some other dusts in rats. Exp Toxicol Pathol 32: 129-152.

Price, B. (2004). Radiographic abnormalities and asbestos exposure: Libby, Montana. Environ Health Perspect 112: A82-A83. http://dx.doi.org/10.1289/ehp.112-a82

Putnam, EA; Smartt, A; Groves, A; Schwanke, C; Brezinski, M; Pershouse, MA. (2008). Gene expression changes after exposure to six-mix in a mouse model. J Immunotoxicol 5: 139-144. http://dx.doi.org/10.1080/15476910802085772

Rahman, I; MacNee, W. (1999). Lung glutathione and oxidative stress: Implications in cigarette smoke-induced airway disease [Review]. Am J Physiol 277: L1067-L1088.

Ramos-Nino, ME; Haegens, A; Shukla, A; Mossman, BT. (2002). Role of mitogen-activated protein kinases (MAPK) in cell injury and proliferation by environmental particulates. Mol Cell Biochem 234-235: 111-118. http://dx.doi.org/10.1023/A:1015924413043

Rasch, EK; Hirsch, R; Paulose-Ram, R; Hochberg, MC. (2003). Prevalence of rheumatoid arthritis in persons 60 years of age and older in the United States: Effect of different methods of case classification. Arthritis Rheum 48: 917-926. http://dx.doi.org/10.1002/art.10897

Rasmussen, DL; Pfau, JC. (2012). Asbestos activates CH12.LX B-lymphocytes via macrophage signaling. J Immunotoxicol 9: 129-140. http://dx.doi.org/10.3109/1547691X.2011.631953

Reeves, GK; Cox, DR; Darby, SC; Whitley, E. (1998). Some aspects of measurement error in explanatory variables for continuous and binary regression models. Stat Med 17: 2157-2177. http://dx.doi.org/10.1002/(SICI)1097-0258(19981015)17:19<2157::AID-SIM916>3.0.CO;2-F

Regnis, JA; Zeman, KL; Noone, PG; Knowles, MR; Bennett, WD. (2000). Prolonged airway retention of insoluble particles in cystic fibrosis versus primary ciliary dyskinesia. Exp Lung Res 26: 149-162. http://dx.doi.org/10.1080/019021400269844

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

Reid, A; Berry, G; de Klerk, N; Hansen, J; Heyworth, J; Ambrosini, G; Fritschi, L; Olsen, N; Merler, E; Musk, A. (2007). Age and sex differences in malignant mesothelioma after residential exposure to blue asbestos (crocidolite). Chest 131: 376-382. http://dx.doi.org/10.1378/chest.06-1690

Reid, A; Berry, G; Heyworth, J; de Klerk, NH; Musk, AW. (2009). Predicted mortality from malignant mesothelioma among women exposed to blue asbestos at Wittenoom, Western Australia. Occup Environ Med 66: 169-174. http://dx.doi.org/10.1136/oem.2007.038315

Reid, A; Franklin, P; Olsen, N; Sleith, J; Samuel, L; Aboagye-Sarfo, P; de Klerk, N; Musk, AW. (2013). All-cause mortality and cancer incidence among adults exposed to blue asbestos during childhood. Am J Ind Med 56: 133-145. http://dx.doi.org/10.1002/ajim.22103

Reiss, B; Tong, C; Telang, S; Williams, GM. (1983). Enhancement of benzo[a]pyrene mutagenicity by chrysotile asbestos in rat liver epithelial cells. Environ Res 31: 100-104. http://dx.doi.org/10.1016/0013-9351(83)90065-8

Rendall, RE; Skikne, MI. (1980). Submicroscopic fibres in industrial atmospheres. In JC Wagner (Ed.), Biological effects of mineral fibres (pp. 837-843). Lyon, France: International Agency on the Research of Cancer. http://apps.who.int/bookorders/anglais/detart1.jsp?sesslan=1&codlan=1&codcol=73&codcch=30

Rendall, REG; Du Toit, RSJ. (1994). The retention and clearance of glass fibre and different varieties of asbestos by the lung. Ann Occup Hyg 38: 757-761. http://dx.doi.org/10.1093/annhyg/38.inhaled_particles_VII.757

Ribak, J; Lilis, R; Suzuki, Y; Penner, L; Selikoff, IJ. (1991). Death certificate categorization of malignant pleural and peritoneal mesothelioma in a cohort of asbestos insulation workers. J Soc Occup Med 41: 137-139. http://dx.doi.org/10.1093/occmed/41.3.137

Richardson, DB. (2009). Lung cancer in chrysotile asbestos workers: analyses based on the two-stage clonal expansion model. Cancer Causes Control 20: 917-923.

Richardson, DB. (2010). Occupational exposures and lung cancer: Adjustment for unmeasured confounding by smoking. Epidemiology 21: 181-186. http://dx.doi.org/10.1097/EDE.0b013e3181c6f7d9

Rogan, WJ; Gladen, BC; Ragan, NB; Anderson, HA. (1987). US prevalence of occupational pleural thickening: A look at chest X-rays from the first National Health and Nutrition Examination Survey. Am J Epidemiol 126: 893-900.

Rogan, WJ; Ragan, NB; Dinse, GE. (2000). X-ray evidence of increased asbestos exposure in the US population from NHANES I and NHANES II, 1973-1978. Cancer Causes Control 11: 441-449. http://dx.doi.org/10.1023/A:1008952426060

Roggli, VL; Vollmer, RT. (2008). Twenty-five years of fiber analysis: What have we learned? Hum Pathol 39: 307-315. http://dx.doi.org/10.1016/j.humpath.2007.07.005

Roggli, VL; Vollmer, RT; Butnor, KJ; Sporn, TA. (2002). Tremolite and mesothelioma. Ann Occup Hyg 46: 447-453. http://dx.doi.org/10.1093/annhyg/mef056

Rohs, A; Lockey, J; Dunning, K; Shukla, R; Fan, H; Hilbert, T; Borton, E; Wiot, J; Meyer, C; Shipley, R; Lemasters, G; Kapil, V. (2008). Low-level fiber-induced radiographic changes caused by Libby vermiculite: a 25-year follow-up study. Am J Respir Crit Care Med 177: 630-637. http://dx.doi.org/10.1164/rccm.200706-841OC

Roller, M; Pott, F; Kamino, K; Althoff, GH; Bellmann, B. (1996). Results of current intraperitoneal carcinogenicity studies with mineral and vitreous fibres. Exp Toxicol Pathol 48: 3-12.

Roller, M; Pott, F; Kamino, K; Althoff, GH; Bellmann, B. (1997). Dose-response relationship of fibrous dusts in intraperitoneal studies. Environ Health Perspect 105: 1253-1256.

Rosenstock, L; Barnhart, S; Heyer, NJ; Pierson, DJ; Hudson, LD. (1988). The relation among pulmonary function, chest roentgenographic abnormalities, and smoking status in an asbestos-exposed cohort. Am Rev Respir Dis 138: 272-277. http://dx.doi.org/10.1164/ajrccm/138.2.272

Ross, M; Nolan, RP; Langer, AM; Cooper, WC. (1993). Health effects of mineral dusts other than asbestos. In GD Guthrie, Jr.; BT Mossman (Eds.), Health effects of mineral dusts (pp. 361-407). Washington, DC: Mineralogical Society of America. http://rimg.geoscienceworld.org/cgi/content/abstract/28/1/361

Rothman, KJ. (1981). Induction and latent periods. Am J Epidemiol 114: 253-259.

Rothman, KJ. (1986). Significance questing. Ann Intern Med 105: 445-447.

Rothman, KJ; Greenland, S. (1998). Modern epidemiology (2nd ed.). Philadelphia, PA: Lippincott, Williams, & Wilkins.

Roushdy-Hammady, I; Siegel, J; Emri, S; Testa, J; Carbone, M. (2001). Genetic-susceptibility factor and malignant mesothelioma in the Cappadocian region of Turkey. Lancet 357: 444-445. http://dx.doi.org/10.1016/S0140-6736(00)04013-7

SAB (Science Advisory Board). (2013). SAB review of EPAs draft assessment entitled toxicological review of Libby Amphibole Asbestos (August 2011). (EPA-SAB-13-001). Washington, DC: U.S. Environmental Protection Agency.

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

http://yosemite.epa.gov/sab/sabproduct.nsf/0/4F2A245C7160456B85257B030072E5D3/$File/EPA-SAB-13-001-unsigned.pdf

Sahu, AP; Dogra, RK; Shanker, R; Zaidi, SH. (1975). Fibrogenic response in murine lungs to asbestos. Exp Pathol (Jena) 11: 21-24.

Salazar, KD; Copeland, CB; Luebke, RW. (2012). Effects of Libby amphibole asbestos exposure on two models of arthritis in the Lewis rat. J Toxicol Environ Health A 75: 351-365. http://dx.doi.org/10.1080/15287394.2012.668164

Salazar, KD; Copeland, CB; Wood, CE; Schmid, JE; Luebke, RW. (2013). Evaluation of anti-nuclear antibodies and kidney pathology in Lewis rats following exposure to Libby amphibole asbestos. J Immunotoxicol 10: 329-333. http://dx.doi.org/10.3109/1547691X.2012.747230

Sanchez, MS; Gunter, ME; Dyar, MD. (2008). Characterization of historical amphibole samples from the former vermiculite mine near Libby, Montana, U.S.A. Eur J Mineral 20: 1043-1053. http://dx.doi.org/10.1127/0935-1221/2008/0020-1866

Scapoli, L; Ramos-Nino, ME; Martinelli, M; Mossman, BT. (2004). Src-dependent ERK5 and Src/EGFR-dependent ERK1/2 activation is required for cell proliferation by asbestos. Oncogene 23: 805-813. http://dx.doi.org/10.1038/sj.onc.1207163

Schiller-Scotland, CF; Hlawa, R; Gebhart, J. (1994). Experimental data for total deposition in the respiratory tract of children. Toxicol Lett 72: 137-144. http://dx.doi.org/10.1016/0378-4274(94)90020-5

Schneider, V; Maurer, RR. (1977). Asbestos and embryonic development. Teratology 15: 273-279. http://dx.doi.org/10.1002/tera.1420150309

Sebastien, P; Billion-Galland, MA; Dufour, G; Bignon, J. (1980). Measurement of asbestos air pollution inside buildings sprayed with asbestos (pp. 80). (EPA-560/13-80-026). Washington, DC: U. S. Environmental Protection Agency, Office of Pesticides and Toxic Substances. http://nepis.epa.gov/Exe/ZyPURL.cgi?Dockey=9100BHQI.txt

Sebastien, P; McDonald, JC; McDonald, AD; Case, B; Harley, R. (1989). Respiratory cancer in chrysotile textile and mining industries: exposure inferences from lung analysis. Br J Ind Med 46: 180-187.

SEER (Surveillance, Epidemiology, and End Results Program). (2010). Table 15.10: Cancer of the lung and bronchus (invasive). SEER incidence of U.S. death rates, age-adjusted and age-specific rates, by race and sex. In SEER cancer statistics review, 1975-2007. Research Triangle Park, NC: U.S. Departmentof Health and Human Services, National Cancer Institute. http://seer.cancer.gov/csr/1975_2010/results_merged/sect_15_lung_bronchus.pdf

Seidman, H; Selikoff, IJ; Gelb, SK. (1986). Mortality experience of amosite asbestos factory workers: Dose-response relationships 5 to 40 years after onset of short-term work exposure. Am J Ind Med 10: 479-514.

Sekhon, H; Wright, J; Churg, A. (1995). Effects of cigarette smoke and asbestos on airway, vascular and mesothelial cell proliferation. Int J Exp Pathol 76: 411-418.

Selevan, SG; Kimmel, CA; Mendola, P. (2000). Identifying critical windows of exposure for children's health. Environ Health Perspect 1083: 451-455.

Selikoff, IJ; Hammond, EC. (1979). Asbestos and smoking. JAMA 242: 458-459. http://dx.doi.org/10.1001/jama.1979.03300050048029

Selikoff, IJ; Lee, DHK. (1978). Asbestos and disease. New York, NY: Academic Press. http://www.sciencedirect.com/science/book/9780126360509

Selikoff, IJ; Seidman, H. (1992). Use of death certificates in epidemiological studies, including occupational hazards: Variations in discordance of different asbestos-associated diseases on best evidence ascertainment. Am J Ind Med 22: 481-492. http://dx.doi.org/10.1002/ajim.4700220403

Serve, KM; Black, B; Szeinuk, J; Pfau, JC. (2013). Asbestos-associated mesothelial cell autoantibodies promote collagen deposition in vitro. Inhal Toxicol 25: 774-784. http://dx.doi.org/10.3109/08958378.2013.848249

Shannahan, J; Schladweiler, M; Padilla-Carlin, D; Nyska, A; Richards, J; Ghio, A; Gavett, S; Kodavanti, U. (2011a). The role of cardiovascular disease-associated iron overload in Libby amphibole-induced acute pulmonary injury and inflammation. Inhal Toxicol 23: 129-141. http://dx.doi.org/10.3109/08958378.2011.551850

Shannahan, JH; Alzate, O; Winnik, WM; Andrews, D; Schladweiler, MC; Ghio, AJ; Gavett, SH; Kodavanti, UP. (2012a). Acute phase response, inflammation and metabolic syndrome biomarkers of Libby asbestos exposure. Toxicol Appl Pharmacol 260: 105-114. http://dx.doi.org/10.1016/j.taap.2012.02.006

Shannahan, JH; Ghio, AJ; Schladweiler, MC; McGee, JK; Richards, JH; Gavett, SH; Kodavanti, UP. (2011b). The role of iron in Libby amphibole-induced acute lung injury and inflammation. Inhal Toxicol 23: 313-323. http://dx.doi.org/10.3109/08958378.2011.569587

Shannahan, JH; Ghio, AJ; Schladweiler, MC; Richards, JH; Andrews, D; Gavett, SH; Kodavanti, UP. (2012b). Transcriptional activation of inflammasome components by Libby amphibole and the role of iron. Inhal Toxicol 24: 60-69. http://dx.doi.org/10.3109/08958378.2011.633942

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

Shannahan, JH; Nyska, A; Cesta, M; Schladweiler, MC; Vallant, BD; Ward, WO; Ghio, AJ; Gavett, SH; Kodavanti, UP. (2012c). Subchronic pulmonary pathology, iron overload, and transcriptional activity after libby amphibole exposure in rat models of cardiovascular disease. Environ Health Perspect 120: 85-91. http://dx.doi.org/10.1289/ehp.1103990

Shannahan, JH; Schladweiler, MC; Richards, JH; Ledbetter, AD; Ghio, AJ; Kodavanti, UP. (2010). Pulmonary oxidative stress, inflammation, and dysregulated iron homeostasis in rat models of cardiovascular disease. J Toxicol Environ Health A 73: 641-656. http://dx.doi.org/10.1080/15287390903578208

Shannahan, JH; Schladweiler, MC; Thomas, RF; Ward, WO; Ghio, AJ; Gavett, SH; Kodavanti, UP. (2012d). Vascular and thrombogenic effects of pulmonary exposure to Libby amphibole. J Toxicol Environ Health A 75: 213-231. http://dx.doi.org/10.1080/15287394.2012.652055

Shtol', AV; Plotko, EG; Seliankina, KP. (2000). [Children's health and environmental air pollution with dust containing asbestos]. Med Tr Prom Ekol 11: 10-13.

Shukla, A; Gulumian, M; Hei, TK; Kamp, D; Rahman, Q; Mossman, BT. (2003). Multiple roles of oxidants in the pathogenesis of asbestos-induced diseases. Free Radic Biol Med 34: 1117-1129. http://dx.doi.org/10.1016/S0891-5849(03)00060-1

Shukla, A; Lounsbury, KM; Barrett, TF; Gell, J; Rincon, M; Butnor, KJ; Taatjes, DJ; Davis, GS; Vacek, P; Nakayama, KI; Nakayama, K; Steele, C; Mossman, BT. (2007). Asbestos-induced peribronchiolar cell proliferation and cytokine production are attenuated in lungs of protein kinase C-delta knockout mice. Am J Pathol 170: 140-151. http://dx.doi.org/10.2353/ajpath.2007.060381

Sichletidis, L; Chloros, D; Chatzidimitriou, N; Tsiotsios, I; Spyratos, D; Patakas, D. (2006). Diachronic study of pleural plaques in rural population with environmental exposure to asbestos. Am J Ind Med 49: 634-641. http://dx.doi.org/10.1002/ajim.20334

Sichletidis, L; Daskalopoulou, E; Chloros, D; Vlachogiannis, E; Vamvalis, C. (1992a). Pleural plaques in a rural population in central Macedonia, Greece. Med Lav 83: 259-265.

Sichletidis, L; Daskalopoulou, E; Tsarou, V; Pnevmatikos, I; Chloros, D; Vamvalis, C. (1992b). Five cases of pleural mesothelioma with endemic pleural calcifications in a rural area in Greece. Med Lav 83: 326-329.

Šimundić, I; Janković, T; Tocilj, J; Gjakun, K; Jurić, I; Roglić, J; Čapkun, V. (2002). Diagnostic value of clinical, radiologic and functional examinations of patients with pulmonary and pleural asbestosis. Acta Clin Croat 41: 73-78.

Smartt, AM; Brezinski, M; Trapkus, M; Gardner, D; Putnam, EA. (2010). Collagen accumulation over time in the murine lung after exposure to crocidolite asbestos or Libby amphibole. Environ Toxicol 25: 68-76. http://dx.doi.org/10.1002/tox.20472

Smith, DD. (2002). Women and mesothelioma. Chest 122: 1885-1886. http://dx.doi.org/10.1378/chest.122.6.1885

Smith, I. (2014). Email from Ivan Smith to Dr. Bob Benson. Re: Letter to Aubrey Miller, EPA Region 8, dated June 7, 2007. Smith, I.

Smith, WE. (1978). Final report on biologic tests of samples 22260p5 and 22263p2. Madison, NJ: Health Research Institute, Fairleigh Dickinson University.

Smith, WE; Hubert, DD; Sobel, HJ; Marquet, E. (1979). Biologic tests of tremolite in hamsters. In R Lemen; JM Dement (Eds.), Dusts and disease (pp. 335-339). Park Forest South, IL: Pathotox Publisher.

Soulat, JM; Lauque, D; Esquirol, Y; Déprés, M; Giron, J; Claudel, R; Carles, P. (1999). High-resolution computed tomography abnormalities in ex-insulators annually exposed to asbestos dust. Am J Ind Med 36: 593-601. http://dx.doi.org/10.1002/(SICI)1097-0274(199912)36:6<593::AID-AJIM1>3.0.CO;2-Z

Spiegelhalter, D; Thomas, A; Best, N; Lunn, D. (2003). WinBugs version 1.4 user manual. Cambridge, UK: MRC Biostatistics Unit. http://www.mrc-bsu.cam.ac.uk/bugs/winbugs/manual14.pdf

Spiegelhalter, DJ; Best, NG; Carlin, BP; Van der Linde, A. (2002). Bayesian measures of model complexity and fit. J R Stat Soc Series B Stat Methodol 64: 583-639. http://dx.doi.org/10.1111/1467-9868.00353

Srebro, SH; Roggli, VL. (1994). Asbestos-related disease associated with exposure to asbestiform tremolite. Am J Ind Med 26: 809-819. http://dx.doi.org/10.1002/ajim.4700260610

Stanton, MF; Layard, M; Tegeris, A; Miller, E; May, M; Morgan, E; Smith, A. (1981). Relation of particle dimension to carcinogenicity in amphibole asbestoses and other fibrous minerals. J Natl Cancer Inst 67: 965-975.

Stanton, MF; Wrench, C. (1972). Mechanisms of mesothelioma induction with asbestos and fibrous glass. J Natl Cancer Inst 48: 797-821.

Straif, K; Benbrahim-Tallaa, L; Baan, R; Grosse, Y; Secretan, B; El Ghissassi, F; Bouvard, V; Guha, N; Freeman, C; Galichet, L; Cogliano, V. (2009). A review of human carcinogens: Part C: Metals, arsenic, dusts, and fibres. Lancet Oncol 10: 453-454. http://dx.doi.org/10.1016/S1470-2045(09)70134-2

Sturm, R. (2011). A computer model for the simulation of fiber-cell interaction in the alveolar region of the respiratory tract. Comput Biol Med 41: 565-573. http://dx.doi.org/10.1016/j.compbiomed.2011.05.009

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

Sturm, R, . (2009). A theoretical approach to the deposition of cancer-inducing asbestos fibers in the human respiratory tract. Open Lung Cancer J 2: 1-11.

Sturm, R; Hofmann, W. (2009). A theoretical approach to the deposition and clearance of fibers with variable size in the human respiratory tract. J Hazard Mater 170: 210-218. http://dx.doi.org/10.1016/j.jhazmat.2009.04.107

Sullivan, PA. (2007). Vermiculite, respiratory disease, and asbestos exposure in Libby, Montana: update of a cohort mortality study. Environ Health Perspect 115: 579-585. http://dx.doi.org/10.1289/ehp.9481

Sussman, RG; Cohen, BS; Lippmann, M. (1991a). Asbestos fiber deposition in a human tracheobronchial cast. I. Experimental. Inhal Toxicol 3: 145-160. http://dx.doi.org/10.3109/08958379109145281

Sussman, RG; Cohen, BS; Lippmann, M. (1991b). Asbestos fiber deposition in a human tracheobronchial cast. II. Empirical model. Inhal Toxicol 3: 161-179. http://dx.doi.org/10.3109/08958379109145282

Suzuki, K; Hei, TK. (1996). Induction of heme oxygenase in mammalian cells by mineral fibers: Distinctive effect of reactive oxygen species. Carcinogenesis 17: 661-667. http://dx.doi.org/10.1093/carcin/17.4.661

Suzuki, Y; Kohyama, N. (1991). Translocation of inhaled asbestos fibers from the lung to other tissues. Am J Ind Med 19: 701-704. http://dx.doi.org/10.1002/ajim.4700190603

Suzuki, Y; Yuen, SR. (2001). Asbestos tissue burden study on human malignant mesothelioma. Ind Health 39: 150-160. http://dx.doi.org/10.2486/indhealth.39.150

Suzuki, Y; Yuen, SR; Ashley, R. (2005). Short, thin asbestos fibers contribute to the development of human malignant mesothelioma: pathological evidence. Int J Hyg Environ Health 208: 201-210. http://dx.doi.org/10.1016/j.ijheh.2005.01.015

Tableman, M, .; Kim, J, . S. (2004). Survival analysis using S: Analysis of time-to-event data. Virginia Beach, VA: Chapman and Hall/CRC Press.

Tan, RJ; Fattman, CL; Watkins, SC; Oury, TD. (2004). Redistribution of pulmonary EC-SOD after exposure to asbestos. J Appl Physiol 97: 2006-2013. http://dx.doi.org/10.1152/japplphysiol.00480.2004

Topping, DC; Nettesheim, P. (1980). Two-stage carcinogenesis studies with asbestos in Fischer 344 rats. J Natl Cancer Inst 65: 627-630. http://dx.doi.org/10.1093/jnci/65.3.627

Tossavainen, A; Karjalainen, A; Karhunen, PJ. (1994). Retention of asbestos fibers in the human body. Environ Health Perspect 102: 253-255.

Truhaut, R; Chouroulinkov, I. (1989). Effect of long-term ingestion of asbestos fibres in rats. In Non-occupational exposure to mineral fibres (pp. 127-133). Lyon, France: International Agency for Research on Cancer.

U.S. EPA (U.S. Environmental Protection Agency). (1986a). Airborne asbestos health assessment update. (EPA/600/8-84/003F). Washington DC: U.S. Environmental Protection Agency, Environmental Criteria and Assessment. http://nepis.epa.gov/Exe/ZyPURL.cgi?Dockey=20009EBT.txt

U.S. EPA (U.S. Environmental Protection Agency). (1986b). Guidelines for mutagenicity risk assessment. (EPA/630/R-98/003). Washington, DC: U.S. Environmental Protection Agency, Risk Assessment Forum. http://www.epa.gov/iris/backgrd.html

U.S. EPA (U.S. Environmental Protection Agency). (1986c). Guidelines for the health risk assessment of chemical mixtures. (EPA/630/R-98/002). Washington, DC: U.S. Environmental Protection Agency, Risk Assessment Forum. http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=22567

U.S. EPA (U.S. Environmental Protection Agency). (1988a). IRIS summary for Asbestos (CASRN 1332-21-4). Washington, DC: U.S. Environmental Protection Agency, Integrated Risk Information System. http://www.epa.gov/iris/subst/0371.htm

U.S. EPA (U.S. Environmental Protection Agency). (1988b). Recommendations for and documentation of biological values for use in risk assessment. (EPA/600/6-87/008). Cincinnati, OH: U.S. Environmental Protection Agency, National Center for Environmental Assessment. http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=34855

U.S. EPA (U.S. Environmental Protection Agency). (1991a). Guidelines for developmental toxicity risk assessment. (EPA/600/FR-91/001). Washington, DC: U.S. Environmental Protection Agency, Risk Assessment Forum. http://www.epa.gov/raf/publications/guidelines-dev-toxicity-risk-assessment.htm

U.S. EPA (U.S. Environmental Protection Agency). (1991b). Health assessment document for vermiculite. (EPA/600/8-91/037). Research Triangle Park, NC: U.S. Environmental Protection Agency, Environmental Criteria and Assessment Office. http://nepis.epa.gov/Exe/ZyPURL.cgi?Dockey=30001LHV.txt

U.S. EPA (U.S. Environmental Protection Agency). (1993). Method for the determination of asbestos in bulk building materials. (EPA/600/R-93/116). Research Triangle Park, NC: U.S. Environmental Protection Agency, Atmospheric Research and Exposure Assessment Laboratory. http://www.rti.org/pubs/Test-Method-for-Determination.pdf

U.S. EPA (U.S. Environmental Protection Agency). (1994a). Interim policy for particle size and limit concentration issues in inhalation toxicity studies. Washington, DC: U.S. Environmental Protection Agency, Office of Pesticide Products. http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=186068

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

U.S. EPA (U.S. Environmental Protection Agency). (1994b). Methods for derivation of inhalation reference concentrations and application of inhalation dosimetry. (EPA/600/8-90/066F). Research Triangle Park, NC: U.S. Environmental Protection Agency, Environmental Criteria and Assessment Office. http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=71993

U.S. EPA (U.S. Environmental Protection Agency). (1995). The use of the benchmark dose approach in health risk assessment. (EPA/630/R-94/007). Washington, DC: U.S. Environmental Protection Agency, Risk Assessment Forum. http://www.epa.gov/raf/publications/useof-bda-healthrisk.htm

U.S. EPA (U.S. Environmental Protection Agency). (1996). Guidelines for reproductive toxicity risk assessment. (EPA/630/R-96/009). Washington, DC: U.S. Environmental Protection Agency, Risk Assessment Forum. http://www.epa.gov/raf/publications/pdfs/REPRO51.PDF

U.S. EPA (U.S. Environmental Protection Agency). (1998). Guidelines for neurotoxicity risk assessment. (EPA/630/R-95/001F). Washington, DC: U.S. Environmental Protection Agency, Risk Assessment Forum. http://www.epa.gov/raf/publications/pdfs/NEUROTOX.PDF

U.S. EPA (U.S. Environmental Protection Agency). (2000a). Sampling and analysis of consumer garden products that contain vermiculite. (EPA/744/R-00/010). Washington, DC: U.S. Environmental Protection Agency, Office of Prevention, Pesticides and Toxic Substances. http://nepis.epa.gov/Exe/ZyPURL.cgi?Dockey=P10014IJ.txt

U.S. EPA (U.S. Environmental Protection Agency). (2000b). Science policy council handbook: risk characterization. (EPA/100/B-00/002). Washington, D.C.: U.S. Environmental Protection Agency, Office of Science Policy. http://www.epa.gov/osa/spc/pdfs/rchandbk.pdf

U.S. EPA (U.S. Environmental Protection Agency). (2000c). Supplementary guidance for conducting health risk assessment of chemical mixtures. (EPA/630/R-00/002). Washington, DC: U.S. Environmental Protection Agency, Risk Assessment Forum. http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=20533

U.S. EPA (U.S. Environmental Protection Agency). (2001). EPA's actions concerning asbestos-contaminated vermiculite in Libby, Montana. (2001-S-7). Washington, DC: U.S. Environmental Protection Agency, Office of the Inspector General. http://www.epa.gov/oig/reports/2001/montana.pdf

U.S. EPA (U.S. Environmental Protection Agency). (2002). A review of the reference dose and reference concentration processes. (EPA/630/P-02/002F). Washington, DC: U.S. Environmental Protection Agency, Risk Assessment Forum. http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=51717

U.S. EPA (U.S. Environmental Protection Agency). (2005a). Guidelines for carcinogen risk assessment. (EPA/630/P-03/001F). Washington, DC: U.S. Environmental Protection Agency, Risk Assessment Forum. http://www.epa.gov/cancerguidelines/

U.S. EPA (U.S. Environmental Protection Agency). (2005b). Supplemental guidance for assessing susceptibility from early-life exposure to carcinogens. In US Environmental Protection Agency, Risk Assessment Forum (pp. 1125-1133). (EPA/630/R-03/003F). Washington, DC: U.S. Environmental Protection Agency, Risk Assessment Forum. http://www.epa.gov/cancerguidelines/guidelines-carcinogen-supplement.htm

U.S. EPA (U.S. Environmental Protection Agency). (2006a). Aging and toxic response: issues relevant to risk assessment. (EPA/600/P-03/004A). Washington, DC: U.S. Environmental Protection Agency, National Center for Environmental Assessment. http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=156648

U.S. EPA (U.S. Environmental Protection Agency). (2006b). A framework for assessing health risk of environmental exposures to children. (EPA/600/R-05/093F). Washington, DC: U.S. Environmental Protection Agency, National Center for Environmental Assessment. http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=158363

U.S. EPA (U.S. Environmental Protection Agency). (2006c). Science policy council peer review handbook 3rd edition. (EPA/100/B-06/002). U.S. Environmental Protection Agency, Science Policy Council. http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=157664

U.S. EPA (U.S. Environmental Protection Agency). (2010a). Activity-based sampling summary report, operable unit 4, Libby, Montana, Superfund site. Denver, CO. http://www.epa.gov/region8/superfund/libby/OU4_ABS_ResultsSummaryReportJune2010.pdf

U.S. EPA (U.S. Environmental Protection Agency). (2010b). Particle size distribution data for Libby Amphiboles structures observed in air at the Libby Asbestos Superfund Site [EPA Report]. Denver, CO.

U.S. EPA (U.S. Environmental Protection Agency). (2011). Vocabulary catalog list detail - Integrated Risk Information System (IRIS) glossary. Available online at http://ofmpub.epa.gov/sor_internet/registry/termreg/searchandretrieve/glossariesandkeywordlists/search.do?details=&glossaryName=IRIS%20Glossary

U.S. EPA (U.S. Environmental Protection Agency). (2012). Benchmark dose technical guidance. (EPA/100/R-12/001). Washington, DC: Risk Assessment Forum. http://www.epa.gov/raf/publications/pdfs/benchmark_dose_guidance.pdf

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

U.S. EPA (U.S. Environmental Protection Agency). (2013a). Integrated science assessment for lead [EPA Report]. (EPA/600/R-10/075F). Research Triangle Park, NC. http://ofmpub.epa.gov/eims/eimscomm.getfile?p_download_id=514513

U.S. EPA (U.S. Environmental Protection Agency). (2013b). Integrated science assessment for ozone and related photochemical oxidants. (EPA/600/R-10/076F). Research Triangle Park, NC: U.S. Environmental Protection Agency, National Center for Environmental Assessment. http://cfpub.epa.gov/ncea/isa/recordisplay.cfm?deid=247492

U.S. GAO (U.S. Government Accountability Office). (2007). Hazardous materials: EPA may need to reassess sites receiving asbestos-contaminated ore from Libby, Montana, and should improve it's public notification process. (GAO-08-71). Washington, DC. http://www.gao.gov/products/GAO-08-71

Ugolini, D; Neri, M; Ceppi, M; Cesario, A; Dianzani, I; Filiberti, R; Gemignani, F; Landi, S; Magnani, C; Mutti, L; Puntoni, R; Bonassi, S. (2008). Genetic susceptibility to malignant mesothelioma and exposure to asbestos: the influence of the familial factor. Mutat Res 658: 162-171. http://dx.doi.org/10.1016/j.mrrev.2007.08.001

Vaslet, CA; Messier, NJ; Kane, AB. (2002). Accelerated progression of asbestos-induced mesotheliomas in heterozygous p53+/- mice. Toxicol Sci 68: 331-338. http://dx.doi.org/10.1093/toxsci/68.2.331

Versar (Versar Inc.). (2003). EPAs pilot study to estimate asbestos exposure from vermiculite attic insulation. Washington, DC: U.S. Environmental Protection Agency. http://www.epa.gov/asbestos/pubs/insulationreport.pdf

Vincent, JH. (2005). Health-related aerosol measurement: a review of existing sampling criteria and proposals for new ones. J Environ Monit 7: 1037-1053. http://dx.doi.org/10.1039/b509617k

Vinikoor, LC; Larson, TC; Bateson, TF; Birnbaum, L. (2010). Exposure to asbestos-containing vermiculite ore and respiratory symptoms among individuals who were children while the mine was active in Libby, Montana. Environ Health Perspect 118: 1033-1038. http://dx.doi.org/10.1289/ehp.0901680

Voisin, C; Marin, I; Brochard, P; Pairon, J. (1994). Environmental airborne tremolite asbestos pollution and pleural plaques in Afghanistan. Chest 106: 974-976. http://dx.doi.org/10.1378/chest.106.3.974

Wagner, J; Chamberlain, M; Brown, R; Berry, G; Pooley, F; Davies, R; Griffiths, D. (1982). Biological effects of tremolite. Br J Cancer 45: 352-360.

Wagner, JC; Berry, G; Skidmore, JW; Timbrell, V. (1974). The effects of the inhalation of asbestos in rats. Br J Cancer 29: 252-269.

Walker, C; Everitt, J; Barrett, JC. (1992). Possible cellular and molecular mechanisms for asbestos carcinogenicity. Am J Ind Med 21: 253-273. http://dx.doi.org/10.1002/ajim.4700210214

Wanner, A; Salathé, M; O'Riordan, TG. (1996). Mucociliary clearance in the airways. Am J Respir Crit Care Med 154: 1868-1902.

Warheit, DB; Hartsky, MA. (1990). Species comparisons of proximal alveolar deposition patterns of inhaled particulates. Exp Lung Res 16: 83-99.

Weill, D; Dhillon, G; Freyder, L; Lefante, J; Glindmeyer, H. (2011). Lung function, radiologic changes and exposure: analysis of ATSDR data from Libby, Montana. Eur Respir J 38: 376-383. http://dx.doi.org/10.1183/09031936.00050210

Weis, C. (2001). Amphibole mineral fibers in source materials in residential and commercial areas of Libby pose an imminent and substantial endangerment to public health. Memo to Paul Peronard, On-scene Coordinator, Libby Asbestos Site. Available online at http://www2.epa.gov/sites/production/files/documents/CWeisMemo20Dec2001.pdf

Weiss, ST. (2010). Lung function and airway diseases. Nat Genet 42: 14-16. http://dx.doi.org/10.1038/ng0110-14

Welch, LS; Haile, E; Dement, J; Michaels, D. (2007). Change in prevalence of asbestos-related disease among sheet metal workers 1986 to 2004. Chest 131: 863-869. http://dx.doi.org/10.1378/chest.06-1155

Wheeler, MW. (2005). Benchmark dose estimation using SAS. In Proceedings of the Thirtieth Annual SAS Users Group International Conference (pp. 201-230). Cary, NC: SAS Institute. http://www2.sas.com/proceedings/sugi30/201-30.pdf

Whitehouse, A. (2004). Asbestos-related pleural disease due to tremolite associated with progressive loss of lung function: Serial observations in 123 miners, family members, and residents of Libby, Montana. Am J Ind Med 46: 219-225. http://dx.doi.org/10.1002/ajim.20053

Whitehouse, A; Black, C; Heppe, M; Ruckdeschel, J; Levin, S. (2008). Environmental exposure to Libby Asbestos and mesotheliomas. Am J Ind Med 51: 877-880. http://dx.doi.org/10.1002/ajim.20620

WHO (World Health Organization). (1938). Manual of the international statistical classification of diseases, injuries, and causes of death. Geneva, Switzerland.

WHO (World Health Organization). (1948). Manual of the international statistical classification of diseases, injuries, and causes of death. Geneva, Switzerland.

WHO (World Health Organization). (1957). Manual of the international statistical classification of diseases, injuries, and causes of death. Geneva, Switzerland.

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

WHO (World Health Organization). (1967). Manual of the international statistical classification of diseases, injuries, and causes of death. Geneva, Switzerland.

WHO (World Health Organization). (1977). Manual of the international statistical classification of diseases, injuries, and causes of death. Geneva, Switzerland.

WHO (World Health Organization). (1992). Manual of the international statistical classification of diseases, injuries, and causes of death. Geneva, Switzerland.

Winters, CA; Hill, WG; Rowse, K; Black, B; Kuntz, SW; Weinert, C. (2012). Descriptive analysis of the respiratory health status of persons exposed to Libby amphibole asbestos. BMJ 2. http://dx.doi.org/10.1136/bmjopen-2012-001552

Witschi, HR; Last, JA. (1996). Toxic responses of the respiratory system. In CD Klaassen (Ed.), Casarett and Doulls toxicology (5th ed., pp. 443-462). New York, NY: McGraw Hill.

Witschi, HR; Last, JA. (2001). Toxic responses of the respiratory system. In LJ Casarett; CD Klaassen; J Doull (Eds.), Casarett and Doull's toxicology: The basic science of poisons (6 ed., pp. 515-534). Columbus, OH: McGraw-Hill Professional.

Wraith, D; Mengersen, K. (2007). Assessing the combined effect of asbestos exposure and smoking on lung cancer: a Bayesian approach. Stat Med 26: 1150-1169. http://dx.doi.org/10.1002/sim.2602

Wright, RS; Abraham, JL; Harber, P; Burnett, BR; Morris, P; West, P. (2002). Fatal asbestosis 50 years after brief high intensity exposure in a vermiculite expansion plant. Am J Respir Crit Care Med 165: 1145-1149. http://dx.doi.org/10.1164/rccm.2110034

Wylie, AG; Skinner, HCW; Marsh, J; Snyder, H; Garzione, C; Hodkinson, D; Winters, R; Mossman, BT. (1997). Mineralogical features associated with cytotoxic and proliferative effects of fibrous talc and asbestos on rodent tracheal epithelial and pleural mesothelial cells. Toxicol Appl Pharmacol 147: 143-150. http://dx.doi.org/10.1006/taap.1997.8276

Wylie, AG; Verkouteren, JR. (2000). Amphibole asbestos from Libby, Montana: Aspects of nomenclature. Am Mineral 85: 1540-1542.

Yano, E; Tanaka, K; Funaki, M; Maeda, K; Matsunaga, C; Yamaoka, K. (1993). Effect of smoking on pleural thickening in asbestos workers. Br J Ind Med 50: 898-901. http://dx.doi.org/10.1136/oem.50.10.898

Yazicioglu, S, . (1976). Pleural calcification associated with exposure to chrysotile asbestos in southeast Turkey. Chest 70: 43-47. http://dx.doi.org/10.1378/chest.70.1.43

Yazicioglu, S; Ilçayto, R; Balci, K; Sayli, BS; Yorulmaz, B. (1980). Pleural calcification, pleural mesotheliomas, and bronchial cancers caused by tremolite dust. Thorax 35: 564-569. http://dx.doi.org/10.1136/thx.35.8.564

Yu, CP; Asgharian, B; Yen, BM. (1986). Impaction and sedimentation deposition of fibers in airways. Am Ind Hyg Assoc J 47: 72-77. http://dx.doi.org/10.1080/15298668691389388

Yu, CP; Ding, YJ; Zhang, L; Oberdörster, G; Mast, RW; Maxim, LD; Utell, MJ. (1997). Retention modeling of refractory ceramic fibers (RCF) in humans. Regul Toxicol Pharmacol 25: 18-25. http://dx.doi.org/10.1006/rtph.1996.1064

Zanella, C; Posada, J; Tritton, T; Mossman, B. (1996). Asbestos causes stimulation of the extracellular signal-regulated kinase 1 mitogen-activated protein kinase cascade after phosphorylation of the epidermal growth factor receptor. Cancer Res 56: 5334-5338.

Zeger, SL; Thomas, D; Dominici, F; Samet, JM; Schwartz, J; Dockery, D; Cohen, A. (2000). Exposure measurement error in time-series studies of air pollution: Concepts and consequences. Environ Health Perspect 108: 419-426. http://dx.doi.org/10.1289/ehp.00108419

Zeka, A; Gore, R; Kriebel, D. (2011). The two-stage clonal expansion model in occupational cancer epidemiology: results from three cohort studies. Occup Environ Med 68: 618-624. http://dx.doi.org/10.1136/oem.2009.053983

Zerva, LV; Constantopoulos, SH; Moutsopoulos, HM. (1989). Humoral immunity alterations after environmental asbestos exposure. Respiration 55: 237-241. http://dx.doi.org/10.1159/000195740

Zhao, XH; Jia, G; Liu, YQ; Liu, SW; Yan, L; Jin, Y; Liu, N. (2006). Association between polymorphisms of DNA repair gene XRCC1 and DNA damage in asbestos-exposed workers. Biomed Environ Sci 19: 232-238.

Zhou, Y; Su, WC; Cheng, YS. (2007). Fiber deposition in the tracheobronchial region: Experimental measurements. Inhal Toxicol 19: 1071-1078. http://dx.doi.org/10.1080/08958370701626634

Zitting, AJ. (1995). Prevalence of radiographic small lung opacities and pleural abnormalities in representative adult population sample. Chest 107: 126-131.

Zitting, AJ; Karjalainen, A; Impivaara, O; Kuusela, T; Mäki, J; Tossavainen, A; Järvisalo, J. (1996). Radiographic small lung opacities and pleural abnormalities in relation to smoking, urbanization status, and occupational asbestos exposure in Finland. J Occup Environ Med 38: 602-609.

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