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TOXICOLOGICAL REVIEW

OF

LIBBY AMPHIBOLE ASBESTOS

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

May 2011

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

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U.S. Environmental Protection Agency
Washington, DC

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LIST OF ABBREVIATIONS AND ACRONYMS

AAHAU	Airborne Asbestos Health Assessment Update
AIC	Akaike information criterion
APC	antigen-presenting cells
ATSDR	Agency for Toxic Substances and Disease Registry
BGL	β-glucuronidase
BMI	body mass index
cc	cubic centimeter
CDF	cumulative distribution frequency
CE	cumulative exposure
CI	confidence interval
COPD	chronic obstructive pulmonary disease
CYP	cytochrome P450
DHE	dehydroergosterol
DIC	deviance information criterion
DLCO	single breath carbon monoxide diffusing capacity
DNA	deoxyribonucleic acid
EC_x	effective concentration
ECSOD	extracellular superoxide dismutase
EDS	energy dispersive x-ray analysis
EPA	U.S. Environmental Protection Agency
EPMA	electron probe microanalysis
FVC	force vital capacity
GSH	glutathione
GST	glutathione S-transferase
HKNM	human pleural mesothelial cells
HO	heme oxygenase
HPRT	hypoxanthine-guanine phosphoribosyltransferase
HTE	hamster tracheal epithelial
IARC	International Agency for the Research of Cancer
ICD	International Classification of Diseases
IFN	interferon
IL	interleukin
IRIS	Integrated Risk Information System

LIST OF ABBREVIATIONS AND ACRONYMS (continued)

IUR	inhalation unit risk
JEM	job exposure matrix
LEC_x	lowest effective concentration
LDH	lactate dehydrogenase
MCMC	Markov chain Monte Carlo
MESA	Mining Enforcement and Safety Administration
MIP-2	macrophage inflammatory protein-2
MnSOD	manganese superoxide dismutase
MOA	mode of action
mppcf	million particles per cubic foot
MPPD	multipath particle dosimetry
MSHA	Mine Safety and Health Administration
NAT2	N-acetyl-transferase 2
NCHS	National Center for Health Statistics
NDI	National Death Index
Nf2	neurofibromatous 2
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute of Occupational Safety and Health
NMRD	non-malignant respiratory disease
NTP	National Toxicology Program
Ogg1	8-oxoguanine-DNA-glycosylase 1
OSHA	Occupational Safety and Health Administration
PARP	poly(ADP-ribose)polymerase
PBS	phosphate buffered saline
PCM	phase contrast microscopy
PCMe	phase contrast microscopy equivalent
$PM_{2.5}$	particulate matter 2.5 μ diameter or less
POD	point of departure
RfC	reference concentration
RfD	reference dose
RNA	ribonucleic acid
RONS	reactive oxygen and nitrogen species
ROS	reactive oxygen species

LIST OF ABBREVIATIONS AND ACRONYMS (continued)

RPM	rat pleural mesothelial
RR	relative risk
RT-PCR	reverse transcription polymerase chain reaction
RTW	residence time-weighted
SAS	Statistical Analysis Software
SEER	Surveillance, Epidemiology and End Results
SEM	scanning electron microscopy
SH	spontaneously hypertensive
SHE	Syrian hamster embryo
SHHF	spontaneously hypertensive-heart failure
SIR	standard incidence ratio
SMR	standardized mortality ratio
SOD	superoxide dismutase
SPF	specific pathogen free
SRR	standardized rate ratio
SSA/Ro52	autoantibody marker for apoptosis
STEM	scanning transmission electron microscopy
SV40	simian virus 40
TEM	transmission electron microscopy
TLC	total lung capacity
TWA	time-weighted average
VAI	vermiculite attic insulation
WHO	World Health Organization
WKY	Wistar Kyoto rat
XRCC	X-ray repair cross complementing
XRD	X-ray diffraction

FOREWORD

The purpose of this Toxicological Review is to provide scientific support and rationale for the hazard and dose-response assessment in IRIS pertaining to chronic inhalation exposure to Libby Amphibole asbestos, a unique mixture of asbestos fibers originating from the vermiculite mine in Libby, Montana. It is not intended to be a comprehensive treatise on the agent or toxicological nature of Libby Amphibole asbestos. The purpose of this document is to establish a Libby Amphibole asbestos-specific reference concentration to address noncancer health effects and to characterize the carcinogenic potential and establish an inhalation unit risk for Libby Amphibole asbestos-related lung cancer and mesothelioma mortality.

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

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

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

Danielle DeVoney, PhD, DABT, PE
Captain in the U.S. Public Health ServiceNational Center for Environmental Assessment
U.S. Environmental Protection Agency
Washington, DC

AUTHORS

Krista Yorita Christensen, Ph.D.
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

Rebecca Dzubow, MPH, MEM
National Center for Environmental Assessment
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, Ph.D.
National Center for Environmental Assessment
U.S. Environmental Protection Agency
Washington, DC

AUTHORS, CONTRIBUTORS, AND REVIEWERS (continued)

CONTRIBUTING AUTHORS

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

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

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

REVIEWERS

This document has been provided for review to EPA scientists.

1. INTRODUCTION

This document presents background information and justification for the Integrated Risk Information System (IRIS) Summary of the hazard and dose-response assessment of Libby Amphibole asbestos, a unique mixture of amphibole fibers found in the vermiculite mine in Libby, MT. IRIS Summaries may include oral reference dose (RfD) and inhalation reference concentration (RfC) values for chronic and other exposure durations, and a carcinogenicity assessment.

The RfD and RfC, if derived, provide quantitative information for use in risk assessments for health effects known or assumed to be produced through a nonlinear (presumed threshold) mode of action. The RfD (expressed in units of mg/kg-day) is defined as an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. The inhalation RfC (expressed in units of mg/m^3) is analogous to the oral RfD, but provides a continuous inhalation exposure estimate. The inhalation RfC considers toxic effects for both the respiratory system (portal-of-entry) and for effects peripheral to the respiratory system (extrarespiratory or systemic effects). Reference values are generally derived for chronic exposures (up to a lifetime), but may also be derived for acute ($\leq$24 hours), short-term (>24 hours up to 30 days), and subchronic (>30 days up to 10% of lifetime) exposure durations, all of which are derived based on an assumption of continuous exposure throughout the duration specified. Unless specified otherwise, the RfD and RfC are derived for chronic exposure duration.

The carcinogenicity assessment provides information on the carcinogenic hazard potential of the substance in question, and quantitative estimates of risk from oral and inhalation exposures may be 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 may be derived from the application of a low-dose extrapolation procedure. If derived, the oral slope factor is a plausible upper bound on the estimate of risk per mg/kg-day of oral exposure. Similarly, an inhalation unit risk is a plausible upper bound on the estimate of cancer risk per $\mu g/m^3$ air breathed. For Libby Amphibole asbestos the RfC and IUR are expressed as fibers/cc and cumulative exposure is expressed as fibers-yr/cc.

The assessment of cancer health effects from exposure to Libby Amphibole asbestos does not estimate risks for non-cancer mortality from inhalation of Libby Amphibole asbestos. There are potential risks of mortality from noncancer disease (e.g. NMRD, potentially cardiovascular

disease). An inhalation RfC addresses noncancer health effects of inhalation exposure to Libby Amphibole asbestos. Libby Amphibole asbestos-specific data are not available to support RfD or cancer slope factor derivations for oral exposures.

Development of these hazard identification and dose-response assessments for Libby Amphibole asbestos has followed the general guidelines for risk assessment as set forth by the National Research Council (1983). 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 Mixtures* (U.S. EPA, 1986a), *Guidelines for Mutagenicity Risk Assessment* (U.S. EPA, 1986b), *Recommendations for and Documentation of Biological Values for Use in Risk Assessment* (U.S. EPA, 1988), *Guidelines for Developmental Toxicity Risk Assessment* (U.S. EPA, 1991), *Interim Policy for Particle Size and Limit Concentration Issues in Inhalation Toxicity* (U.S. EPA, 1994a), *Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry* (U.S. EPA, 1994b), *Use of the Benchmark Dose Approach in Health Risk Assessment* (U.S. EPA, 1995), *Guidelines for Reproductive Toxicity Risk Assessment* (U.S. EPA, 1996), *Guidelines for Neurotoxicity Risk Assessment* (U.S. EPA, 1998), *Science Policy Council Handbook*: *Risk Characterization* (U.S. EPA, 2000a), *Benchmark Dose Technical Guidance Document* (U.S. EPA, 2000b), *Supplementary Guidance for Conducting Health Risk Assessment of Chemical Mixtures* (U.S. EPA, 2000c), *A Review of the Reference Dose and Reference Concentration Processes* (U.S. EPA, 2002), *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a), *Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens* (U.S. EPA, 2005b), *Science Policy Council Handbook: Peer Review* (U.S. EPA, 2006a), and *A Framework for Assessing Health Risks of Environmental Exposures to Children* (U.S. EPA, 2006b).

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

1.1. RELATED ASSESSMENTS

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

The IRIS assessment for asbestos was posted online in IRIS in 1988 and includes an IUR of 0.23 excess cancers per 1 fiber/cc (U.S. EPA, 1988). (This unit risk is given in units of the fibers as measured by phased contrast microscopy [PCM].) The IRIS IUR for asbestos is derived by estimation of excess cancers for a continuous lifetime exposure and is based on the central tendency, not the upper bound, of the risk estimates (U.S. EPA, 1988) and is applicable to exposures across a range of exposure environments and types of asbestos (CAS Number 1332-21-4). Although other cancers have been associated with asbestos (e.g., laryngeal, stomach, ovarian) (Straif et al., 2009), the IRIS IUR for asbestos accounts for only lung cancer and mesothelioma. Additionally, pleural and pulmonary effects from asbestos exposure (e.g., asbestosis, pleural plaques, reduced lung function) are well documented, though, currently, there is no RfC for these noncancer health effects.

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

Table 1-1. Derivation of the current IRIS inhalation unit risk for asbestos from the lifetime risk tables in the AAHAU

Gender	Deaths per 100,000[a]			Risk	Unit risk
	Mesothelioma	Lung cancer	Total		
Female	183	35	218.5	2.18 E-03	
Male	129	114	242.2	2.42 E-03	
All	156	74	230.3	2.30 E-03	0.23

[a]Data are for exposure at 0.01 f/cc for a lifetime.
AAHAU = Airborne Asbestos Health Assessment Update.
Source: U.S. EPA (1988).

1.1.2. EPA Health Assessment for Vermiculite (1991)

An EPA health assessment for vermiculite reviewed available health data, including studies on workers in mines without significant amphibole fiber contamination. The cancer and noncancer health effects observed in the Libby, MT miner cohort were not seen in studies of workers exposed to vermiculite from mines with similar exposure to vermiculite, but much lower exposures to asbestos. Therefore, it was concluded that the health effects observed from the materials mined from Zonolite Mountain near Libby, MT, were most likely due to amphibole fibers, not the vermiculite itself (U.S. EPA, 1991). At the time, EPA recommended the application of the IRIS IUR for asbestos fibers (0.23 per fiber/cc) in addressing potential risk of the amphibole fibers entrained in vermiculite mined in Libby, MT.

1.2. LIBBY AMPHIBOLE ASBESTOS-SPECIFIC HUMAN HEALTH ASSESSMENT

Libby Amphibole asbestos is a complex mixture of amphibole fibers, both mineralogically and morphologically (see Section 2.2). The mixture primarily includes tremolite, winchite, and richterite fibers with trace amounts of magnesioriebeckite, edenite, and magnesio-arfvedsonite. These fibers exhibit a complete range of morphologies from prismatic crystals to asbestiform fibers (Meeker et al., 2003). Exposure to Libby Amphibole asbestos results in the same types of adverse health effects as are seen with exposure to other amphibole mineral fibers. Epidemiologic studies of workers exposed to Libby Amphibole asbestos fibers indicate increased lung cancer and mesothelioma, as well as asbestosis, and other nonmalignant respiratory diseases (Lockey et al., 1984; McDonald et al., 1986a,b, 2004; Amandus and Wheeler, 1987; Amandus et al., 1987a,b; Peipins et al., 2003; Sullivan, 2007; Rohs et al., 2008; Larson et al., 2010a,b, Moolgavkar et al., 2010).

The IRIS IUR for asbestos is based on a synthesis of 14 epidemiologic studies that included occupational exposure to chrysotile, amosite, or mixed mineral exposures (chrysotile, amosite, crocidolite) (U.S. EPA, 1988, 1986a). There is some uncertainty in applying the resulting IUR to exposure environments and minerals different from those analyzed in the AAHAU (U.S. EPA, 1986a). There is currently no RfC derived for asbestos.

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

2.1. HISTORICAL BACKGROUND

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

The primary commercial product from the Zonolite mining operation was vermiculite ore. When heated to approximately 150°C, the vermiculite mineral expands like popcorn into a light porous material. The unexpanded mineral exhibits a sheetlike structure that is seen in related minerals (e.g., mica) (Figure 2-2). This process of expanding the mineral ore is termed "exfoliation" or "popping" and occurs when the silicate sheets within the ore are rapidly dehydrolyzed by applying high heat. Since the vermiculite product was contaminated with fibers of Libby Amphibole asbestos, fibers were released during this energetic process potentially exposing workers and resulting in asbestos contamination of the finished product sold to consumers. The Libby mine produced approximately 80% of the world's supply of vermiculite ore during its operation from 1923 to 1990. Expanded vermiculite from the Libby, MT site was used as attic insulation, packing material, and a soil conditioner, and in the production of gypsum wall board.

The refined vermiculite ore concentrate (after milling and size selection) was then loaded onto railcars and transported across the country to expansion plants where it was exfoliated and distributed locally (see Figure 2-3). ATSDR (2008) has surveyed 28 of these facilities, identifying potential community exposures both to amphibole asbestos fibers from the

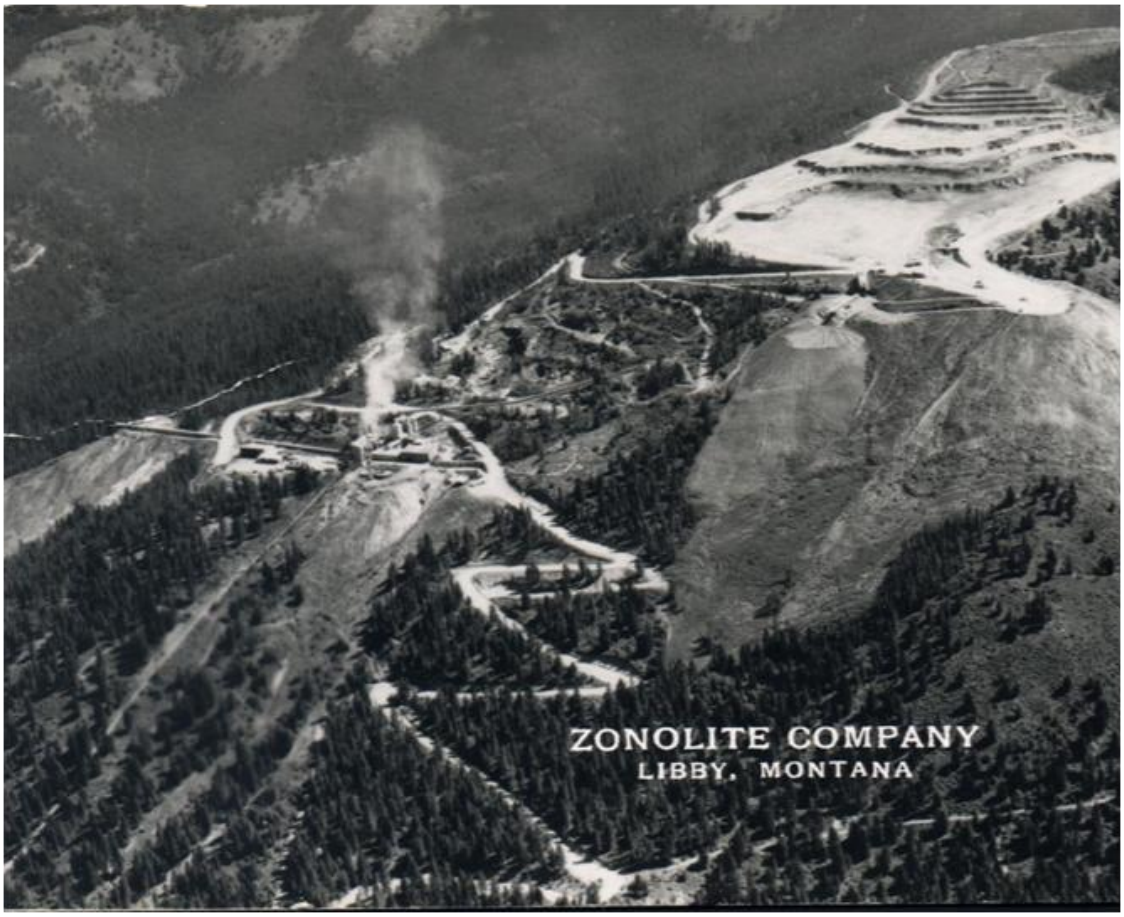


Figure 2-1. Vermiculite mining operation on Zonolite Mountain, Libby, Montana.

(a) (b)

Figure 2-2. Expanded vermiculite used as a soil conditioner (a) or attic insulation (b).

Source: U.S. EPA (2010).

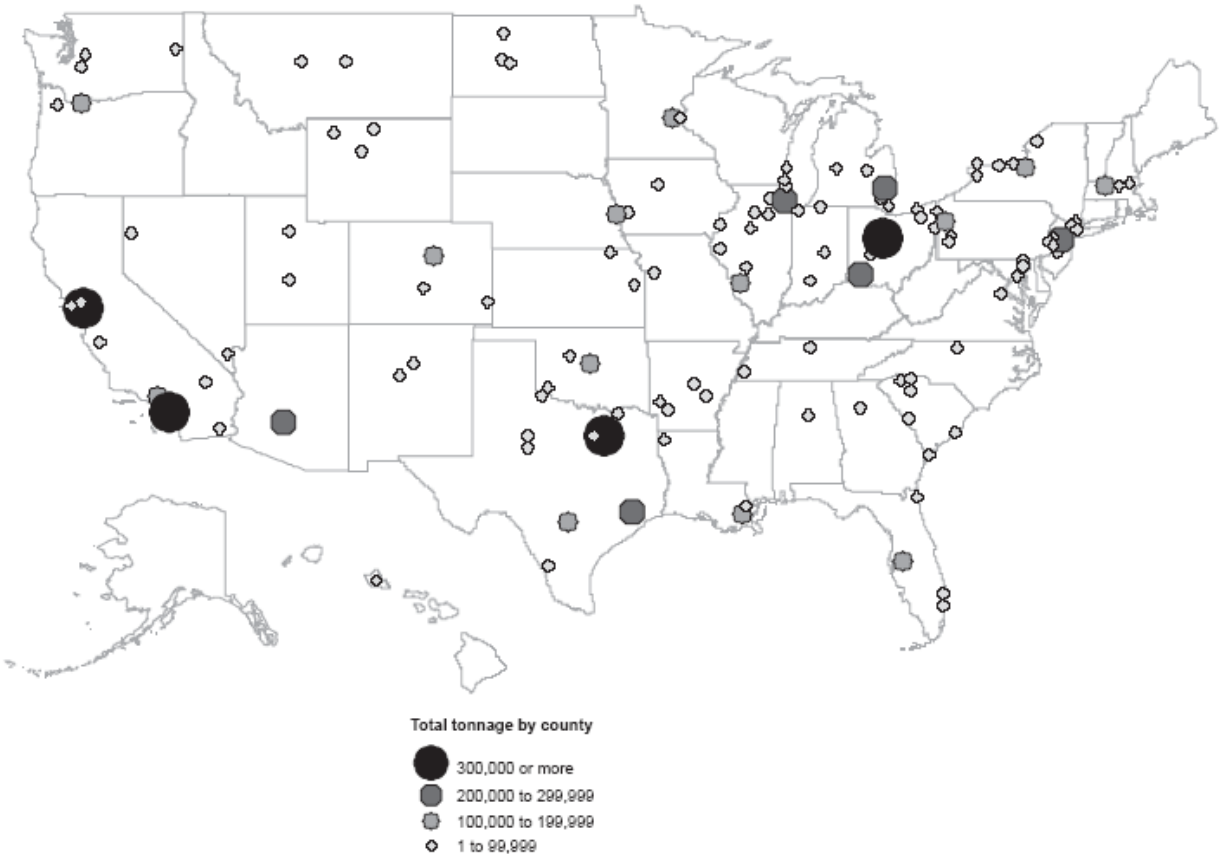


Figure 2-3. Nationwide Distribution of Libby Ore by County (in tons). Data on the distribution of ore are based on approximately 80,000 invoices that EPA obtained from W.R. Grace, which document shipments of vermiculite ore made from the Libby mine between 1964 to 1990. EPA tabulated this shipping information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

Source: GAO (2007).

vermiculite concentrate before exfoliation, during exfoliation and processing and waste rock from the processing plants (see Section 4.1.4 and Figure 4-1).

2.2. GEOLOGY, MINERALOGY, AND FIBER MORPHOLOGY OF LIBBY AMPHIBOLE ASBESTOS

A large vermiculite deposit is located on Zonolite Mountain, northeast of Libby, MT, within a geologic unit known as the Rainy Creek complex. Geologic processes within the Rainy Creek complex have resulted in the formation of fibrous amphiboles adjacent to igneous intrusions into the complex (veins and dikes of alkaline granite, pegmatite, and quartz) (Boettcher, 1996). The amphibole fibers identified fall within the tremolite-richterite-

magnesioriebecktite field (e.g. winchite, richterite and tremolite) (Meeker et al., 2003). An appropriate understanding of the mineralogy and geology of these materials is helpful in defining the mineral fibers specific to Libby Amphibole asbestos.

Geological terms provide fiber and mineral definitions based on habit of formation and fiber morphology. Conversely, the analytical methods that have been used to count fibers in air samples, in both historical and current exposure environments, define microscopic fibers based on dimensional characteristics and mineralogy (depending on the analytical method). Current analytical methods do not have specific procedures for determining fiber morphology at the microscopic level. Because the human and experimental animal data on adverse health effects of asbestos rely on available analytical methods to document exposure, these definitions are relevant to determining what constitutes a fiber for this health assessment. Therefore, available data on the fiber morphology and fiber-size distribution of Libby Amphibole asbestos are presented in the following sections.

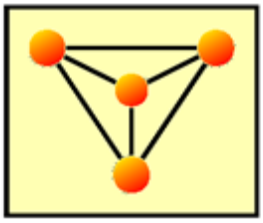
2.2.1. Silicate Minerals

Silicate minerals are basically made up of oxygen and silicon, two of the most abundant elements in the Earth's crust. Approximately 25% of known minerals and 40% of the common minerals are silicates. With a few minor exceptions, all igneous rock-forming minerals are silicates, which mean that silicates comprise more than 90% of the Earth's crust (Klein and Hurlbut, 1977).

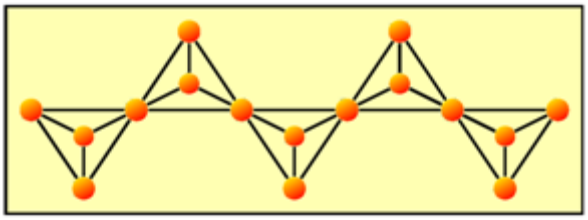
Some silicates are very hard, infusible, and insoluble. Even in acid, they are not easily soluble. Specific gravity ranges from fairly light to intermediate, luster is commonly glassy, and most crush to a light powder even when the bulk specimen is black prior to crushing. Silicates chiefly occur as components of rocks, segregations in rocks, or crystals lining cavities in rocks. Most hard silicates are primary minerals, not products of weathering. Secondary silicates typically contain water (Klein and Hurlbut, 1977).

The basic chemical unit of silicates is the $[SiO_4]^{4-}$ tetrahedron-shaped anionic group. The basic unit consists of four oxygen molecules at the apices of a regular tetrahedron surrounding and coordinated with one silicon ion (Si^{4+}) at the center. The chemistry is such that the oxygen molecules can bond to another silicon ion and, therefore, link one $[SiO_4]^{4-}$ tetrahedron to another, and then another, and so forth by the process of polymerization. The silicates can form as single units, double units, chains, sheets, rings, and framework structures (see Figure 2-4). Silicate minerals can be defined by chemical structure, crystal structure, trace minerals, and habit of formation.

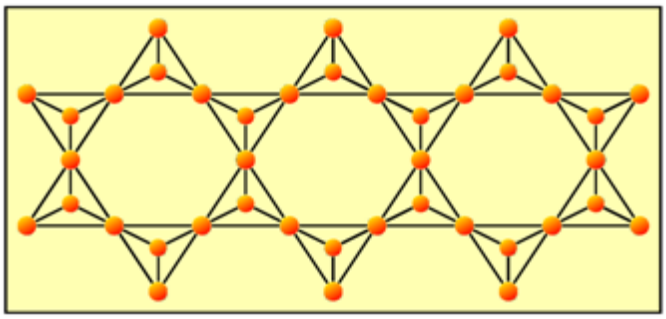
(a) Nesosilicates or single tetrahedron. The single tetrahedron comprises four oxygen molecules covalently bound to the silicon, at the center of the $[SiO_4]^{4-}$-tetrahedron.



(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 $Ca_2(Mg,Fe)_5Si_8O_{22}(OH)_2$. 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 a sheet silicates include chrysotile $Mg_3Si_2O_5(OH)$And vermiculite $[(Mg, Fe,A)_3(Al,Si)_2O_{10}(OH)_2 \bullet 4H_2O]$.

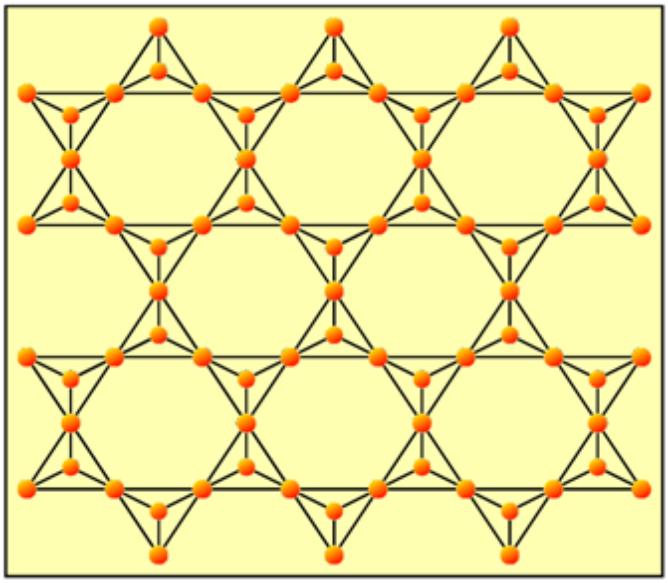


Figure 2-4. Structure of the silicate minerals, illustrating silicate subclasses by the linking of the basic silicon tetrahedron (a) into more complex structures (b, c, or d).

Silicates are divided by structure into the following subclasses:

- Nesosilicates (single tetrahedrons)
- Sorosilicates (double tetrahedrons)
- Inosilicates (single and double chains)
- Cyclosilicates (rings)
- Phyllosilicates (sheets)
- Tectosilicates (frameworks)

Each subclass of silicates has many mineral members. Specific minerals are defined by the structure, chemistry, and morphology of the mineral. The minerals of interest in this assessment are vermiculite (a sheet silicate) and various forms of amphibole asbestos (which are within the class of inosilicates) (see Figure 2-5). The flat, layered sheets give vermiculite its perfect cleavage and its unique ability to expand when heated. Chrysotile is also a sheet silicate, but can present with an asbestiform morphology where the sheets role into fibrils, forming asbestiform fibers. The habit of formation depends on conditions (e.g., pressure, temperature, and cooling rate) that favor a particular form, such as fibrous versus crystalline (see Section 2.2.2 on fiber morphology).

2.2.1.1. *Mineralogy and Structure of Amphiboles*

Amphibole minerals are double-chain inosilicates, meaning the chemical building block for amphiboles is connected chains of the silicon tetrahedron (see Figure 2-4c). Amphiboles form when edge-shared octahedra link two of the double-chain $[SiO_4]^{4-}$ plates (see Figure 2-4d). The specific cations between the two double-chain plates define the chemistry of the mineral, while the ratio of these cations in each location is used to classify amphiboles within a solution series. The cation sites are designated as A, B, and C in the equation below, which shows the general chemical formula for double-chain inosilicate amphiboles:

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

where:

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

The mineral subgroup within amphiboles is determined by cationic chemistry (shown above).

- Tremolite subgroup (Ca amphiboles)
- Anthophyllite subgroup (Fe-Mg-Li orthoamphiboles)
- Richterite subgroup (Ca-Na amphiboles)
- Cummingtonite (Fe-Mg-Li clinoamphiboles)

Cation sites between the double-chain silicate plates could host one or more cations as noted in the above formula. Sites A, B, and C in the crystal structure refer to cations that covalently link the amphibole plates at different locations in the crystalline structure (see Figure 2-5). Based on the above formula, Site A could contain Na or K or both in varied proportions; Site B could contain any of the cations listed (Na, Li, Ca, Mn, Fe^{2+}, Mg); and Site C could contain Mg, Fe^{2+}, Mn, Al, Fe^{3+}, or Ti. Minerals often have a mixture of ions between the plates at each location (site A, B or C) and these cations will be in varied proportions depending on the specific geologic deposit.

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

Cation changes observed in Libby Amphibole asbestos demonstrate how mineral content can change in a solution series (Figure 2-7) where the trace minerals at each site (A, B, or C) are used to define the mineral subgroup and solution series.

It is the complexity of the amphiboles that historically has given rise to a proliferation of mineral names with no systematic basis (Hawthorne, 1981). Currently, amphiboles are identified by a clear classification scheme based on crystal chemistry that uses well-established names based on the basic mineralogy, with prefixes and adjective modifiers indicating the presence of substantial substitutions that are not essential constituents of the end members (Leake et al., 1997).

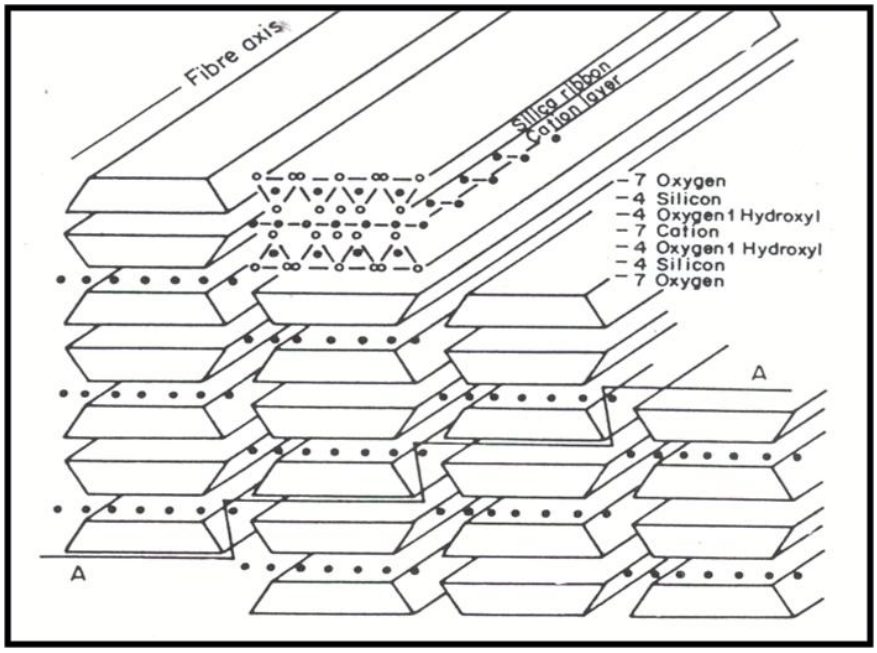


Figure 2-5. Cross-section of amphibole fibers showing the silicon tetrahedrons (Δ) that make up each double-chain plate (shown along the fiber axis). Cations (shown as the darkened dots) occur between the plates forming the basic fiber.

Source: Kirk-Othmer Encyclopedia of Chemical Technology (2010).

Figure 2-6. Vermiculite sample. Brinton's Quarry, near West Chester, Chester County, Pennsylvania, USA.

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

2.2.1.2. *Fiber Morphology*

Fiber morphology is a function of the structural form of the silicate and the geologic habit of formation. Silicates can occur in crystalline or massive form without the presence of distinct fibers. Some silicates can form asbestiform fibers in specific growth habits. The long, slender, hairlike fibers of commercial asbestiform minerals are visual to the naked eye; they have high tensile strength and in some cases, can be woven (e.g., chrysotile). The fibrils of asbestiform chrysotile are due in part to the structure and chemistry specific to chrysotile—*the mineralogy*, which allows the sheet silicate to roll, forming fibrils. These fibrils, however, are also a function of the temperature and pressure conditions during crystallization—*habit of formation*.

Amphibole fiber morphology is more complex than serpentine asbestos fibers. As with chrysotile, habit of formation determines whether the amphibole mineral forms a crystalline structure (massive) or is fibrous. The double-chain form of the amphibole fibers, however, can result in a range of fiber morphologies, including not only the asbestiform, but also, fibrous,

acicular, and prismatic. Additionally, crystalline amphibole can fracture, breaking along the cleavage plane of the crystal, forming shards or cleavage fragments.

The geologic terms for fiber morphology arise from classification of field samples based on the macroscopic appearance of the crystals and fibers (AGI, 1972):

Acicular: A crystal that is needlelike in form.

Fibrous: A mineral that is elongated with thin, needle-like grains or fibers (e.g., asbestos).

Asbestiform: A mineral that is fibrous–that is, like asbestos.

Fibers, crystals, and cleavage fragments can appear to be the same under transmission electron microscopes (TEM) (e.g., fibers with parallel sides) (see Figure 2-10). Therefore, the use of these definitions to describe individual fibers viewed by TEM can be problematic (Meeker et al., 2003). Important characteristics such as crystal structure and surface chemistry cannot be adequately categorized solely with visually determined definitions developed for classification of field samples.

2.2.2. Vermiculite

Vermiculite is the mineralogical name given to hydrated laminar magnesium-aluminum-ironsilicate, which resembles mica in appearance [Figure 2-6; $(Mg, Fe,A)_3(Al,Si)_2O_{10}(OH)_2 \bullet 4H_2O$] (AGI, 1972). Vermiculite is in the clay mineral group of the phyllosilicates, which also includes kaolinite and montmorillonite. Mica, talc, and serpentine (e.g., chrysotile asbestos) minerals are other well-known sheet silicates. These sheet-like structures are produced by rings of tetrahedrons that are linked to other rings by shared oxygen ions in a two-dimensional plane (see Figure 2-4d). The silicate sheet can extend broadly, and the layered appearance of the mineral reflects this sheet-like structure. The symmetry of these minerals is controlled primarily by the symmetry of the rings, which is usually altered to a lower symmetry by other ions and other layers. Typically, crystals of this subclass are flat, platy, and book-like, as in the mica group, and the sheets are then connected to each other by layers of cations. These cation layers are weakly bonded and often have water molecules and other neutral atoms or molecules trapped between the sheets. When subjected to heat, vermiculite has the unusual property of exfoliating or expanding into "worm-like" pieces. The term vermiculite is derived from the Latin *vermiculare*, which means to breed worms (The Vermiculite Association, http://www.vermiculite.org). Vermiculite exfoliation occurs at approximately 150°C, producing

a lightweight and highly absorbent material (AGI, 1972). Additional properties of vermiculite are listed in Table 2-1. Vermiculite ore is shown in Figure 2-6.

Table 2-1. Properties of vermiculite

Mineral class/subclass	Mineral silicates/phyllosilicate
Chemical formula	$(Mg, Fe,A)_3(Al,Si)_2O_{10}(OH)_2 \bullet 4H_2O$
Crystal habit of formation	Clay, scaly, aggregate
Hardness (Mohs scale)	203
Cleavage	Perfect
Specific gravity	2.4–2.7

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

2.2.3. The Mineralogy of Libby Amphibole Asbestos

2.2.3.1. *Mineralogy*

Various research groups have characterized the mineralogical composition and morphology of amphiboles from the Rainy Creek deposit near Libby, Montana (Gunter and Sanchez, 2009; Sanchez et al., 2008; Meeker et al., 2003; Wylie and Verkouteren, 2000; Ross, 1993; and Moatamed et al., 1986). For the purposes of this document, the material from this mine will be called Libby Amphibole. Libby Amphibole asbestos is in the tremolite subgroup and historically has been reported as a sodium-rich tremolite (Larsen, 1942; Boettcher, 1966; Leake, 1978). However, a more exact analysis of Libby Amphibole asbestos, characterizing the cation composition of individual fibers to better define the amphiboles present, indicates winchite and richterite are also components as well as traces of related minerals (Meeker et al., 2003). The minerals identified are classified by the number of cations present in specific sites within the amphibole crystalline structure (e.g. sites A, B C and T, see section 2.1.1.1) (Leake, 1978; Leake et al., 1997). Figure 2-7 shows the compositional variations between the predominate minerals found in the Libby amphibole asbestos (winchite, richterite and tremolite).

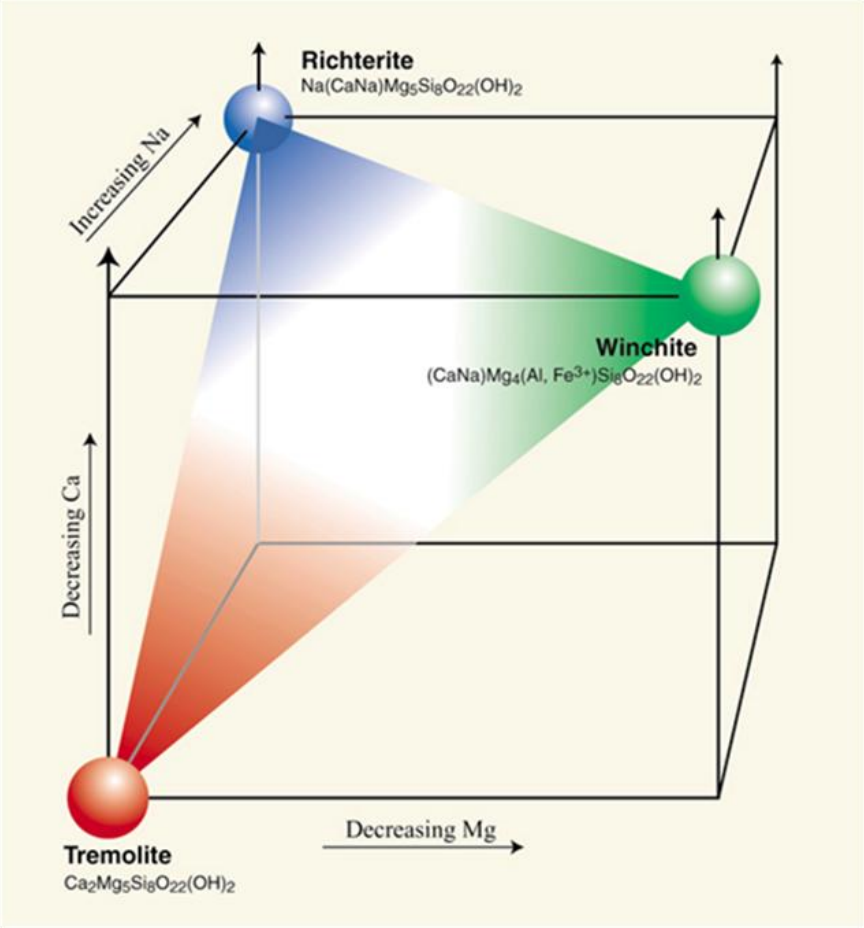


Figure 2-7. Solution series linking tremolite, winchite, and richterite amphibole fibers. (See Section 2.2.1.1 for the general form of the equations shown for each mineral species.)

Source: Meeker et al. (2003).

Although these are reported as discrete mineral compositions they are in fact graded across the solid solution series shown in the figure. For example, tremolite is one endmember of the solid solution series. As calcium decreases and sodium increases, the fibers transition to richterite. Similarly, as fibers have decreased magnesium and calcium with respect to tremolite, they are defined as winchite. The sodium content that distinguishes these amphiboles has been redefined over time in the International Mineral Association's mineral classification system, most recently in 1997 (Leake, 1978; Leake et al., 1997). As a result, some amphibole fibers previously defined as tremolite prior to the new classification system are currently considered

winchite based on chemical composition (Leake et al., 1997). The following discussion uses only the most recent classification system.

Libby Amphibole asbestos is not only made up of the end members of these groupings, but the spectrum of fibers in between each end of the solution series shown, as well as traces of other minerals. Additionally, samples collected from different areas of the mine and representing different habits of formation can have a higher or lower proportion of any of the various minerals (Meeker et al., 2003). Figure 2-8 shows data from 30 samples across the mine. The cation composition identified for each fiber analyzed at specific sites within the crystalline structure, determines its mineral identity (Leaky et al., 1997). Here the USGS used two different techniques to identify the cation content of each fiber [Energy dispersive x-ray analysis (EDS) and Electron Probe Microanalysis (EPMA)]. Regardless of analytical technique used, similar mineralogy was identified (Figure 2-8). Most Libby Amphibole fibers are classified as winchite (84%), with lesser amounts of richterite (11%) and tremolite (6%), based on the current mineralogical nomenclature (Meeker et al. (2003). There are also trace amounts of magnesioriebeckite, edenite, and magnesio-arfvedsonite present in Libby Amphibole asbestos (Meeher et al., 2003.). All of these would be within the tremolite-richterite-magnesioriebecktite series of mineral. All of the amphiboles found at the mine site, with the possible exception of magnesioriebeckite, can occur in fibrous habit. These amphibole materials, even when originally present as massive material, can produce abundant, extremely fine fibers by gentle abrasion or crushing.

2.2.3.2. *Morphology of the Libby Amphibole Asbestos*

Rock samples taken from the mine include veins of asbestiform amphibole and various fiber morphologies in surrounding rock (Meeker et al., 2003). A sample viewed by scanning electron microscope from the Zonolite Mountain mine illustrates the broad range of fiber morphologies and fiber size in the Libby Amphibole asbestos material (see Figure 2-9). The U.S. Geological Survey has described asbestiform fibers, acicular particles, particles showing curvature, and cleavage fragments all within Libby Amphibole asbestos (Meeker et al., 2003). As individual fibers and fiber bundles are viewed under greater magnification under a transmission electron microscope, the range of fiber types can be more clearly seen (Figure 2-10)

2.2.3.3. *Dimensional Characteristics of Libby Amphibole Asbestos*

Cumulative particle size distribution frequencies (CDF) were developed for Libby ore grade 3 and Libby ore grade 3 expanded by EPA Region 8 using the procedure described in detail in Appendix C. As shown in Figure 2-11 the particle size distribution frequency for the

Libby grade 3 ore and the Libby grade 3 ore expanded were similar to the particle size distribution frequency in the ambient air monitoring samples in Libby, MT. In the figure, CDF is cumulative distribution frequency. Data from the ambient air monitoring in Libby are presented in Appendix B. The data to construct the plot are described in Appendix B and Appendix C. There are slight shifts towards longer and thicker fibers in the ore samples compared to the air samples, with the aspect ratios being almost identical in the ore and air samples. However, all of these differences are minor and all of these fibers are respirable.

Mineralogical characterization of the fibers from the Libby ore grade 3 and the expanded product using energy dispersive x-ray analysis [EDX] and selected area electron diffraction [SAED] provided further confirmation of the similarity between the fibers from the Libby grade 3 ore and Libby Amphibole (methodology described in Sec 2.3; Appendix B). EDX spectra yielded an elemental fingerprint with sodium and potassium peaks that were highly consistent with values reported for the winchite richterite solution series described for the Libby, MT ores (Meeker et. al., 2003).

Based on these data, it is reasonable to conclude that the fibers from the Libby grade 3 ore and expanded ore are similar in physical and mineralogical characteristics to the Libby Amphibole fibers found in samples of air in Libby, MT. Therefore, the exposure and health effects information from the Marysville facility may be used to derive an RfC that can be applied in the Libby community and other sites that received vermiculite ore from Libby, Montana.

The Marysville, Ohio facility also used vermiculate ore from Virginia, South Africa, and South Carolina. Dr. Lockey obtained samples of the Virginia and South Africa ores from the Marysville facility in 1980 and supplied these ores to EPA for analysis. The Virginia and South African ores were tested for the presence of fibers as described in Appendix F. As described in Appendix E, the Virginia and South African ores released only a small quantity of amphibole fibers.

EPA was unable to obtain an ore sample from South Carolina. However, vermiculite ore from the Enoree mine in South Carolina is known to contain fibers (Appendix F; U.S. EPA, 2000d; McDonald et al., 1988).

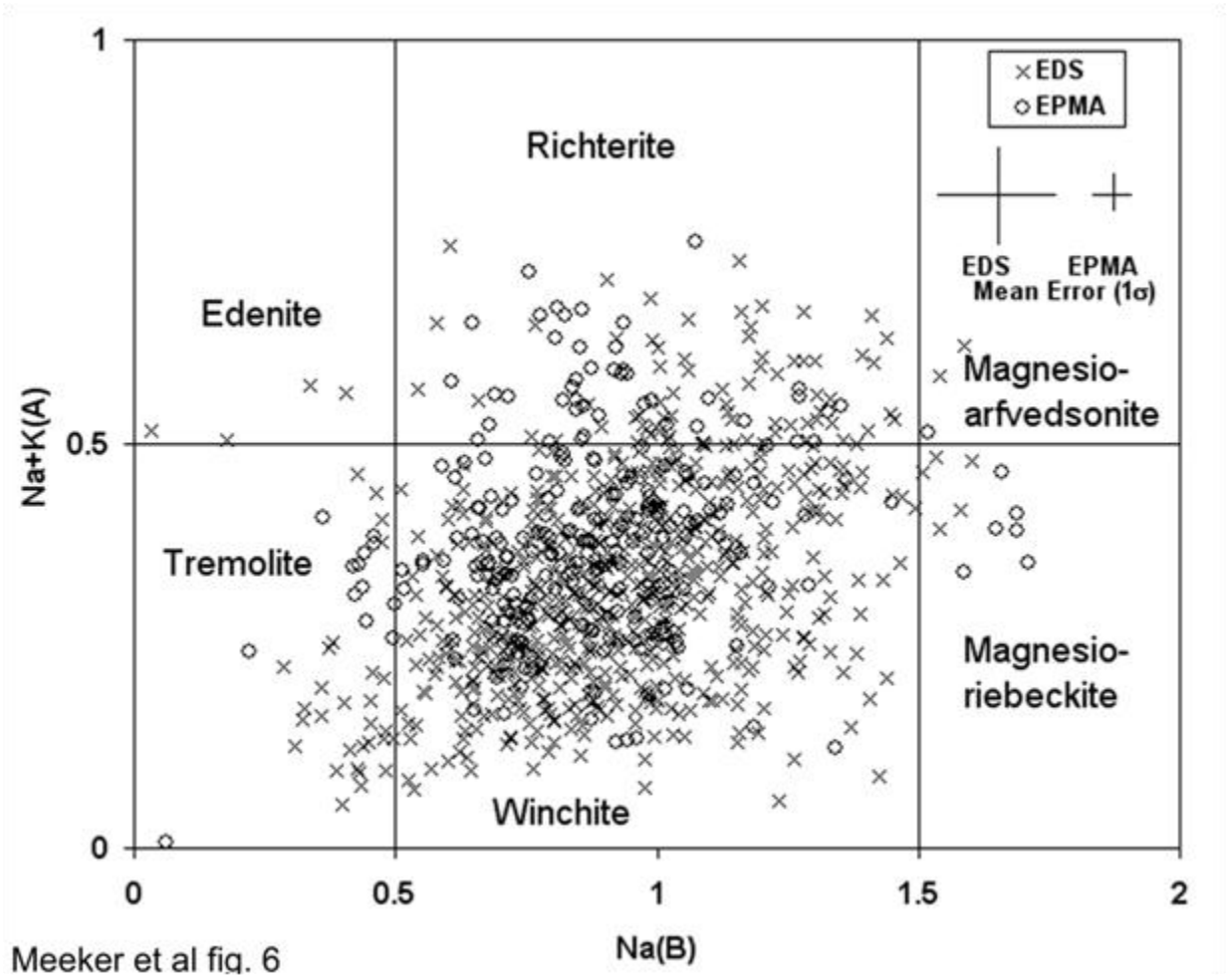


Figure 2-8. Mineralogy of Libby Amphibole asbestos fibers from samples taken from the Zonolite Mountain site. An evaluation of the textural characteristics shows the material to include a complete range of morphologies from prismatic crystals to fibers. Each data point represents the cation composition (number of occupied sites) for a single fiber. The x axis shows the number 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 fibers taken from of 30 different field samples from various locations within the mine. Notes: EDS is Energy dispersive x-ray analysis; EPMA is Electron Probe Microanalysis

Source: Meeker et al. (2003).

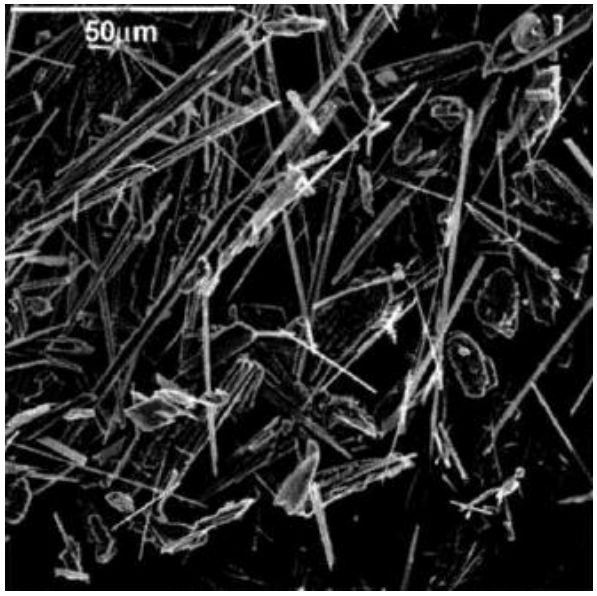


Figure 2-9. **Scanning electron microscope image of Libby Amphibole asbestos fibers.** Acicular, bundles, prismatic crystals, and curved fibers are all present.

Source: Meeker et al. (2003).

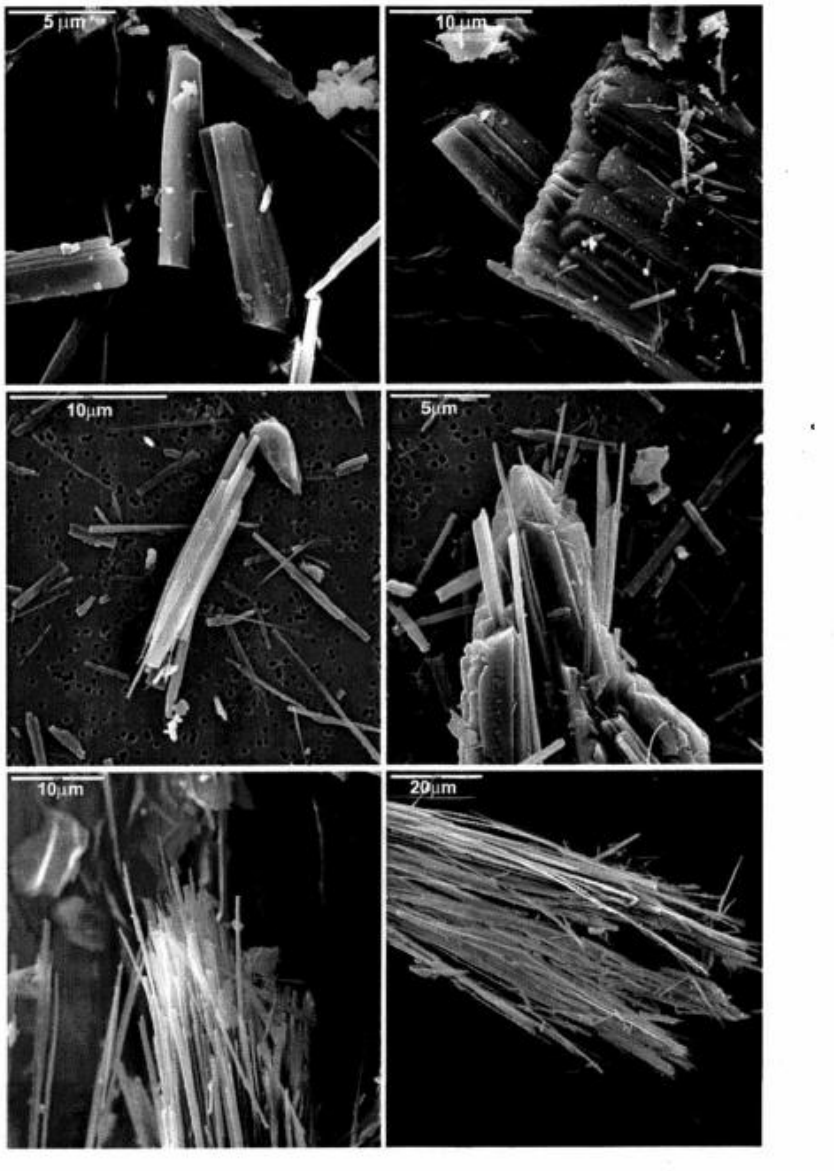


Figure 2-10 Fiber morphology of Libby amphibole asbestos viewed under a transmission electron microscope.

Source: Meeker et al. (2003).

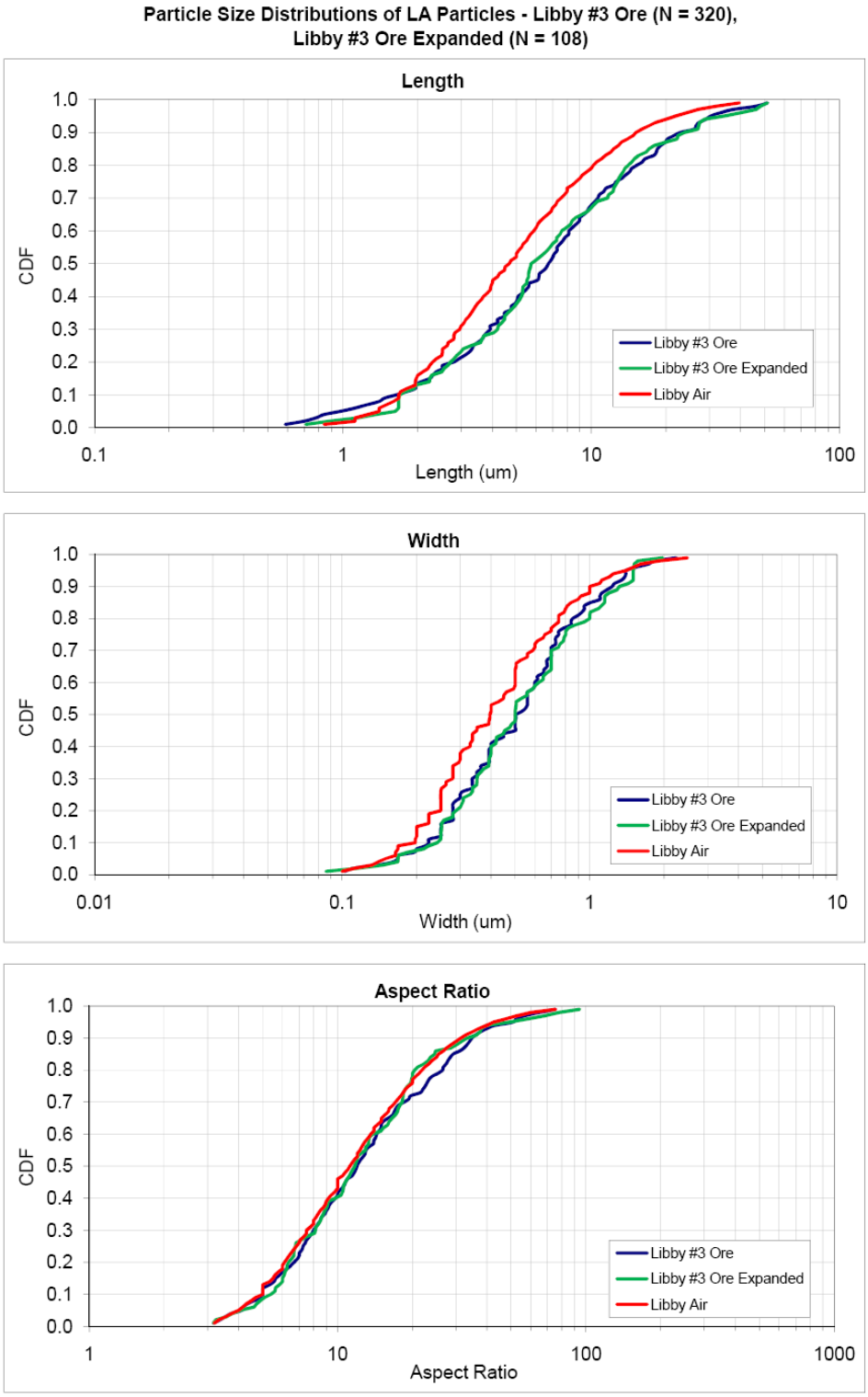


Figure 2-11. Particle Size (length, width, aspect ratio), fibers in Libby ore and Libby air.

CDF = cumulative distribution frequency; Source: U.S. EPA, 2010

2.3. ANALYTICAL TECHNIQUES FOR FIBER ANALYSIS

Various techniques are available to measure particles and fibers in air samples. Fibers are considered elongated particles, often defined as having as aspect ratio (generally a ratio of length to diameter) of 3:1 or greater. As inhalation exposure is of primary concern in determining adverse health effects of asbestos and other mineral fibers, an understanding of air sampling methods and analytic techniques is germane to a discussion of how to define mineral fibers. Historically, exposure measurements in industrial settings have been based on particle counts (midget impinger, thermal precipitator) and membrane filter counts. Particle counts (total dust) were measured as mass per unit air or as particles counted per unit of air. The midget impinger particle-counting method collects the particles in a liquid sample and particles are visually counted under a light microscope. Midget impinger results are reported as million particles per cubic foot of air (mppcf). This method counts particles regardless of their shape, aspect ratio), or the composition of the particle. Thus total dust air sampling results may be useful to compare the relative dustiness of different working environments but do not specifically measure either fibers in general or asbestos.

The collection of fibers on an air filter, visually counted under a phase contrast microscope[1] (PCM) was first described in 1934 by the Dutch physicist Frits Zernike. The specification of a fiber as >5 µm in length and length-to-diameter ratio (i.e., aspect ratio) of at least 3:1 resulted from this method. As a light microscope technique, the PCM method cannot distinguish between asbestos and nonasbestos fibers or determine fiber mineralogy. The U.S. Public Health Service developed and tested a standard air sampling method based on PCM detection (NIOSH Method # 7400), which has been used in industrial settings and is the basis of the IRIS IUR for asbestos (U.S. EPA, 1988). The method specifies the analyst count fibers >5 µm in length with an aspect ratio of at least 3:1. Fibers viewed and counted by the PCM method are referred to as 'PCM fibers.' Since PCM cannot distinguish between asbestos and nonasbestos fibers, the NIOSH method provides for the examination of fibers by transmission electron microscope where use of x-ray diffraction techniques allows for the mineralogical identification of the fiber.

This PCM metric was never intended to define biologically active fibers. The authors aptly point out in the AAHAU (U.S. EPA, 1986) that PCM fiber counts include nonrespirable fibers and that many smaller, respirable fibers are not quantified by this method. Dement and Harris (1979) report that approximately 98% of crocidolite, 95% of chrysotile, and 45% of amosite fibers were less than 5 µm long. These fiber-length profiles were calculated with a

[1] PCM is a contrast-enhancing optical technique that can be used to produce high-contrast images of transparent specimens.

lower length cut-off of 0.08 μm applied during fiber counting with transmission electron microscopy (Dement and Harris, 1979). The PCM metric measure, however, can be used as a surrogate for the material present. The proportion of fibers >5-μm long varies by mineral type, sample, and handling.

Electron microscopy employs electrons rather than light to visualize the specimen. Furthermore, instead of using glass lenses to focus the light wavelengths, electromagnetic lenses are used to focus electrons on the sample. The analytical techniques included in electron microscopy for asbestos testing are transmission electron microscopy (TEM), scanning electron microscopy (SEM), and scanning transmission electron microscopy (STEM). TEM produces two-dimensional (2-D) images that generally use a magnification factor of about 500 to 500,000×. SEM produces three-dimensional (3-D) images that generally result in about 10 to 300,000× magnification. STEM can produce both 2-D and 3-D images that generally result in about 10 to 500,000× magnification. X-ray diffraction (XRD) may be used with the above techniques to differentiate crystalline structure of minerals in solid materials and provides information on the availability of the total mineral present. Thus, XRD can determine the mineral form of asbestos fibers and structures. Although SEM and STEM are available for from commercial laboratories and for research, standard analytical techniques for enumerating asbestos structures in air samples have been developed for TEM (ISO 10312).

TEM analytical techniques are more specific than PCM for visualizing asbestos fibers and identifying types of asbestos. TEM analysis can detect fibers smaller than 0.006 μm in diameter and can determine the specific mineralogy by selected area electron diffraction and crystallography of asbestos fibers, thus distinguishing between asbestos fibers and nonasbestos fibers, as well as among different types of asbestos fibers by energy dispersive spectroscopy. TEM analysis is often used to determine asbestos in environmental and ambient air samples since asbestos structures can be identified. The International Standard method (ISO 10312) enumerates structures much smaller than the PCM fibers with a minimum length requirement of 0.5 μm. Additionally, structures with an aspect ratio of at least 5:1 are considered fibers, rather than 3:1 as with PCM analysis. The ISO 10312 method also defines other structures (fiber bundles, clusters, and matrices) that are included in the structure count. Therefore, the term structure rather than fiber is used when presenting air sampling results from ISO 10312 where structures per cc of air (s/cc) are reported. Although TEM has the advantages of viewing much smaller structures, counting various types of structures and mineralogical identification; there are some limitations of the method. As TEM is generally used at much higher magnifications than PCM in order to view the smaller structures, larger fibers and structures may be undercounted.

Additionally, a much smaller portion of the air filter is viewed under the greater magnification, impacting method detection limits.

EPA often employs a modified version of the TEM technique when assessing environmental sites. The *OSWER Framework for assessing asbestos-contaminated sites* (U.S. EPA, 2008) recommends that air samples be analyzed by TEM and then it specifies that a subset of the fibers visible under TEM be counted such that the fiber counts are considered equivalent to the subset of fibers that would have been observable using PCM; it recommends this subset of TEM fibers be used for site risk assessment (U.S. EPA, 2008). These PCM equivalent fibers (or PCMe fibers) are defined as those fibers viewed on TEM that meet the PCM analytical requirements: ≥5 μm in length and an aspect ratio of at least 3:1. Although the PCM methodology does not specify a minimum fiber width, current PCM analytical methods reliably detect fibers of 0.25 μm in width (WHO, 1980), which EPA employs to define PCMe fibers (U.S. EPA, 2008).

2.4. EXPOSURE POTENTIAL

Although the occurrence of Libby Amphibole asbestos is limited to a relatively small geographic area, the potential for exposure to it has been greatly enhanced by the historical mining, milling, and distribution of vermiculite operations in Libby, MT. Additionally, material was sent to processing plants across the nation where plant workers and community contacts may have been exposed. Lastly, consumer products containing vermiculite mined near Libby are contaminated with the Libby Amphibole asbestos, and consumers may have been exposed to Libby amphibole asbestos while using the products. For example, asbestos–contaminated vermiculite attic insulation from Libby remains in homes today across North America, where there is the potential for residential exposures. This section summarizes the potential for current exposures to the Libby amphibole asbestos in vermiculite in the Libby community, other communities potentially impacted by processing plants, and from in-place Libby vermiculite attic insulation. Historical exposures for the workers in Libby, MT, and other facilities are discussed in Section 4.1, where data are available.

There are also lifestyle, activity and lifestage factors which may influence one's exposure potential to asbestos. For example, children spend more hours outside and may engage in activities which impact exposure level compared to adults (NRC, 1993; U.S. EPA 2006). In general, children inhale more air per unit body weight (U.S. EPA, 2008) and spend more time outdoors than adults (Bateson and Schwartz, 2008; NRC, 1993), which could have resulted in increased inhalation exposure to Libby Amphibole asbestos in children compared with adults. In contrast, some adult activity patterns may also result in increased exposures, such as gardening

and home repair, where Libby Amphibole asbestos may be present. Thus for the various environments where people may be exposed to Libby Amphibole asbestos, the potential activities and pathways of exposure are discussed below, and where available exposure measurements given for various exposure environment and activities.

2.4.1. Libby Community

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

During plant operations, individuals may have been exposed to materials inadvertently transported from the workplace to vehicles, homes, and other establishments, typically on the clothing, shoes, and hair of workers. This transport of material may result in "take-home exposure" for the workers, their families, and other co-residents. The magnitude of these exposures was not measured, so the levels to which individuals in the home might have been exposed are not known. Based on studies of other industrial take-home exposures, individuals doing laundry and cleaning house (often women) can be exposed to materials on workers' clothing. Also, children who play on the floor might be more exposed than adults to dust from take-home exposures (Kelly et al., 2006). The community health screening studies from Libby showed that men were more likely to have both occupational and non-occupational exposures, while women were more likely to have household contact with exposed workers (ATSDR, 2001; Peipins et al., 2003). There could also be gender differences in types of activities (e.g., household chores such as laundry and cleaning) or in intensity or duration of occupational and recreational activities (Peipins et al., 2003).

Expanded vermiculite, as a finished product, was used as a soil amender and for attic insulation. Community members may have been exposed and are possibly still exposed to these consumer products. In a survey of Libby residents conducted by ATSDR in 2000–2001, almost 52% reported using vermiculite for gardening and 8.8% used vermiculite around the home and 51% reported handling vermiculite attic insulation (Peipins et al., 2003). As vermiculite ore, waste rock, and product were present in the community, numerous activities may have resulted in exposure. Individuals also reported exposures from the following activities: participating in

recreational activities along Rainy Creek Road, the road leading to the mine (67%); playing at the ball field near the expansion plant (66%); playing in the vermiculite piles (34%); heating the vermiculite to make it expand/pop (38%); or other activities in which there was contact with vermiculite (31%) (Peipins et al., 2003). Memoranda from Christopher Weis (U.S. EPA) states that asbestos mineral fibers were detected in outdoor sources (yard soil, garden soil, driveway material, and assorted mine-waste materials) and indoor sources (dust and vermiculite insulation) in Libby (U.S. EPA, 2001a, b). Prior to plant closure, there are no measurements of exposure levels in the community for the materials and activities from various exposure pathways.

EPA has conducted more recent exposure sampling in the Libby community. Limited data are available from sampling conducted in 2000/2001 to assess airborne asbestos levels from various activities (see Table 2-2). Air samples were taken in the community during activities considered appropriate for various potential exposure scenarios. Personal air monitors were placed on the investigator conducting the activity, and a second air sample was taken from a fixed location (area sample). Asbestos fibers were collected on filters and counted by two different laboratory methods: 1) PCM and 2) TEM. Although TEM analysis can count smaller fibers, results are shown here for PCM size fibers used to estimate risk, called PCM equivalent fibers, or PCMe (See Section 2.2.3.1)

EPA continues to conduct air monitoring in the Libby community to support clean-up and risk assessment activities. Ambient air monitoring conducted in 2006/2007 at 18 locations across the area indicated that low levels of asbestos fibers are occasionally detected in the air, even with no localized disturbance of asbestos-contaminated material (U.S. EPA, 2009b). Fibers were counted by TEM, and structures $\geq$0.5 µm in length and with an aspect ratio $\geq$3 were included (structures per cc of air, s/cc). Average ambient air levels for the various sampling locations ranged from 8×10^{-6} s/cc to 1.9×10^{-5} s/cc (U.S. EPA, 2009b). Both ambient and activity-based air monitoring have been completed in five community schools (U.S. EPA, 2010). Outdoor activities conducted that were considered relevant to children's exposures at the schools included playing sports, using playground equipment, and running/walking in outdoor areas. Outdoor activities to assess exposure of the school maintenance workers included digging/raking, power sweeping parking lots, and mowing/ and edging school lawns. Additionally, ambient air samples were taken in each school (i.e., classrooms, cafeteria, gymnasium, and hallways). Asbestos PCMe fibers were detected by TEM analysis in 5 of 63 outdoor activity-based samples, ranging from 0.0022 to 0.039 f/cc. No PCMe fibers were detected in indoor air samples. However, 2 of 50 indoor area samples detected TEM asbestos structures not considered PCMe fibers (5.1×10^{-4} s/cc and 5.9×10^{-4} s/cc), which is within the range of analytical sensitivity for the

indoor air samples (U.S. EPA, 2010). It should be noted that indoor air sampling did not include any activity-based sampling to assess student or employee exposures.

Table 2-2. Air sampling results for disturbance of Libby amphibole asbestos-contaminated materials in Libby, MT

Activity		Air sampling results		
		Type of air sample	PCM (f/cc)[1]	TEM (PCME-asb) (f/cc)
Rototilling	Vermiculite-contaminated soil	Area sample	0.020	0.019
		Personal air monitor	0.227	0.066
Active cleaning	Household dust	Area sample	0.021[2] (0.007–0.068)	0.008 (0.007–0.010)
		Personal air monitor	0.112 (0.014–1.017)	0.010 (0.004–0.013)
Routine activity	Household dust	Area sample	0.006 (0.002–0.012)	0.009 (0.0003–0.036)
		Personal air monitor	0.007 (0.001–0.014	0.035 (0.023–0.048)
Simulated home remodeling	Vermiculite insulation	Area sample	0.142 (0.035–0.324)	0.309 (0.023–0.789)
		Personal air monitor	0.568 (0.118–1.62)	0.309 (0.042–1.057)

Source: EPA (2001).

Notes: 1) Air sampling is reported in fibers per cc of air (f/cc). PCM fibers are greater than 5 μ in length with an aspect ratio of at least 3:1.

2) Where multiple measurements were taken, the mean air concentration is given followed by the range of detected air levels.

Although data are limited, there are reports that milling operations in the city of Libby resulted in increased ambient air levels measured as PCM fibers. In efforts to document historical air transport of asbestos fibers, researchers have examined tree bark. A study conducted in Libby determined that trees may act as reservoirs for Libby Amphibole asbestos fibers, which may have become embedded in the bark by diffusion or impaction-type processes (Ward et al., 2006; Webber et al., 2006). Therefore, loggers and others in the timber industry in the Libby area could have had additional exposure to Libby Amphibole asbestos. Because trees act as reservoirs for Libby Amphibole asbestos, inhalation exposures could have occurred where wood is burned to provide heat (Ward et al., 2009).

2.4.2. Communities near Vermiculite Expansion and Processing Plants

The ATSDR Summary Report on the 28 Libby vermiculite expansion and processing facilities reported that household residents were exposed by contact with vermiculite from the workers' clothes, shoes, and hair. Workers' personal vehicles likely contained vermiculite dust from the facility emissions and from vermiculite that fell from their clothing and hair on the drive home after work. The O.M. Scott Company reported that company policy was to launder work clothes for their employees and to make showers available for use after work. Had these services been used, exposure via household contact could have been greatly reduced (ATSDR, 2005). Whether other facilities made these services available or how frequently they might have been used is unknown.

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

For the O.M. Scott Company facility in Marysville, Ohio, about 185 people currently live within 1 mile of the facility, but only about 60% of the housing units within the 1-mile radius existed while the Libby vermiculite was being exfoliated. Community members living farther from the facility, however, might still have been exposed through ambient air because many individuals used the swimming pool at the company facility (ATSDR, 2005). More detailed information on the community exposures near this facility is not available.

Waste rock from an exfoliation facility in Minnesota was made available to residents of the community, and personal use was encouraged. Individuals used the material to landscape, to fill in driveways, and as a soil additive. The waste rock was dumped outside the plant, and plant employees and children reported playing in and around the piles. Substantial airborne emissions also were measured close to the plant (ATSDR, 2003).

2.4.3. Exposures from Zonolite and Vermiculite for Homeowners, Contractors, and Other Populations

It is estimated that 80% of the vermiculite used in the United States, and consumer products include Zonolite vermiculite attic insulation (VAI) and potting soil amended with expanded vermiculite came from the mine in Libby, MT. EPA conducted a study to estimate the potential for exposure to asbestos in homes containing VAI. Air samples were taken to define

exposure levels in the homes under various conditions: no activity (e.g., ambient air), as well as during simulated remodeling activities and removal of the VAI (U.S. EPA, 2003). Samples were taken in the both the living space of the homes as well as attic space.

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

A second study on potential exposures to Zonolite VAI was conducted by an environmental firm hired by attorneys representing individuals with VAI in their homes (Ewing et al., 2010). This study was conducted in three homes containing Zonolite VAI, and air sampling was taken, representing ambient conditions (no disturbance of VAI), remodeling, activity in the attic, and removal of the VAI by various methods (see Table 2-3). Disturbance of the asbestos-contaminated VAI resulted in airborne asbestos levels, both in the personal air monitors and area samples (Ewing et al., 2010).

Table 2-3. Air sampling results for asbestos from Zonolite VAI in three homes

Activity	Personal samples		Area samples
	PCM[1] (f/cc)	TEM[2] (PCME, s/cc)	TEM (PCME, s/cc)
No activity	NS[3]	NS	<0.003
Cleaning items in the attic	1.54	<0.42	0.07
Cleaning storage area in the attic	2.87	2.58	0.47
Cutting a hole in the ceiling below the VAI	5.80	1.32	0.52
VAI removal (various methods)	2.9–12.5[4]	0.98–10.3	0.53–1.47

Air sampling results reported as fibers analyzed by phased contrast microscopy (PCM).
Air sampling results reported as structures, PCM equivalent (PCME) as analyzed by transmission electron microscope (TEM).
NS—not sampled, personal samples were not taken for background levels.
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. However, to help inform the reader as to the expected toxicokinetics of Libby Amphibole asbestos, this section contains a general summary description of toxicokinetics of fibers. A more detailed discussion of fiber toxicokinetics is beyond the scope of this document, but is reviewed elsewhere (NIOSH, 2011; ICRP, 1994).

Understanding fiber toxicokinetics and retained fiber dose is a complex component of analyzing asbestos toxicity. The principal components of fiber toxicokinetics in mammalian systems are (1) deposition at the lung epithelial surface, and (2) clearance from the lung due to physical and biological mechanisms including both translocation from the lung to other tissues (including the pleura), and elimination from the body (see Figure 3-1).

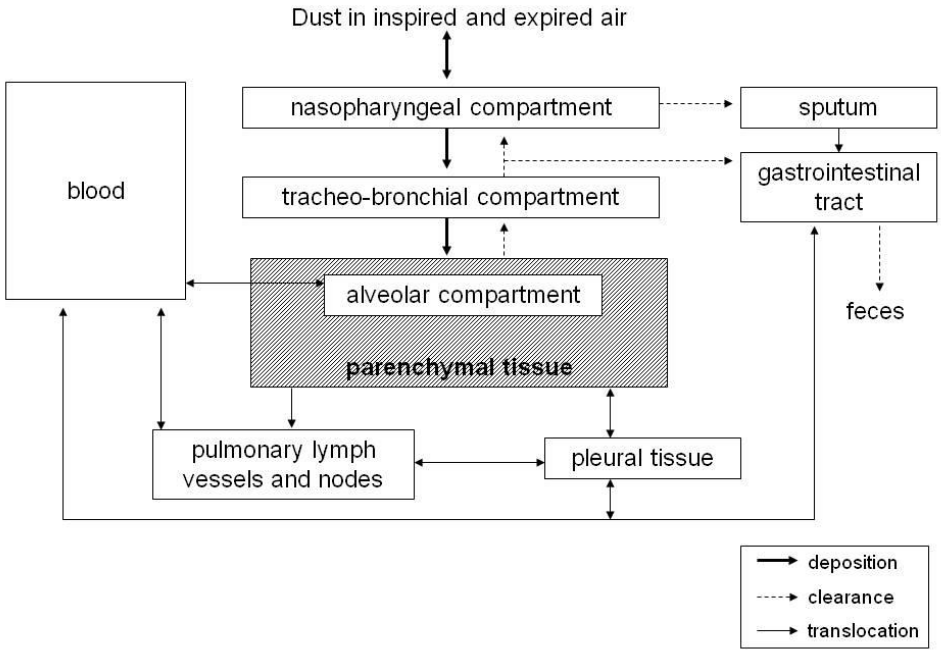


Figure 3-1. General scheme for fiber deposition, clearance, and translocation of fibers from the lung and GI tract. General scheme for fiber deposition (heavy arrows), clearance (light dotted arrows), and translocation (light arrows). Diagram of Bignon et al. (1978) derived from ICRP lung model by the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

Source: ICRP (1994).

The fiber characteristics of the sample to be studied define the toxicokinetics of that specific sample. These characteristics vary among fiber types, and in many cases, among samples of the same fibers. Libby Amphibole asbestos 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, 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 workplace also document a large percentage of respirable[1] fibers as well as fibers <5um-long (see Section 4.1.1.2 and Table 4-3). The importance of the size of fibers and how they deposit following inhalation is described below. Due to a lack of data specific to Libby Amphibole asbestos, these deposition steps are discussed for asbestos in general.

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

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

[1] Respirable fibers are those that can be inhaled into the lower lung where gas exchange occurs and are defined by their aerodynamic diameter ($d_a \leq 3\mu m$, NIOSH).

et al., 1983; Harris and Fraser, 1976; Harris and Timbrell, 1975). Factors influencing dose to other tissues in the body (e.g., pleura, peritoneum, stomach, ovaries) are not as well known, but they are discussed below where data are available.

3.1. DEPOSITION OF FIBERS IN THE RESPIRATORY TRACT

The deposition of fibers in the respiratory tract is dependent on the aerodynamic properties of the fiber (length, width, and density) and the anatomy and physiology of the respiratory tract (NIOSH, 2008; ATSDR, 2001; Myojo and Takaya, 2001; Witschi and Last, 1996; Yu et al., 1986; Griffis et al., 1983; Harris and Fraser, 1976; Harris and Timbrell, 1975). Thicker fibers are deposited in the upper airways; thinner fibers are carried deeper into the airways and alveolar regions. All fibers with aerodynamic diameters less than approximately 3 μm meet the physical criteria necessary for deposition in the terminal bronchioles and beyond to the alveoli. The site of fiber deposition within the respiratory tract has implications related to lung retention and surface dose of fibers. The respiratory tract encompasses the upper respiratory tract (nose, nasal passages, and throat), respiratory airways (larynx, trachea, bronchi and bronchioles) and the lungs (respiratory bronchioles, alveolar ducts, alveolar sacs and alveoli). A full review of the anatomy and architecture of the respiratory tract is beyond the scope of this document but has been reviewed by ICRP (1995).

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

Impaction: The momentum of the fiber causes it to directly impact the airway surface as the airflow changes direction. This is the predominant method of deposition in the upper airways where airflow is swift and larger fibers/particles are present.

Interception: A special case of impaction where the edge of the fiber touches the airway surface and is prevented from continuing along the airway. This mechanism is important in the transmitting airways (trachea and bronchi), where the airflow is slower and laminar flow along the airway surface is conducive to interception.

Sedimentation: Gravitational forces and air resistance cause fibers/particles to settle out of the air column onto the airway surface. For sedimentation to occur, air flow velocities must be low, to allow the particle/fiber to settle, and this is a predominant mechanism to the smaller conductive airways.

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; this Brownian motion increases with decreasing fiber size (<0.5 μm diameter).

Electrostatic Precipitation: A special case of diffusion, where fiber motion towards the airway surface is a function of static charge between the fiber and airway surface.

As with classic diffusion, this primarily occurs in the alveolar region where airflow is negligible and the electrostatic forces can predominate.

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	Nasopharyngeal region (upper airway passages – nose and throat)	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	Trachea, bronchial and bronchiolar region (windpipe and larger branches of the lungs)	Sedimentation, impaction, interception	Epithelial cell uptake	Mucociliary apparatus Macrophage: phagocytosis and transport	Mucous Macrophage	Gastrointestinal tract Mucosa-associated lymphoid tissue, lymph system Pleura
1 µm or less	Alveolar region (smaller branches of lung and the air exchange area)	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 Klaasen et al., 1986 in Casarett and Doull's *Toxicology: The Basic Science of Poisons*, 3rd edition, p. 343.

Aerodynamic diameter (also called aerodynamic equivalent diameter) of fibers accounts for dimensional properties that influence the movement of the fiber's center of gravity through the airways, so aerodynamic diameter is important in all depositional mechanisms. The aerodynamic diameter is the diameter of a unit density ($1 g/cm^3$) sphere that has the same gravitational settling velocity as the particle of interest. Since the aerodynamic diameter informs the deposition patterns of fibers, it is used in modeling to determine the expected fiber deposition in the respiratory tract. Impaction and interception, however, are also heavily influenced by fiber length. Where the physical length of the fiber greatly exceeds the aerodynamic diameter, impaction and interception can be underpredicted by modeling the center of gravity of the fiber. 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). Electrostatic precipitation occurs when fiber charges induce opposite charges on the airway surfaces and the fiber is drawn to the airway walls (Lippmann, 1990).

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

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

The conducting airways beyond the nasopharyngeal region include the trachea and bronchi, which have branched bifurcations with decreasing internal diameters. The aerodynamic diameter of fibers that can deposit in the tracheobronchial region is in the range of 1–5 μm. Fibers with aerodynamic diameter <1 μm can deposit in the bronchioles and then farther to the alveoli (ICRP, 1994).

Generally, fibers with aerodynamic characteristics conducive to deposition at the primary or secondary bronchioles and alveoli can cause fibrogenesis and associated disease by either retention in the alveoli or penetration into the peribronchiolar space. All fibers (aerodynamic diameter less than approximately 2 μm), including Libby Amphibole asbestos, meet the physical criteria necessary for deposition in the deeper regions of the respiratory tract at the level of the terminal bronchioles or alveoli.

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

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

Modeling of fiber deposition has been examined for various fiber types (e.g., refractory ceramic fibers, chrysotile asbestos) (Sturm 2009; Zhou et al., 2007; Lentz et al., 2003; Dai and Yu, 1998; Yu et al., 1997; Coin et al., 1992), but not for Libby Amphibole asbestos. In general, fibers are expected to share patterns of deposition similar to particles which is well-studied (reviewed in ICRP 1994). For example, the multipath particle dose (MPPD) model (Jarabek et al., 2005; Brown et al., 2005) uses information on the physical properties of the particles (length and width [also called bivariate distribution] and density), the anatomy and architectural features of the airways, airflow patterns that influence the amount and the location of the

deposition of the particles, and dissolution and clearance mechanisms that are operative to estimate the retained dose in the target tissue. However, although this model has not been fully developed for fiber deposition, due to similarities with particle deposition this can be used to inform deposition of fibers.

3.2. CLEARANCE

Complex relationships exist among different mechanisms that affect fiber accumulation: the amount of exposure, the duration of exposure, the physiological clearance from the lung, and the toxicological response observed in the body. In general, adverse health effects increase with an increase in exposure duration or dose (Bernstein et al., 2003, 2005; Cullen et al., 1997; Ehrlich et al., 1992; Seidman et al., 1986).

Clearance from one tissue may involve translocation to another tissue. For example, following fiber deposition in the respiratory tract fibers may then clear via translocation to extrapulmonary tissues like the pleura. The specific mechanism and translocation route depend both on fiber characteristics and the tissue of deposition. Whether or not fibers are translocated appears to depend on their physical-chemical characteristics, including two-dimensional size (length and width); durability; solubility; and reactivity. This translocation is aided by high biopersistence and inflammation-induced increase in permeability but is hindered by fibrosis. Deposition occurs in the respiratory tract as described above; translocation from the respiratory tract may in turn lead to fibers 'depositing' in extrapulmonary sites. Movement of fibers within the respiratory tract can also influence inflammatory reactions and cause tissue injury remote from the site of deposition. A general scheme for deposition and clearance of fibers is illustrated in Figure 3-1.

3.2.1. Inhalation

3.2.1.1. *Respiratory Tract*

Once fibers deposit on the surface of the respiratory tract, they may be removed (cleared) from the lungs in several ways, including physical clearance, dissolution, phagocytosis, or encapsulation. Some of these mechanisms, such as dissolution of the fibers, or removal via the mucociliary apparatus may result in the fibers being cleared from the body (see Figure 3-1). Other clearance mechanisms may remove fibers from the surface of the respiratory tract but result in transport of the fibers to other tissues by translocation. Translocation of fibers from the terminal bronchioles and alveoli into the transbroncheolar space, lymph nodes, and pleura of the lungs has been implicated in disease causation (e.g., pleural plaques, mesothelioma) (Dodson et al., 2001). In human studies, the translocation of asbestos fibers following inhalation has been

observed to varying degrees throughout the pulmonary and extrapulmonary tissues (Suzuki and Kohyama, 1991; Dodson et al., 2005; Kohyama and Suzuki, 1991; Dodson et al., 2001; Sebastien et al., 1980), as well as other organs, including the brain, kidney, liver (Miserocchi et al., 2008), and ovaries (Langseth et al., 2007). In many cases, the type of fiber is not defined, and the individual exposure information is not available. Fibers that are not cleared may remain at the epithelial surface or enter the parenchymal tissue of the lung.

Berry (1999) provided a review of the animal toxicity literature specifically for fiber clearance. There are limited data on clearance patterns based on autopsy studies in humans. Two studies estimated increased clearance half-life for amphibole asbestos (~20 years) as compared to chrysotile asbestos (~10 years) (Churg and Vedal 1994; Finkelstein and Dufresne 1999); in evaluating the data on lung fiber burden, Berry et al. (2009) estimated the range of the half-life for crocidolite to be between 5 and 10 years. Generally, studies have focused on determining the size and type of asbestos retained in specific tissues (Dodson et al., 1990; Gibbs et al., 1991; Suzuki et al., 2005; Dumortier et al., 1998; Suzuki and Yuen 2001; McDonald et al., 2001) and did not discuss changes in fiber content since exposure. Sebastien et al. (1980) concluded that lung fiber burden could not be used as an accurate reflection of pleural fiber burden.

3.2.1.1.1. Physical clearance of fibers

Large fibers deposited in the nasal passages can be removed by physical clearance. When breathing occurs through the nose, many fibers are filtered by the turbulent airflow in the nasal passages, impacting against the hairs and nasal turbinates, as well as becoming entrained in mucus in the upper respiratory tract where they can be subsequently removed by reflexive actions such as coughing or sneezing. Fibers can also translocate due to physical forces associated with respiration (Davis, 1989). Fibers with aerodynamic characteristics that cause them to impact at the nasopharyngeal or tracheobronchial regions of the respiratory tree are likely to be quickly removed (in minutes or hours) by the action of the mucociliary escalator. The mucociliary escalator removes fibers through ciliary movement of the sticky mucus lining (Churg et al., 1989; Wanner et al., 1996). Fibers removed from the pulmonary space through this mechanism are either coughed out, or subsequently swallowed and enter the digestive tract where they may adversely affect the tissue, enter the body via the blood, or be excreted. Clearance of fibers via this mechanism is rapid and is usually complete within minutes or hours. However, the mucociliary escalator extends only to the level of the terminal bronchioles of the respiratory tree and not to the alveoli. Therefore, particles that reach these deeper regions cannot be cleared through this process.

Some fibers are not cleared from the lung, leading to an accumulation with time (Case et al., 2000; Finkelstein and Dufresne, 1999; Jones et al., 1988). The fibers that remain in the lung may undergo a number of processes including translocation, dissolution, fragmentation, splitting along the longitudinal axis, or encapsulation with protein and iron. Available data indicate prolonged clearance from the lung of longer serpentine chrysotile fibers (>5 μm) or either long (>5 μm) or short amphibole fibers (Coin et al., 1994; Tossavainen et al., 1994). The prolonged clearance times for long amphibole fibers have led some investigators to conclude that long amphibole fibers are predominant in the cause of disease despite the relatively small numbers of these longer fibers in comparison to short fibers. However, Dodson et al. (2003) argue that fibers of all lengths induce pathological responses and urge caution in excluding any population of fibers based on their length, from contributing to the disease process. There are no data available with Libby Amphibole to resolve the issue about short or long fibers. The important feature illustrated by Figure 2-4 is that all of the fibers identified from the Libby ore samples are potentially respirable and can penetrate to the alveoli.

Apparent translocation of fibers throughout the respiratory tract is evident from experimental animal research done by several investigators following exposure by both intrapleural injection and inhalation (Bignon et al., 1979; Holt, 1982; Smith et al., 1974, 1979, 1980; Miserocchi et al., 2008). Conflicting results from another study, however, indicate no evidence of fiber translocation from the central to peripheral compartments following inhalation exposure in rats, although this could be due to the short duration of the study (29 days post exposure) (Coin et al., 1992). The data from most studies show that fibers can and do translocate among tissues and organs and move by both physiological and physical mechanisms (Cook and Olson, 1979; Holt, 1982, 1983).

3.2.1.1.2. Dissolution of fibers

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

3.2.1.1.3. Removal of fibers through phagocytosis

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

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

A number of processes can disrupt the normal phagocytic function of the alveolar macrophages. These processes include death of phagocytes due to ingestion of highly reactive fibers, due to a high burden of deposited fibers (overload), or an attempt by the macrophages to engulf fibers that exceed the macrophage length (often termed "frustrated phagocytosis") (NIOSH, 2008). All of these processes can induce inflammatory and fibrogenic responses.

3.2.1.1.4. Encapsulation of fibers

Fibers that are too large to be easily engulfed by the alveolar macrophage can stimulate the formation of asbestos bodies. Asbestos bodies are fibers that are coated with proteins, iron and calcium oxalate. The mechanisms that result in the formation of asbestos bodies are poorly understood, although most appear to be formed around amosite fibers (Dodson et al., 1996). The iron in the coating, however, is derived from the asbestos fiber, cells, or medium surrounding the fiber and can remain highly reactive (Ghio et al., 1992; Lund et al., 1994). These bodies are sometimes referred to as "ferruginous" bodies because of their affinity for iron-loving histological stains. Ferruginous bodies can remain in the lung throughout the lifetime of the exposed individual. Asbestos bodies comprise a minor portion of the overall fiber burden of the lung, and, after the fiber is fully coated, these fibers might or might not participate directly in asbestos disease. The presence of iron in the coating, however, could provide a source for catalysis of reactive oxygen species similar to that observed with fibers.

3.2.1.1.5. Translocation to extrapulmonary tissues

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

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

Sebastien et al. (1980) found chrysotile was the predominant fiber in parietal pleura of autopsy cases, while the amphibole fibers found in the lungs ranged from 0 to 100% (mean 56%). Bignon et al. (1979) found similar distributions but also found increased amphibole fibers in the associated lymph nodes. In this study, chrysotile and amphibole fibers were found together in the lung parenchyma and alveolar spaces. Other studies show fewer amphibole fibers at the site of diseased tissue in the pleura and mesothelial tissue than chrysotile (Churg, 1988; Kohyama and Suzuki, 1991). Sebastien et al. (1989) examined fiber types in lungs of chrysotile textile and mining workers from South Carolina and Quebec to better understand the unknown reason for differences in disease risk in each cohort. Both groups were exposed to similar material, yet the South Carolina cohort had a much greater risk of respiratory cancer. This study examined only lungs, although some of those exposed had nonpulmonary cancers. Overall, the

number of tremolite fibers was higher than that of chrysotile fibers in both cohorts. Size distribution showed that most fibers measured were 5.8−8.0 µm long, although measurements were not made for anything smaller than this. Tremolite fibers had a greater mean diameter in both cohorts (0.35 µm) as compared to chrysotile (0.10 µm), while chrysotile had more "Stanton" fibers (25.2–31.8%) as compared to tremolite (5.9–6.3%). Stanton fibers are defined as >8 µm long and <0.25 µm in diameter (Stanton et al., 1981, reviewed in Appendix G).

3.2.1.2. *Pleural Cavity and Extrapulmonary Sites*

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

3.2.2. Ingestion

Although ingestion is a potential route of exposure, limited research has examined clearance (e.g., translocation) of fibers following ingestion, and no clearance studies are available specific to Libby Amphibole asbestos. An early study to examine the tissue response to asbestos fibers is not truly representative of a natural ingestion exposure, as the researchers directly injected a suspension of amosite fibers into the duodenal wall (Meek and Grasso, 1983). This study, however, also examined oral ingestion of amosite in healthy animals and those with gastrointestinal ulcers to determine if translocation of fibers occurs through ulcers. Following injection of amosite, granulomatous lesions were observed. Ingestion of the same material

resulted in no such lesions or in any other histopathological changes in either healthy or compromised rats. Thus, no translocation was observed from either the healthy or the compromised rat gastrointestinal tracts in this study. A later International Agency for Research on Cancer study (Truhaut and Chouroulinkov, 1989) examined the effects of chrysotile and crocidolite ingestion in Wistar rats. No translocation was observed. No further studies have been found on clearance or translocation of fibers from the gastrointestinal tract.

3.2.3. Dermal

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

3.3. SUMMARY

Although oral or dermal exposure to fibers does occur, inhalation is considered the main route of human exposure to fibers, and therefore has been the focus of more fiber toxicokinetic analyses. Exposure to Libby Amphibole asbestos is proposed to be through all three routes of exposure, although information specific toxicity based on differential routes of exposure is not available. Generally, fiber deposition in the respiratory tract is fairly well defined based on fiber dimensions and density, although the same cannot be said for fiber translocation to extrapulmonary sites (e.g., pleura). The deposition location within the respiratory tract and extrapulmonary sites plays a role in the clearance of the fibers from the organism.

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

Multiple fiber characteristics play a role in the toxicokinetics of fibers (e.g., dimensions, density, and durability). For this reason, careful attention has been paid to these fiber characteristics when analyzing research studies on Libby Amphibole asbestos and tremolite, another amphibole fiber that comprises part of Libby Amphibole asbestos (see Appendix D). No toxicokinetic data is available specific to Libby Amphibole asbestos, tremolite, richterite or winchite. When available, this information is presented in the discussion of each paper in relation to the toxic endpoints described.

4. HAZARD IDENTIFICATION OF LIBBY AMPHIBOLE ASBESTOS

Several human studies are available that provide evidence for the hazard identification of Libby Amphibole asbestos. This discussion focuses primarily on data derived from studies of people exposed to Libby Amphibole asbestos—either at work or in the community. The adverse health effects in humans are supported by the available Libby Amphibole asbestos experimental animal and laboratory studies. Libby Amphibole asbestos contains winchite (84%), with lesser amounts of richterite (11%) and tremolite (6%) with trace amounts of magnesioriebeckite, edenite, and magnesio-arfvedsonite (Meeker et al., 2003) (see Section 2 for a more complete discussion). Adverse health effects from tremolite exposure have been reported in both human communities and laboratory animals; these effects are consistent with the human health effects reported for Libby Amphibole asbestos. The hazard identification discussion for Libby Amphibole asbestos (including tremolite) is not limited to cancer incidence and mortality data, the noncancer health effects—and mechanistic data related to these effects—are also described. Some pathogenic pathways might be shared between some noncancer health effects (e.g., inflammation, fibrosis) and cancer; thus, these effects can be considered relevant to the subsequent development of cancer. The presentation of noncancer and cancer health effects provides a comprehensive review of adverse health effects observed from exposures to the Libby Amphibole asbestos.

Few data specific to Libby Amphibole asbestos are currently available on which to base a detailed understanding of mechanisms for its adverse effects. Similarly, specific questions about susceptible populations are not fully addressed by Libby Amphibole asbestos data alone. Therefore, the discussions of the mode(s) of action (Section 4.3.2) and susceptible populations (Section 4.4) also draw from the literature on mineral fiber toxicity but are not intended to be a comprehensive review of the broader subject.

4.1. STUDIES IN HUMANS—EPIDEMIOLOGY

The Libby Amphibole asbestos epidemiologic database includes studies conducted in occupational settings examining exposures to workers, and community-based studies, which can include exposures to workers, exposures to family members of workers, and exposures from environmental sources. Occupational epidemiology studies exist for two work sites where workers were exposed to Libby Amphibole asbestos. These are the mine and mill at the Zonolite Mountain operations near Libby, MT, and a vermiculite processing plant in Marysville, OH. Worker cohorts from each site and the study results are described in Section 4.1.1.

Whitehouse et al. (2008) described the occurrence of 11 cases of mesothelioma among individuals who lived in or around Libby, MT, who had not worked in the mining or milling operations. The Agency for Toxic Substances and Disease Registry (ATSDR) has conducted community health consultations for Libby, MT, including an evaluation of cancer mortality data, and a health screening of current and former area residents (including workers) that collected medical and exposure histories, chest x-rays, and pulmonary function tests (ATSDR, 2000, 2001). Several published papers are available based on data from this health screening. ATSDR, in conjunction with state health departments, also conducted health consultations for 28 other communities around vermiculite processing plants that were potentially exposed to Libby Amphibole asbestos (see Section 4.3). These health consultations consisted of analyses of cancer incidence or mortality data; results from nine of these studies are currently available. The other studies have not been completed at the time of this assessment.

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

4.1.1. Studies of Libby, MT Vermiculite Mining Operation Workers

Several studies of mortality from specific diseases among workers in the Libby, MT mining operations have been conducted, beginning in the 1980s with the studies by McDonald et al. (1986a,b) and Amandus (1987a,b; Amandus and Wheeler, 1987). McDonald et al. (2002, 2004) published an update with mortality data through 1999, and Sullivan (2007) updated the National Institute of Occupational Safety and Health (NIOSH) cohort (referred to in this document as the Libby worker cohort) with mortality data through 2001. Additionally, Larson et al. (2010a) reconstructed a worker cohort and analyzed mortality through 2006 in this same study population, while another study examined changes in lung abnormalities using x-rays taken between 1955 and 2004 of 88 workers (Larson et al., 2010b).

4.1.1.1. *Description of Mining and Milling Operations*

The vermiculite mining and milling operations have been described in considerable detail (ATSDR, 2000). An open-pit vermiculite mine began limited operations in 1923, and production increased rapidly between 1940 and 1950. This mine is located on Zonolite Mountain, several miles east of the town of Libby (ATSDR, 2000). The Kootenai River runs between the town and the mine. The mining and milling operations continued until 1990 (ATSDR, 2000).

The drilling and blasting procedures used in the strip mining operations generated considerable dust exposures, although the mining operations had lower intensity exposures compared to the milling operations. Amandus et al. (1987a) 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 use a screening or sifting procedure to separate vermiculite flakes from other particles and increase the concentration of vermiculite 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 conditions in the dry mill was the installation of a ventilation fan in 1964. Exposure to asbestos 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 away from the shop area around the mill. 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 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 concentrate was constructed at the loading dock near the river. Two processing plants operated within the town of Libby (ATSDR, 2001). These expansion or exfoliation plants heated the ore concentrate, resulting in additional release of the Libby Amphibole asbestos fibers in the area.

4.1.1.2. *Exposure Estimation*

In the early 1980s, two research groups conducted parallel studies of the mortality experienced by workers in the Libby mining and milling operations. One study was undertaken by NIOSH, and the other by researchers from McGill University. The exposure assessment procedures used by the two groups relied on the same exposure measurements and used similar assumptions in creating exposure estimates for specific job activities and time periods (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. Varying job codes and air exposures were used for different time periods as appropriate to describe plant operations. Individual exposure metrics (e.g., lifetime cumulative exposure) were calculated using the work history of each individual in the study in conjunction with the plant job exposure matrix. The specific study details for the Libby, MT worker cohort are described in more detail below, with differences between the research groups highlighted.

Before 1970, exposure estimates were based on midget impinger samples taken primarily in the dry mill, by state and federal inspectors. Total dust samples were measured as million particles per cubic foot (mppcf) by the midget impinger method. Amandus et al. (1987a) describe the period during which most of the midget impinger measurements were made as 1962–1967, and McDonald et al. (1986a) describe this period as 1962–1969, with a few additional measures in earlier years.[1] The number of samples available before 1970 was 336 (Amandus et al., 1987a). Membrane-filter air samples for fibers, taken at various locations within the operations, began in 1967, and data are available from company records as well as State and Federal Agencies (Table 4-2). Stationary and short-term (i.e., 20-minute to less than 4-hour) measurements were primarily used prior to 1974. The number of membrane-filter samples available was 4,116. Air samples collected through membrane filters were analyzed by

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

Table 4-1. Exposure assessment methodologies used in evaluations of Libby, MT and Marysville, OH worker cohorts

Operation and study cohort	Asbestos fiber quantification and job exposure classification	Studies using methodology
Libby, MT mining and milling operations; NIOSH cohort	Exposure based on phase-contrast microscopy of fibers >5-μm long and aspect ratio >3:1 (1967-1982), and midget impinger data (1956-1969). Samples assigned to 25 "occupation locations" to estimate exposures for specific jobs and time periods 1945–1982. Membrane-filter measurement to impinger conversion ratio: 4.0 f/cc per mppcf.	Amandus et al., 1987a, b; Amandus and Wheeler, 1987
Libby, MT mining and milling operations; NIOSH cohort	Modification to Amandus et al. (1987a) job classification: laborers and "unknown" jobs assigned weighted-average exposure for all unskilled jobs in work area (if known) during calendar time period, rather than lower mill yard exposure. Weights based on the number of workers assigned to unskilled jobs during same calendar time period.	Sullivan, 2007; Moolgavkar et al., 2010
Libby, MT mining and milling operations; ATSDR cohort assembled from NIOSH records	Extension of Amandus et al. (1987a) exposure data, with additional application of exposure estimates to job titles from early 1980s through 1993	Larson et al., 2010a, b
Libby, MT mining and milling operations; McGill University cohort	Similar to Amandus (1987a), except with 28 "occupation locations," and conversion ratio = 4.6 for dry mill pre- and post 1964.	McDonald et al., 2004, 1986a, b
Marysville, OH fertilizer production facility using Libby, MT vermiculite	Plant operated since 1957; Libby, MT vermiculite ore used in the plant 1963–1980.[a] Industrial hygiene monitoring began 1972 (based on fibers >5-μm long, diameter <3 μm, ≥aspect ratio 3:1). Breathing zone samples used after 1976. Fiber analysis by PCM.	Lockey et al., 1984; Rohs et al., 2008

[a]Rohs et al. (2008) use 1963 as the beginning date of the use of Libby, MT vermiculite at the Marysville, OH plant, citing the Agency for Toxic Substances and Disease Registry (ATSDR) Health Consultation document (ATSDR, 2005). That document cites personal communication with company personnel as a source for a start date of 1967, however. Another ATSDR document, a review of 28 vermiculite exfoliation plants, reported the likely period of use was 1963–1980 (ATSDR, 2008). Lockey et al. (1984) used 1957 as the beginning date. Additional information was used to conclude that the beginning date for use of Libby vermiculite ore was 1959 (Appendix F)
NIOSH = National Institute for Occupational Safety and Health.

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

Source	Unit of measurement	Years	Number of samples
State of Montana	mppcf[a]	1956-1969[b]	336
NIOSH	f/cc[c]	1967-1968	48
MESA/MSHA	f/cc	1971-1981	789
Company records	f/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]MESA: U.S. Mining and Enforcement and Safety Administration (former name of MSHA).
[c]Fibers per cc of air drawn through a filter and examined under a phased contrast light microscope. Objects >5 µ and with an aspect ratio >3 were reported as fibers (see Section 2 for details).
[d]MSHA: U.S. Mining and Safety Administration.

Source: Amandus et al. (1987a).

phased contrast microscopy (PCM), which visually counts fibers greater than >5-µm long and having an aspect ratio >3:1 (Amandus et al., 1987a). PCM methods from the 1960s allowed reliable characterization of fibers with widths greater than approximately 0.4 µm (Skikne, 1980; Amandus et al., 1987a). Further standardization of the PCM method provides better visualization of thinner fibers, and 0.25-µm width is considered the resolution for fiber width (WHO, 1986).

The samples taken from specific work locations within the plant were used to estimate exposures in specific jobs and time periods, based on professional consideration of temporal changes in facilities, equipment, and job activities. The analysis by McDonald et al. (1986a) was based on 28 occupation locations, while the work of Amandus et al. (1987a) was based on 25 occupation locations. For the years after 1968, data from filter samples were available for all locations, and NIOSH researchers used the average (arithmetic mean) exposure when more than one sample was available for a given location or job task and time period. McDonald et al. (1986a) used an alternative procedure described by Oldham (1965) to estimate the mean of log-normal distributions.

For exposures occurring prior to 1968, both research groups estimated exposures for all location operations[2] except the dry mill based on post-1968 PCM air sampling results and

[2] Location Operations were defined by the respective research groups to categorize tasks and locations across the mining milling and shipping operations. The intention of the location operations is to group like tasks, with respect to exposure potential, for evaluation. Both research groups established similar location operations for the Libby cohort.

reasonable assumption regarding historical exposures. McDonald et al. (1986) estimated pre-1968 exposure measurements for 26 LOs; assumptions were made and estimates based on data from later years or related operations, although these assumptions are not stated by the authors. McDonald et al. (1986) did recognize the uncertainty in these calculations, and for four areas, provided high and low estimates (drilling, ore loading, river dock, and bagging plant). Similarly, NIOSH researchers interviewed company employees, considered relative exposure levels between locations post 1968, employing best available judgment to estimate task specific exposure levels. Amandus et al. (1987a) expanded the procedures described in McDonald et al. (1986a, 1987a) and used various assumptions to estimate pre-1968 exposures for four location operations (drilling, ore loading, river dock, and bagging plant). "Low" and "high" estimates were generated using different assumptions; the detailed results for the various assumptions were not presented, but the differences between them were described by the authors as "slight," and the results presented were based on the high estimate of exposure. Their decisions and specific assumptions are detailed (Amandus et al., 1987a). The authors acknowledge there is uncertainty in exposure estimates prior to 1968 for many of these locations. They do note that variability in sample results for the midget impinger was low and that, in general, sample variability was low for fiber air sampling results for areas where the greatest numbers of employees worked (mill, service area, loading and bagging.)

To estimate dry mill exposures prior to 1967, when fiber counts from phase contrast microscopy air samples began to be used to measure exposures, Amandus et al. (1987a) established a conversion factor from total dust counts (mmpcf) to fiber counts (fibers/cc). The conversion ratio was based on a comparison of 336 impinger samples taken in 1965–1969 and 81 filter samples taken in 1967–1971. Both sets of samples were taken in the dry mill. Using different subsets of the samples (i.e., different years) resulted in ratios that ranged from 1.9 fibers/cc:1.0 mppcf to 11.5 fibers/cc:1.0 mppcf. The ratio based on the average fiber counts from air samples (1967-1971) to the average total dust measurements in sample years 1965-1969 was 4.0 fibers/cc:1.0 mppcf. This was the ratio used in the analyses in the NIOSH studies (Amandus et al., 1987a, b; Amandus and Wheeler, 1987) 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 count based on phase contrast microscopy but not midget impinger data were available. This dust–to-fiber conversion factor was only used to estimate exposures in the dry mill. The resulting exposure concentrations of 168 f/cc in 1963 and all prior years and 35.9 fibers/cc in 1964-1967 were applied to dry mill exposures (Amandus et al., 1987a).

McDonald et al. (1986a) used a different procedure, based on the estimated reduction in dust exposure with the installation of the ventilation system in 1964. Rather than develop a direct dust-to-fiber conversion factor, they observed that total dust levels dropped approximately 4.6-fold after the installation of ventilation in the dry mill. Therefore, exposures in the dry mill prior to 1965 were 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).

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

4.1.1.2.1. Characteristics of historical fiber exposures

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

Transmission electron microscopy[3] (TEM) analysis of airborne asbestos fibers indicated a range of fiber morphologies—including long fibers with parallel sides, needlelike fibers, and curved fibers (McDonald et al., 1986a). Of the fibers examined by TEM, >62% were >5 um in length and a wide range of dimensional characteristic were noted: length (1-70 um), width (0.1-2 um), and aspect ratios from 3-100. Energy dispersive spectroscopy was used to determine the mineral analysis indicated fibers that would be in the actinolite-tremolite solution series, but sodium rich (McDonald et al., 1986a). This analysis is consistent with the current understanding of amphibole asbestos found in the Libby mine (Section 2).

At the time of their study, when exposure concentrations were reduced to generally less than 1 f/cc, NIOSH researchers obtained eight air filters from area air samples collected in the

[3] Transmission electron microscopy (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: energy dispersive spectroscopy (EDS) and selected area electron diffraction (SAED).

new wet mill and screening plant (provided by the mining company). These samples were analyzed by phased contrast microscopy using the appropriate analytical method for the time (NIOSH Physical and Chemical Analytical Method No. 239). From early method development through current PCM analytical techniques, the PHS, OSHA, and NIOSH methods have defined a fiber by PCM analysis as having an aspect ratio greater than 3:1 (Edwards and Lynch, 1967; NIOSH method 7400). NIOSH reported the dimensional characteristics of the fibers from these filters including aspect ratio, width, and length (Table 4-3) (Amandus et al.,1987a). Data for 599 fibers from the 8 area air samples collected in the wet mill and screening plant are provided. These data are limited in one sense by the minimum diameter and length cutoffs (>4.98-µm long, >0.44-µm wide, aspect ratio >3.0). Even with these limitations, where thinner fibers are not viewed, 96% of the fibers had aspect ratios greater than 10:1, with 16% greater than 50:1 aspect ratio. Only 7% of the fibers had a width greater than 0.88 um, with one fiber reported of the 559 with a width greater than 1.76. It should be noted that as NIOSH was examining PCM visible fibers, these data do not give the full fiber-size distribution of Libby amphibole asbestos fibers (Section 2.2.3.3.)

Table 4-3. Dimensional characteristic of fibers from air samples collected in the vermiculite mill and screening plant, Libby, MT. Fibers were viewed and counted by Phase Contract Microscopy (PCM)

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

Source: Amandus et al. (1987a).

4.1.1.2.2. Descriptions of cohorts

The cohort studies conducted in the 1980s were similar in terms of exposure assessment (as described in the previous section, Table 4-1), and other aspects of the study design (Table 4-4). 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. McDonald et al. (1986a) included men hired before 1963 (n = 406) with follow-up through 1983. A later analysis (McDonald et al., 2004) extended this follow-up through 1999. A more recent analysis of the Libby, MT workers expanded the cohort to include all workers hired prior to 1970, regardless of duration of employment. 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 in Table 4-4. Analyses presented in the report were based on follow-up from 1960–2001. This beginning point was chosen because comparison rates for asbestosis, an outcome of interest, were not available before 1960 in the NIOSH Life Table Analysis System, the analytic software used in the analysis (Sullivan, 2007). Few deaths had occurred before 1960 (95 men dead or lost to follow-up before 1960 were excluded), so this exclusion criterion would not be expected to result in a substantial loss of outcomes. Because mesothelioma was not coded separately until 1999, the published mesothelioma analysis is based on data from 1999–2001.

In the study by Sullivan (2007), comparison rates for standardized mortality ratio (SMR) analyses were calculated from U.S. population cause-specific mortality data, limited to white males, and adjusted for age and calendar year of follow-up (using 5-year groups). McDonald et al. (2002) also used comparison rates from the U.S. population and included additional analyses for the category of respiratory cancers using Montana population rates.

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

The studies of the Libby worker cohort by Amandus and Wheeler (1987), Sullivan (2007), and Larson et al. (2010a) defined lung cancer mortality based on a more limited range of diagnostic codes compared to the broader classification of "all respiratory cancer" used by McDonald et al. (1986a, 2004). For example, the International Classification of Diseases (ICD)-

9 codes used for deaths occurring during the applicable years (1979 to 1999) in the NIOSH cohort in Sullivan (2007) were ICD-9 162 (trachea, bronchus, and lung) and 163 (pleura); ICD-10 codes C33-C34 were used for deaths in 2000 or later. In the first McDonald et al. (1986a) analysis, ICD-9 codes 160–163 for respiratory cancer were used, which also included cancer of the larynx (ICD-9 code 161) and some types of "other" respiratory cancers (ICD-9 code 160). The updated follow-up for 1999 included ICD-9 codes 160–165 for respiratory cancer, adding to the "other" respiratory cancer group (ICD-9 codes 164 and 165). In the national Surveillance, Epidemiology, and End Results (SEER) cancer data from 2001–2005, the age-adjusted incidence rate for cancer of the larynx was 3.6, compared to 63.9 per 100,000 person-years for lung and bronchial cancer (NCI, 2009). Thus, these additional categories (larynx and "other" respiratory cancers) represent a relatively small proportion of respiratory cancers, but could be a source of some misclassification of the outcome if these other cancers are not related to asbestos exposure.

The classification of mesothelioma was more difficult because of the lack of a unique ICD code for mesothelioma prior to the 10^{th} revision, implemented in the United States in 1999. The updated NIOSH study by Sullivan (2007) identified 15 deaths for which mesothelioma was mentioned on the death certificate. Only two of these deaths occurred between 1999 and 2001; these were coded using the ICD-10 mesothelioma coding (C45). Larson et al. (2010) classified any death certificate listing mesothelioma as an immediate or underlying cause of death as ICD-10 code C45. The updated McGill study (McDonald et al., 2004) also noted that the classification of mesothelioma was based on a nosologist's review of death certificates; only 5 of the 12 cases classified as mesothelioma had a cause of death listed as pleural cancer (ICD-9 code 163).

Table 4-4. Respiratory cancer mortality and lung cancer dose-response analyses based on studies of the vermiculite mine workers in Libby, MT[a]

Reference(s)	Inclusion criteria and design details	Standardized mortality ratio (SMR) (95% CI)	Dose-response analyses – lung cancer
Amandus and Wheeler, 1987	Men, hired before 1970, worked at least one year, follow-up through 1982 (n = 575); 161 deaths (159 with death certificates). Mean duration: 8.3 years (0 worked less than 1 year). Mean fiber-years: 200.3. 12 female workers not included in this analysis.	*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 years 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-yrs / 6 / 1.5 (not reported) 50–99 fibers/cc-yrs / 2 / 1.6 (not reported) 100–399 fibers/cc-yrs / 2 / 1.1 (not reported) ≥400 fibers/cc-yrs / 10 / 5.8 (not reported, but $p < 0.01$) *20 or more years since first hire (20-year latency)* Cumulative Exposure / n / SMR (95% CI)[b] 0.0–49 fibers/cc-yrs / 2 / 0.85 (not reported) 50–99 fibers/cc-yrs / 2 / 2.3 (not reported) 100–399 fibers/cc-yrs / 1 / 1.1 (not reported) ≥400 fibers/cc-yrs / 7 / 6.7 (not reported, but $p < 0.01$) In a linear regression analysis of data with at least 20 years latency, the results per fiber-year were: beta (standard error) = 0.60 (0.13) and 0.58 (0.08) for threshold and nonthreshold models. Using a survival (Cox) model, the corresponding estimate is 0.11 (0.04). All estimates are statistically significant ($p < 0.05$).
McDonald et al. 2004; McDonald et al., 1986a	Men, hired before 1963, worked at least one year (n = 406); follow-up through – 1999 (McDonald et al., 2004); 165 deaths before July 1983 (163 with death certificates); 120 deaths July 1983–1999; cause of death from National Death Index. Mean duration: 8.7 years (0 worked less than 1 year). Mean fiber-years: 144.6.	Respiratory (n = 44) SMR: 2.4 (1.7, 3.2) Mesothelioma (n = 12) 4.2% of deaths were from mesothelioma	*Excluding first 10 years of follow-up:* Cumulative Exposure / n / RR (95% CI)[d] 0.0–11.6 fibers/cc-yrs / 5 / 1.0 (referent) 11.7–25.1 fibers/cc-yrs / 9 / 1.7 (0.58, 5.2) 25.2–113.7 fibers/cc-yrs / 10 / 1.9 (0.63, 5.5) ≥113.8 fibers/cc-yrs / 16 / 3.2 (1.2, 8.8) per 100 fibers/cc-yrs / – / 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.

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

Reference(s)	Inclusion criteria and design details	Standardized mortality ratio (SMR) (95% CI)	*Dose-response analyses – lung cancer*
Sullivan, 2007	White men, enumerated in 1982, alive in 1960 or hired after 1960, worked at least one day, follow-up 1960–2001 (n = 1,672); 767 deaths (95% with known cause of death). Mean duration: 4.0 years (808, ~50% worked less than 1 year). Median fibers/cc-years: 8.7. Underlying cause of death data from death certificates or National Death Index-Plus.	*15 year exposure lag:* All cancer (n = 202) SMR: 1.4 (1.2, 1.6) Lung (n = 89) SMR: 1.7 (1.4, 2.1) Mesothelioma (n = 2, 1999–2001) SMR: 15.1 (1.8, 54.4) Pleural (n = 4) SMR: 23.3 (6.3, 59.5)	*15 year exposure lag:* Cumulative Exposure / n / SMR (95% CI)[b] / SRR (95% CI)[c] 0.0–4.49 fibers/cc-yrs / 19 / 1.5 (0.9, 2.3) / 1.0 (referent) 4.5–22.9 fibers/cc-yrs / 24 / 1.6 (1.1, 2.5) / 1.1 (0.6, 2.0) 23.0–99.0 fibers/cc-yrs / 23 / 1.8 (1.1, 2.7) / 1.4 (0.7, 2.7) ≥100 fibers/cc-yrs / 23 / 1.9 (1.2, 2.9) / 1.5 (0.8, 2.8) Duration / n / SMR (95% CI)[b] / SRR (95% CI)[c] <1 year / 41 / 1.6 (1.1, 2.1) / 1.0 (referent) 1–9.9 years / 34 / 1.7 (1.1, 2.3) / 1.1 (0.7, 1.8) ≥10 years / 14 / 2.5 (1.4, 4.3) / 1.8 (0.9, 3.4)
Larson et al. (2010b)	Inclusion criteria not described (n = 1,862); 952 deaths (80% with known cause of death). Median duration: 0.8 years; Median fibers/cc-yr = 4.3. Immediate and underlying cause of death data (i.e., multiple cause of death) from death certificates or National Death Index-Plus.	Lung (n=104) SMR:1.6 (1.3, 2.0)	*20 year exposure lag:* Cumulative Exposure / n / SMR (95% CI)[b] / RR (95% CI)[e] 0.0–<1.4 fibers/cc-yrs / 19 / (not reported) / 1.0 (referent) 1.4 to < 8.6 fibers/cc-yrs / 20 / (not reported)) / 1.1 (0.6, 2.1) 8.6 to < 44.0 fibers/cc-yrs / 21 / (not reported) / 1.7 (1.0, 3.0) ≥ 44.0 fibers/cc-yrs / 38 / (not reported) / 3.2 (1.8, 5.3)

[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-years for the observed cohort across all duration (or cumulative level of exposure) categories. The Life Table Analysis System provides the SRR for each duration (or cumulative level of exposure) group compared to the referent group. The cutoff points for the categories must be specified by the user (e.g., 0–100 ppm-years might define the referent group, 100–200 ppm-years might define the next group). 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.

4.1.1.3. *Cancer Mortality Risk*

4.1.1.3.1. Lung cancer

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

The analysis of McDonald et al. (2004) is limited to 406 male workers who were hired before 1963 and who were employed for at least 1 year. The mean duration of work was 8.7 years. Cause of death data were obtained from the National Death Index, with expected rates based on age-, race- and sex- specific rates. A total of 44 deaths due to respiratory cancers were observed, for an SMR = 2.4 (95% confidence interval [CI] = 1.7, 3.2). A pattern of increasing mortality with increasing cumulative exposure was seen, with relative risks of 1.0 (referent), 1.7, 1.9, and 3.2 in categories of 0.0–11.6, 11.7–25, 25.2–113.7, and ≥113.8 fibers/cc-yrs, respectively (Table 4-4). The estimated linear increase in RR of respiratory cancer risk per 100 fibers/cc-years cumulative exposure was 0.36 (95% CI = 0.03, 1.2) (p = 0.02). McDonald et al. (2004) reported that similar results were obtained with measures of exposure intensity and measures of residence-weighted exposure, but the data were not presented in the paper.

Sullivan (2007) included 1,672 white male workers who were alive in 1960 or hired after 1960. There was no minimum duration of employment required for inclusion in this analysis, and approximately 50% of the cohort (n = 808) had worked less than 1 year. Mortality follow-up was conducted through 2001, with 767 identified deaths. The exposure assessment protocol was based on that described by Amandus et al. (1987a), with a modification to the estimated intensity of exposure to laborers and to those with "unknown" jobs. Sullivan (2007) assigned weighted-average exposure for all unskilled jobs in work area (if known) during a calendar time period, rather than lower mill yard exposure used by Amandus et al. (1987a). The weights are based on the number of workers assigned to unskilled jobs during the same calendar time period. In the Sullivan (2007) follow-up, SMRs, using underlying cause-of-death data (based on death certificates) obtained through the National Death Index and from individual States, and expected mortality based on national age-, race-, and sex-specific rates, were calculated. Using a 15-year exposure lag, SMRs were increased for lung cancer (n = 89, SMR = 1.7, 95% CI = 1.4, 2.1) and for all cancer mortality (n = 202, SMR = 1.4, 95% CI = 1.2, 1.6) (Table 4-4). Additionally, an

internal referent group was used for analyses of risk in relation to cumulative exposure and duration. The results of these internal analyses are presented as standardized relative risks (SRR) for white men, controlling for age group. Increasing risks across categories of cumulative exposure and duration were observed with both types of analyses, indicating a positive exposure-response relationship. The SMR estimates for lung cancer mortality were 1.5, 1.6, 1.8, and 1.9 in the 1- to 4.49-, 4.5- to 22.9-, 23.0- to 99.0-, and ≥100 fibers/cc-year exposure categories, respectively. The SRR estimates were 1.0, 1.1., 1.4, and 1.5, respectively, across these same exposure categories (Table 4-4). For comparison to the earlier work by McDonald et al. (1986a), an SMR was provided for all respiratory cancer in those employed at least 1 year (SMR 2.0 {1.5-2.5}). For the full cohort employed at least 1 day, the SMR for all respiratory cancer was 1.7 {1.4-2.1} (Sullivan, 2007).

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

Smoking patterns in the U.S. population changed considerably over the period corresponding to the data reported by Amandus and Wheeler (1987). In the National Health Interview Surveys conducted between 1974 and 1983, the prevalence of smoking in males age 20 and older decreased from 42.1 to 35.5% (DHHS, 1989, p.269). In addition, the prevalence of former smokers can depend on the definition used. Based on 1986 survey data, the percentage of adults age 17 and older classified as former smokers varied between 14.7 and 25.8% using different definitions for time since last smoked (e.g., from quitting 5 or more years ago to quitting within the past 3 months) (DHHS, 1989). Thus given the lack of information pertaining to the period in which smoking information was collected and the specifics of the

questions that were used, EPA concludes there is considerable uncertainty regarding the evidence for differences in smoking rates between the workers and a comparison population.

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

4.1.1.3.2. Mesothelioma

McDonald et al. (2004) presented dose-response modeling of mesothelioma risk based on 12 cases. Using Poisson regression, the mesothelioma mortality rate across increasing categories of exposure was compared to the rate in the lowest exposure category. Note that the referent group was also at excess risk of dying from mesothelioma; that is, one to three cases of mesothelioma were observed in the referent group, depending on the exposure index. Three exposure indices were used in analysis: average intensity over the first 5 years of employment, cumulative exposure, and residence-weighted cumulative exposure. Because of the requirement for 5 years of employment data, 199 individuals (including 3 mesothelioma cases) were excluded from the analysis of average intensity. The residence-weighted cumulative exposure was based on the summation of exposure by year, weighted by years since the exposure. This metric gives greater weight to exposures that occurred a longer time ago. Although all exposure groups were clearly at excess risk of dying from mesothelioma, there was little evidence of increasing RR with increasing average intensity or cumulative exposure. For the cumulative exposure metric, the RR estimates were 1.0 (referent), 3.72, 3.42, and 3.68 based on 1, 4, 3, and 4, cases, respectively. The mean exposure levels in these four quartiles were 8.6, 16.7, 53.2, and 393.8 fibers/cc-years, respectively. Evidence of an exposure-response relationship was greater for residence-weighted cumulative exposure, with an RR of 1.57 reported among those with

500.1–1826.8 fibers/cc-yrs exposure, and an RR of 1.95 among workers with higher residence-weighted cumulative exposure.

Sullivan (2007) identified 15 deaths from mesothelioma through a manual review of death certificates, with 14 classified as "pleural or unspecified," and 1 classified as "peritoneal." Only two of these deaths occurred between 1999 and 2001, the period for which comparison data using the ICD-10 classification criteria were available. Based on these two mesothelioma deaths, the SMR was 14.1 (95% CI = 1.8, 54.4).

Larson et al. (2010b) identified 19 mesothelioma deaths (coding any mention of mesothelioma on the death certificate as the ICD-10 classification of C45). Comparison data were based on multiple causes of death data (1960 to 2002). The SMR for mesothelioma was 94.8 (95% CI 57.0, 148.0). However, since the ICD-10 coding scheme was not used before 2000, reference rates based on data from 2000 to 2006, used with observations of mesothelioma cases from 1960 to 2006, could result in an upwardly biased SMR if the true but unobserved reference rates for mesothelioma during the same time period as the deaths (1960-2006) were higher than from 2000-2006. An increase was seen across the quartiles of exposure in the analysis using an internal referent group and a 20-yr lag period, with RR of 1.0 (referent) in the <1.4 fibers/cc-yr group, 1.9 (95% CI: 0.3, 13.6) in the 1.4 to <8.6 fibers/cc-yr group, 4.5 (95% CI 0.8, 24.6) in the 8.6 to < 44.0 group, and 17.1 (95% CI 3.7, 78.1) in the ≥44.0 fibers/cc-yr group.

4.1.1.3.3. Other cancers

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

4.1.1.3.4. Summary of cancer mortality risk in Libby, MT vermiculite mining operation workers

The studies conducted in the 1980s (Amandus and Wheeler, 1987; McDonald et al., 1986a) as well as the extended follow-up studies published in more recent years (Sullivan et al., 2007; McDonald et al., 2004; Larson et al., 2010) provide clear evidence of an increased risk of lung cancer mortality and of mesothelioma mortality among the workers in the Libby vermiculite mining and processing operations. An increasing risk with increasing exposure is seen. A plateauing of the increased risk may be seen, depending on the cut-point used to examine risk in

the highest exposure groups (Sullivan, 2007; Larson et al., 2010). This type of pattern is commonly seen in occupational cohort mortality studies (Stayner et al., 2003).

4.1.1.4. *Noncancer Effects*

4.1.1.4.1. Asbestosis and other non-malignant respiratory disease mortality

The studies described previously also reported noncancer mortality data, with a specific focus on respiratory diseases (Table 4-5). In Sullivan (2007), the SMR for asbestosis (ICD-9 code 501) was 166 (based on n = 22, underlying cause of death compared to a U.S. white male referent group). In Larson et al. (2010a), the SMR (based on 69 observed asbestosis-related deaths using multiple-causes-of-death data) was 143 (95% CI 111, 181). Increasing cumulative exposure was observed to increase the risk for asbestosis mortality in both of these analyses (Table 4-5). A two- to three-fold increase was also seen for other categories of nonmalignant respiratory disease in Larson et al. (2010), with an SMR of 2.4 (95% CI 2.2, 2.6) for all non-malignant respiratory disease, and SMR = 2.8 (95% CI 2.3, 3.4) for diseases other than asbestosis, chronic obstructive pulmonary disease, and silicosis. These results are similar to the nonmalignant respiratory disease mortality data from studies of this cohort using underlying cause-of-death data. A markedly higher risk of nonmalignant respiratory disease mortality was also observed in the cumulative exposure category of ≥300 or ≥400 fibers/cc-years in Sullivan (2007) (Table 4-5). Larson et al. (2010) used a Monte Carlo simulation to estimate the potential bias in non-malignant 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 ($RR_{unadjusted}/RR_{adjusted}$ = 1.2) reduced the overall RR estimate from 2.1 to 1.8.

Table 4-5. Non-malignant respiratory mortality studies of the vermiculite mine workers in Libby, MT[a]

Reference(s)	Respiratory disease (SMR, 95% CI)	Dose-response analyses: Nonmalignant respiratory diseases and asbestosis
Amandus and Wheeler, 1987 (NIOSH)	*No exclusions:* Non-malignant respiratory diseases (n = 20) SMR: 2.4 (1.5, 3.8) *20 year latency:* Non-malignant respiratory diseases (n = 12) SMR: 2.5 ($p < 0.05$)	*No exclusions*: Non-malignant respiratory diseases Cumulative Exposure — n — SMR (95%CI)[b] 0.0–49 fibers/cc-yrs — 8 — 2.2 (not reported) 50–99 fibers/cc-yrs — 2 — 1.7 (not reported) 100–399 fibers/cc-yrs — 3 — 1.8 (not reported) ≥400 fibers/cc-yrs — 10 — 4.0 (not reported, but $p < 0.01$) *20 or more years since first hire (latency)*: Non-malignant respiratory diseases Cumulative Exposure — n — SMR (95%CI)[b] 0.0–49 fibers/cc-yrs — 7 — 3.3 (not reported, but $p < 0.05$) 50–99 fibers/cc-yrs — 2 — 2.8 (not reported) 100–399 fibers/cc-yrs — 0 — 0 (not reported)

Reference(s)	Respiratory disease (SMR, 95% CI)	Dose-response analyses: Nonmalignant respiratory diseases and asbestosis
		≥400 fibers/cc-yrs 3 2.8 (not reported)
McDonald et al. 2004; McDonald et al., 1986a (McGill)	Non-malignant respiratory diseases (n = 51) SMR: 3.1 (2.3, 4.1)	*Excluding first 10 years of follow-up*: Non-malignant respiratory diseases Cumulative Exposure — n — RR (95%CI)[d] 0.0–11.6 fibers/cc-yrs — 5 — 1.0 (referent) 11.7–25.1 fibers/cc-yrs — 13 — 2.5 (0.88, 7.2) 25.2–113.7 fibers/cc-yrs — 14 — 2.6 (0.93, 7.3) ≥113.8 fibers/cc-yrs — 19 — 3.1 (1.2, 8.4) per 100 fibers/cc-yrs — – — 0.38 (0.12, 0.96) (p = 0.0001)
Sullivan, 2007 (NIOSH)	*15 year exposure lag:* Asbestosis (n = 22) SMR: 166 (104, 251) Non-malignant 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 non-malignant respiratory diseases (n = 19) SMR: 2.7 (1.6, 4.2)	*15 year exposure lag:* Asbestosis Cumulative Exposure — n — SMR (95% CI)[b] — SRR (95% CI)[c] 0.0–49.9 fibers/cc-yrs — 3 — 37 (7.5, 122) — 1.0 (referent) 50.0–249.9 fibers/cc-yrs — 8 — 213 (91.6, 433) — 7.3 (1.9, 28.5) ≥250 fibers/cc-yrs — 11 — 749 (373, 1368) — 25.3 (6.6, 96.3) *15 year exposure lag*: Non-malignant respiratory diseases Cumulative Exposure — n — SMR (95%CI)[b] — SRR (95% CI)[c] 0.0–4.49 fibers/cc-yrs — 18 — 1.8 (1.1, 2.8) — 1.0 (referent) 4.5–19.9 fibers/cc-yrs — 24 — 2.0 (1.3, 3.0) — 1.2 (0.6, 2.3) 20.0–84.9 fibers/cc-yrs — 26 — 2.2 (1.5, 3.3) — 1.5 (0.8, 2.9) 85.0–299.9 fibers/cc-yrs — 20 — 2.6 (1.6, 4.0) — 1.4 (0.7, 2.7) ≥300 fibers/cc-yrs — 23 — 4.8 (3.1, 7.3) — 2.8 (1.3, 5.7)
Larson et al., 2010a	Asbestosis (n = 69) SMR: 143 (111, 181) Non-malignant 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 non-malignant respiratory (n = 120) SMR: 2.8 (2.3 3.4)	*20 year exposure lag:* Asbestosis Cumulative Exposure — n — SMR (95% CI)[b] — RR (95% CI)[e] < 1.4 fibers/cc-yrs — 4 — (not reported) — 1.0 (referent) 1.4–< 8.6 fibers/cc-yrs — 8 — (not reported) — 2.8 (1.0, 7.6) 86–<44.0 fibers/cc-yrs — 25 — (not reported) — 8.0 (3.2, 19.5) ≥44.0 fibers/cc-yrs — 32 — (not reported) — 11.8 (4.9, 28.7) *20 year exposure lag*: Non-malignant respiratory diseases Cumulative Exposure — n — SMR (95% CI)[b] — RR (95% CI)[e] < 1.4 fibers/cc-yrs — 43 — (not reported) — 1.0 (referent) 1.4–< 8.6 fibers/cc-yrs — 46 — (not reported) — 1.4 (0.9, 2.1) 86–<44.0 fibers/cc-yrs — 56 — (not reported) — 1.8 (1.3, 2.7) ≥44.0 fibers/cc-yrs — 58 — (not reported) — 2.5 (1.7, 3.6)

[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-years for the observed cohort across all duration (or cumulative level of exposure) categories. The Life Table Analysis System provides the SRR for each duration (or cumulative level of exposure) group compared to the referent group. The cutoff points for the categories must be specified by the user (e.g., 0–100 ppm-years might define the referent group, 100–200 ppm-years might define the next group). 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 internal referent group.

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

SMR = standardized mortality ratio, CI = confidence interval, SRR = standardized rate ratio, RR = relative risk.

4.1.1.4.2. Cardiovascular-related mortality

Larson et al. (2010) presents data on mortality due to cardiovascular diseases, with SMRs of 0.9 (95% CI 0.9, 1.0) seen for heart disease (n=552) and 1.4 (95% CI 1.2, 1.6) seen for circulatory system diseases (n=258). Deaths due to heart diseases were further categorized into ischemic heart disease (n=247) and other heart disease (n=120, for pericarditis, endocarditis, heart failure, and ill-defined descriptions and complications of heart disease), with SMRs of 0.7 (95% CI: 0.6, 0.8) and 1.5 (95% 1.2, 1.8), respectively. Circulatory diseases included hypertension without heart disease (n=42), with an SMR of 1.7 (95% CI 1.2, 2.4) and diseases of arteries, veins, or lymphatic vessels (n=136), SMR = 1.6 (95% CI 1.4, 2.0). The combined category of cardiovascular-related mortality resulted in modestly increased risks across quartiles of exposure, with RR of 1.0 (referent), 1.3 (95% CI: 1.0, 1.6), 1.3 (95% CI: 1.0, 1.6), and 1.5 (95% CI: 1.1, 2.0) with exposure groups of <1.4, 1.4 to <8.6, 8.6 to <44.0, and ≥44.0 fibers/cc-yrs, respectively. Larson et al. (2010) used a Monte Carlo simulation to estimate the potential bias in cardiovascular disease risk that could have been introduced by differences in smoking patterns between exposed and unexposed workers in the cohort. The bias-adjustment factor ($RR_{unadjusted}/RR_{adjusted}$ = 1.1) reduced the overall RR estimate from 1.6 to 1.5. Because Larson et al. (2010) analyzed multiple causes of death, the observed association between exposure and cardiovascular disease-related mortality may reflect, at least in part, a consequence of an underlying respiratory disease.

4.1.1.4.3. Radiographic anomalies

Respiratory disease risk is also evidenced by chest radiographs showing pleural thickening and anomalies in the Libby, MT worker cohorts (Table 4-6). Two of these studies were conducted in the 1980s and were based on x-rays of a subset of workers taken for either an annual workplace screening or as part of a study examination. The subset McDonald et al. (1986b) selected included 164 workers currently employed at the Libby facility, 80 former employees, and 47 area residents without known dust exposure. The subset selected by Amandus et al. (1987b) included workers with at least 5 years tenure who had worked at Libby at some time during 1975–1982. The most recent x-ray film for each worker, which NIOSH obtained from the Libby hospital that performed the screening, was read by three qualified readers using the International Labor Organization 1981 classification system. Consensus readings were used for pleural findings, while the median reading was used to determine the profusion category of small opacities. In the McDonald et al. (1986b) study, there was 90% agreement among readers that the chest x-rays contained evidence of pleural calcification and pleural thickening, and 80% agreement that there was evidence of small opacities, pleural plaques, and diffuse thickening. Amandus et al. (1987b)

provided a more detailed breakdown of the correspondence between categories for the rating of small opacities, and reported that the overall difference of 6% in the prevalence of opacities was similar to that seen in other studies. Other design details are described in Table 4-6.

Table 4-6. Pulmonary radiographic studies of the Libby, MT vermiculite mine workers

Reference(s)	Inclusion criteria and design details	Results
McDonald et al. (1986b)	Men employed on July 1, 1983 (n = 164). Former male employees living within 200 miles; hired before 1963 (n = 80), worked at least one year (80 participants from 110 eligible); 43 had a previous x-ray. Men without known dust exposure (n = 47); x-rays taken for other reasons (mostly employment related) at same place during study period; 24 had a previous x-ray. Data from 9 women employed on July 1, 1983 not included in this report.	Pleural thickening observed in 15.9% of current employees and 52.5% of past employees. Small opacities (≥1/0) observed in 9.1% of current employees and 37.5% of past employees. Both abnormalities increased with age. Age-adjusted and age-stratified (>60 years old) analyses showed increasing risk of both abnormalities with increasing cumulative exposure.
Amandus et al. (1987b)	Men, employed during 1975–1982 with at least 5 years tenure (n = 191); 184 with previous chest x-rays; 121 with smoking questionnaires. Annual radiographs taken since 1964; most recent radiograph evaluated. Mean employment duration: 14 years. Mean fiber-years: 123 (all workers), 119 (workers with radiographs).	Pleural thickening observed in 13% Small opacities (≥1/0) observed in 10%. Both abnormalities increased with increasing cumulative exposure.
Whitehouse (2004)	n = 123 (86 former employees of W.R. Grace, 27 family members of employees, and 10 Libby residents with only environmental exposures). Average age 66 years; 80% males. 56 patients had interstitial changes at profusion category 0/1 or 1/0. Chest x-rays and/or HRCT scans; pulmonary function tests (FVC, TLC, and DLCO).	Average yearly loss (n = 123): FVC 2.2% TLC 2.3% DLCO 3.0% Average yearly loss (n = 94 with worsening lung function): FVC 3.2% TLC 2.3% DLCO 3.3%
Larson et al. (2010b)	Men with 2 or more x-rays spanning a period of 4 or more years, with consensus reached by panel of 3 NIOSH B raters (n=84).	Latency (time from hire to observed change), median (25^{th}, 75^{th} percentile) yrs: Circumscribed pleural plaque 8.6 (1.4, 14.7) Any pleural calcification 17.5 (8.1, 24.2) Diffuse pleural thickening 27.0 (10.7, 29.8)

DLCO = single breath carbon monoxide diffusing capacity ; FVC = forced vital capacity; TLC = total lung capacity.

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

Both Amandus et al. (1987b) and McDonald (1986b) provided categorical exposure-response data as well as logistic models for various endpoints (e.g., small opacities, pleural calcification, pleural thickening). In McDonald et al. (1986b), the regression coefficient for cumulative exposure was 0.0024 per unit increase in cumulative exposure for the log odds of the presence of pleural thickening, adjusting for age and smoking. In the analysis of small opacities, the beta was 0.0035 per unit increase in cumulative exposure. Amandus et al. (1987b) reported similar results to those of McDonald et al. (1986b).

Whitehouse (2004) examined changes in pulmonary function measures in 123 patients seen in a pulmonary disease practice serving the Libby, MT area, with a mean follow-up time of 35 months. This study population included 86 former employees of W.R. Grace, 27 family members of employees, and 10 Libby residents with only environmental (i.e., non-occupational, non-family-related) exposures. The average age at the time of the first pulmonary study was 66 years, and 80% were male. Chest x-rays or high resolution computed tomography (HRCT) 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. Pulmonary function tests included forced vital capacity (FVC), total lung capacity (TLC), and the single breath carbon monoxide diffusing capacity (DLCO). The average yearly loss was 2.2% for FVC, 2.3% for TLC, and 3.0% for DLCO. The subset of 94 patients who experienced a loss of FVC was characterized as the group with worsening lung function. Among this group, the

average yearly loss was 3.2% for FVC, 2.3% for TLC, and 3.3% for DLCO. This decline was noted by the author to be greater than seen in other studies of asbestos-exposed patients.

Larson et al. (2010b) analyzed data from a subset of workers for whom pleural and/or parenchymal abnormalities were seen on the most recently available x-ray and who had one or more previous x-rays covering a span of at least 4 years available for comparison. Three NIOSH B readers reviewed each of the available x-rays in reverse chronological order to determine the latency (i.e., length of time between first exposure, as measured by date of hire and observed abnormality), and the degree of progression by type of lesion. Stored x-rays were found for 184 workers and 84 were included in the analysis. Exclusions were based on the following: 76 did not have at least one x-ray over the span of at least 4 years, 20 declined to participate, consensus classification was not reached for three, and one worker did not have any detectable abnormality. Circumscribed pleural plaque was seen in 83 of these 84 workers who were known to have had pleural and/or parenchymal abnormalities at a median latency of 8.6 years. Any pleural calcification was seen in 37 workers, with a median latency of 17.5 years, and diffuse pleural thickening was seen in 12 workers (median latency: 27.0 years). The latency period increased with increasing profusion categories, from a median of 18.9 years for ≥1/0, 33.3 years for progression to ≥2/1, and 36.9 years for progression to ≥3/2.

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

The risk of mortality related to asbestosis and other forms of non-malignant respiratory disease is elevated in the Libby vermiculite mining and processing operations, with increasing risk seen with increasing exposure in studies conducted in the 1980s (Amandus and Wheeler, 1987; McDonald et al., 1986a) and in the extended follow-up studies published in more recent years (Sullivan et al., 2007; McDonald et al., 2004; Larson et al., 2010). Radiographic evidence of pleural thickening and pleural plaques has also been shown in studies of Libby workers (McDonald et al., 1986b; Amandus et al., 1987b; Whitehouse, 2004; Larson et al., 2010b).

4.1.2. Libby, MT Community Studies

In addition to worker exposures, the operations of the Zonolite Mountain mine are believed to have resulted in both home exposures and community exposures. Potential pathways of exposure (discussed below) range from release of airborne fibers into the community, take-home exposure from mine workers (e.g., clothing), and recreational activities including gardening and childhood play activities. Due to a potential for a broader community concern,

ATSDR conducted several studies and health actions responding to potential asbestos contamination in the Libby, MT area.

4.1.2.1. *Geographic-Based Mortality Analysis*

ATSDR conducted a location-specific analysis of mortality risks and a community health screening for asbestos in the Libby area (Table 4-7). The mortality analysis was based on death certificate data from 1979–1998, with geocoding of current residence at time of death. The six geographic areas used in the analysis were defined as the Libby city limits (1.1 square miles around the downtown); the extended boundary of Libby (2.2 square miles around the downtown); the boundary based on air modeling (16 square miles, based on computer modeling of asbestos fiber distribution); the medical screening boundary (25 square miles, including the town of Libby and areas along the Kootenai River); the Libby valley (65 square miles); and central Lincoln County (314 square miles, based on a 10-mile radius around downtown Libby) (ATSDR, 2000).

The 1990 population estimates were 2,531, 3,694, 4,300, 6,072, 8,617, and 9,512, respectively, for these six areas. Age-standardized SMRs were calculated using underlying cause-of-death information obtained from death certificates issued during the study period for 413 of 419 identified decedents, and U.S. and Montana populations were used as reference groups. Increased SMRs were observed for both asbestosis and pulmonary circulation diseases (Table 4-7). The SMR for lung cancer ranged from 0.9–1.1 and 0.8–1.0 in the analyses for each of the six geographic boundaries using Montana and U.S. reference rates, respectively. In addition, four deaths due to mesothelioma were observed during the study period. These analyses did not distinguish between deaths among workers and deaths among other community members.

4.1.2.2. *Community Health Screening*

The ATSDR community health screening was conducted from July–November 2000 and July–September 2001 with 7,307 total participants (6,149 in the first phase) (ATSDR, 2001; (Table 4-8). Eligibility was based on residence, work, or other presence in Libby for at least 6 months before 1991. The total eligible population was not explicitly determined, but the participation rate was approximately 70% of 10,250 persons, which was the estimated population of Libby, MT, in 2000. In addition to a standardized interview regarding medical history, symptoms, work history, and other potential exposures, clinical tests included spirometry (forced expiratory volume in one second, FEV1, and forced vital capacity, FVC) and chest x-rays (for participants aged 18 years and older). Moderate to severe restriction (defined as FVC <70%

predicted value) was observed in 2.2% of the men and 1.6% of women but was not observed in individuals less than age 18.

Table 4-7. Cancer mortality and non-malignant respiratory disease mortality in the Libby, MT community

Reference(s)	Inclusion criteria and design details	Results
ATSDR, 2000	1979–1998, underlying cause of death from death certificates; geocoding of street locations (residence at time of death) within 6 geographic boundaries (ranging from 2,532 residents in Libby city limits to 9,521 in central Lincoln County in 1990). Inquiries to postmaster were required because of P.O. Box address for 8% (n = 32); information on 47 of 91 residents of elderly care facilities resulted in reclassification of 16 of 47 (34%) to non-residents of Libby. U.S. Census data corresponding to the same 6 geographic boundaries of Libby, MT. 419 decedents identified, 418 death certificates obtained, 413 with geocoding. Age-standardized SMRs based on Montana and U.S. comparison rates. Asbestosis SMRs were somewhat higher using the United States referent group, but choice of referent group had little difference on SMRs for most diseases. 4 deaths from mesothelioma observed in the study area.	Lung cancer (n = 82), SMR (95% CI) Comparison area (Montana reference rates): Libby city limits 1.1 (0.8, 1.5) Extended Libby boundary 1.1 (0.8, 1.5) Air modeling 1.0 (0.8, 1.4) Medical screening 0.9 (0.7, 1.2) Libby valley 0.9 (0.7, 1.2) Central Lincoln county 0.9 (0.7, 1.1) Pancreatic cancer (n = 10) Comparison area (Montana reference rates): Libby city limits 1.0 (0.5, 2.1) Extended Libby boundary 0.9 (0.4, 1.7) Air modeling 0.7 (0.3, 1.4) Medical screening 0.7 (0.3, 1.2) Libby valley 0.6 (0.3, 1.0) Central Lincoln county 0.5 (0.3, 1.0) Prostate cancer (n = 14) Comparison area (Montana reference rates): Libby city limits 0.8 (0.4, 1.5) Extended Libby boundary 0.8 (0.4, 1.5) Air modeling 0.7 (0.4, 1.2) Medical screening 0.6 (0.3, 1.1) Libby valley 0.6 (0.3, 1.0) Central Lincoln county 0.5 (0.3, 0.9) Asbestosis (n = 11) Comparison area (Montana reference rates): Libby city limits 40.8 (13.2, 95.3) Extended Libby boundary 47.3 (18.9, 97.5) Air modeling 44.3 (19.1, 87.2) Medical screening 40.6 (18.5, 77.1) Libby valley 38.7 (19.3, 69.2) Central Lincoln county 36.3 (18.1, 64.9) Comparison area (United States reference rates): Libby city limits 63.5 (20.5, 148) Extended Libby boundary 74.9 (30.0, 154) Air modeling 71.0 (30.6, 140) Medical screening 66.1 (30.2, 125) Libby valley 63.7 (31.7, 114) Central Lincoln county 59.8 (29.8, 107) Pulmonary circulation (n = 14) Comparison area (Montana reference rates): Libby city limits 2.3 (1.1, 4.4) Extended Libby boundary 1.9 (0.9, 3.7) Air modeling 1.8 (0.9, 3.3) Medical screening 1.6 (0.8, 2.9)

Reference(s)	Inclusion criteria and design details	Results
		Libby valley 1.6 (0.9, 2.7) Central Lincoln county 1.5 (0.8, 2.5)

Two board-certified radiologists (B readers) examined each radiograph, and a third reader was used in cases of disagreement. Readers were aware that the radiographs were from participants in the Libby, MT health screening but were not made aware of exposure histories and other characteristics (Peipins et al., 2003; Price, 2004; Peipins, 2004). The radiographs revealed pleural abnormalities in 17.9% of participants, with prevalence increasing with increasing number of "exposure pathways" (defined on the basis of potential work and residential exposure to asbestos within Libby and from other sources) (Table 4-8). Detailed results of an analysis excluding the former Libby workers cohort were not presented, but the authors noted that the relationship between number of exposure pathways and increasing prevalence of pleural anomalies was somewhat attenuated with this exclusion. The prevalence of pleural anomalies decreased from approximately 35% to 30% in individuals with 12 or more exposure pathways when these workers were excluded from the analysis. Among individuals with no definable exposure pathways, the prevalence of pleural anomalies was 6.7%, which is higher than reported in other population studies (Price, 2004; Peipins, 2004). No information is provided regarding analyses excluding all potential work-related asbestos exposures.

Table 4-8. Pulmonary radiographic, and other health studies in the Libby, MT community

Reference(s)	Inclusion criteria and design details	Results
Health screening and pulmonary radiographic changes		
Peipins et al., 2003; ATSDR, 2001	Resided, worked, attended school, or participated in other activities in Libby for at least 6 months before 1991 (including mine employees and contractors). Health screening between July and November 2000. Conducted interviews (n = 6,149, 60% of Libby residents based on 2000 Census data) and chest x-rays (n = 5,590, 18 years and older), and determined spirometry—forced expiratory volume in one second (FEV1), forced vital capacity (FVC1), and ratio (FEV1/FVC <70% = moderate to severe restriction). 19 "exposure pathways" included 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	Peipins (2003) and ATSDR (2001): Pleural abnormalities seen in 17.9% of participants; increasing prevalence with increasing number of exposure pathways (6.7% with no specific pathways, 34.6% with 12 or more pathways). ATSDR (2001): Moderate to severe FVC1 restriction (FVC <70% predicted): 2.2% men >17 years old; 1.6% women >17 years old; 0.0% men or women <18 years old.

Reference(s)	Inclusion criteria and design details	Results
	recreational use of vermiculite. Peipins et al. (2003) similar to ATSDR, 2001 except longer screening period (July–November 2000 and July–September 2001). Conducted interviews (n = 7,307) and chest x-rays (n = 6,668).	Also includes data on self-reported lung diseases and symptoms.
Vinikoor et al. (2010)	Same as above (ATSDR, 2001 and Peipins et al., 2003). Analysis limited to n=1,003 ages 10-29 years at time of health screening (≤ age 18 in 1990 when the mining/milling operations closed). Excluded if worked for W.R. Grace, or for a contractor of W.R. Grace, exposed to dust at other jobs, or expose to vermiculite at other jobs. Exposure characterized by 6 activities (never, sometimes, or frequently participated in 1-2 or ≥ 3 activities). Analysis of history of respiratory symptoms (usually have cough, coughed up bloody phlegm in past year, shortness of breath) and spirometry data (obstructive, restrictive or mixed).	Little difference across exposure levels in prevalence of physician-diagnosed lung disease or abnormal spirometry. Association (OR, 95% CI) seen between ≥ 3 activities and: Usual cough 2.93 (0.93, 9.25) Shortness of breath 1.32 (0.51, 3.42) Bloody phlegm 1.49 (0.41, 5.43)

Vinikoor et al. (2010) used the 2000–2001 health screening data to examine respiratory symptoms and spirometry results among 1,224 adolescents and young adults who were ≤ age 18 in 1990 when the mining/milling operations closed. At the time of the health screening, the ages in this group ranged from 10 to 29 years. Exclusion criteria for this analysis included previous work for W.R. Grace, work for a contractor of W.R. Grace, exposure to dust at other jobs, or exposure to vermiculite at other jobs. The total number of exclusions was 221, leaving 1,003 in the analysis. The potential for vermiculite exposure was classified based on responses to questions about six activities (handling vermiculite insulation, participation in recreational activities along the vermiculite-contaminated gravel road leading to the mine, playing at the ball fields near the expansion plant with large piles of vermiculite, playing in or around the vermiculite piles, heating the vermiculite, and other activities involving vermiculite). The medical history questionnaire included information on three respiratory symptoms and one diagnosis: usually have a cough (n = 108, 10.8%), are troubled by shortness of breath when walking up a slight hill or when hurrying on level ground (n = 145, 14.5%), have coughed up phlegm that was bloody in the past year (n = 59, 5.9%), and have a history of physician-diagnosed lung disease (n = 51, 5.1%). The spirometry results were classified as normal in 896 (90.5%), obstructive in 62 (6.3%), restrictive in 30 (3.0%), and mixed in 2 (0.2%). Information on smoking history was also collected in the questionnaire: 15.8% and 7.3% were classified as current and former smokers, respectively. Approximately half of the participants lived with someone who smoked. The analyses adjusted for age, sex, personal smoking history and living with a smoker. For usually having a cough, the ORs were 1.0 (referent), 1.88 (95% CI: 0.71, 5.00), 2.00 (95% CI: 0.76, 5.28) and 2.93 (95% CI 0.93, 9.25) for never, sometimes, frequently

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

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

4.1.2.3. *Other Reports of Asbestos-related Disease among Libby, MT Residents*

Whitehouse et al. (2008) recently 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 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 exposure to asbestos. Pathology reports were obtained for 10 of the 11 patients; for the other patient, diagnosis was based on medical records obtained from the patient's physician. Given the relatively small population in the study area (approximately 9,500 for central Lincoln County), Whitehouse et al. (2008) note that the occurrence of 11 cases of mesothelioma during the approximate 15 years (or 150,000 person-years) covered by this analysis is considerably higher than the estimated background incidence of 1 case per 1,000,000 person-years. Whitehouse et al. (2008) used information from a W.R. Grace unpublished report of measures taken in 1975 to estimate that exposure levels of 1.1 fibers/cc were found in Libby, and 1.5 fibers/cc were measured near the mill and railroad facilities. Because the mining and milling operations continued past 1990, and

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

4.1.2.4. *Summary of health effects in Libby, MT community studies*

The geographic-based mortality analysis of 1997-1998 mortality data indicates that asbestosis-related mortality is substantially increased in Libby, MT, and the surrounding area, with rates 40 times higher compared with Montana rates and 60-70% higher compared with United States rates (ATSDR, 2000). However, because this analysis did not distinguish between deaths among workers and deaths among other community members, it is not possible based on these data to estimate the risk of asbestos-related mortality experienced by residents who were not employed at the mining or milling operations. The community health screening studies provide more detailed information regarding exposure pathways in addition to occupation (ATSDR, 2001). Data from this study indicate that the prevalence of pleural abnormalities, identified by radiographic examination, increases with the number of exposure pathways, from 6.7% with no specific pathways to 34.6% with 12 or more pathways (Peipins et al., 2003). In addition, the prevalence of some self-reported respiratory symptoms among 10-29-year old adolescents and young adults was associated with certain exposure pathways. These participants were ≤ age 18 in 1990 when the mining/milling operations closed (Vinikoor et al., 2010). A better understanding of the community health effects and the examination of the potential progression of adverse health effect in this community would benefit from additional research to establish the clinical significance of these findings. The observation by Whitehouse et al. (2008) of cases of mesothelioma among individuals with no direct occupational exposure to the mining and milling operations indicates the need for continued surveillance for this relatively rare cancer.

4.1.3. Marysville, OH Vermiculite Processing Plant Worker Studies

Libby vermiculite was used in the production of numerous commercial products, including as a potting soil amender and a carrier for pesticides and herbicides. A Marysville, OH plant that used Libby vermiculite in the production of fertilizer from approximately 1963–1980 is the location of the two studies described in this section. Although vermiculite operation may have begun in the late 1950s (1957 or 1959), use of vermiculite from Libby, MT, is not documented until 1963.

The processing facility had eight main departments, employing approximately 530 workers, with 232 employed in production and packaging of the fertilizer and 99 in maintenance; other divisions included research, the front office, and the polyform plant (Lockey,

1985). Six departments were located at the main facility (trionizing, packaging, warehouse, plant maintenance, central maintenance, and front offices). Research and development and a polyform fertilizer plant were located separately, approximately one-quarter mile from the main facility. In the trionizing section of the plant, the vermiculite ore was delivered 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, formaldehyde, potash, herbicides), packaged, and stored. Changes to the expander type and dust-control measures began in 1967, with substantial improvement in dust control in 1974.

Information about exposure assessment at the Marysville, OH plant is summarized in the final row of Table 4-1. Industrial hygiene monitoring at the plant began in 1972, and limited industrial hygiene sampling data from 1972–1974 are available. Lockey (1985) and 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. Task-level samples were conducted, and measurements were determined using polarized light microscopy and transmission electron microscopy (based on particles >5-μm long, <3-μm diameter, and ≥3:1 aspect ratio).

Based on measurements and knowledge of plant operations, three categories of exposure levels were defined. Group I (considered to be the non-exposed group) consisted of the chemical processing, research, and front office workers. The chemical process plant was about 1 quarter mile from the main vermiculite facility, but the same chemicals were used in both locations. The 8-hour time-weighted average for vermiculite exposure in this group, both before and after 1974, was estimated as 0.049 fiber/cc (based on a single stationary sample taken outside the main facility), which was characterized as similar to the background levels in the community. Group II was the "low exposure" category and included central maintenance, packing, and warehouse workers. The 8-hour time-weighted averages for vermiculite exposures in this group were estimated as approximately 0.1–0.4 fibers/cc before 1974 and 0.03–0.13 fibers/cc in and after 1974. Group III was the "highest exposure" category, and included vermiculite expanders, plant maintenance, and pilot plant workers. The 8-hour time-weighted averages for vermiculite exposures in this group were approximately 1.2–1.5 fibers/cc before 1974 and 0.2–0.43 fibers/cc in and after 1974. Cumulative fiber exposure indexes, expressed as fibers-yr/cc, were derived for each worker from available industrial hygiene data and individual work histories (Lockey, 1985) and those with less than 1 fiber/cc-year were assumed to be equivalent to a community population (in terms of exposure) and were used as the comparison group. The estimated cumulative exposure for the work force ranged from 0.01 to 39.9 fibers-yr/cc using an 8-hour

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

The first study of pulmonary effects in the Ohio plant workers was conducted in 1980 and involved 512 workers (97% of the 530 workers previously identified with past vermiculite exposure) (Table 4-9; Lockey et al., 1984). The distribution by exposure group was 112 in Group I, 206 in Group II, and 194 in Group III. Physical examination (for detection of pulmonary rales and nail clubbing), spirometry, and chest-x-rays were performed, and information pertaining to smoking history, work history at the plant, and other relevant work exposures was collected using a trained interviewer. Radiographs were read by two board-certified radiologists (B readers), with a consensus reading by a third reader when needed. The number of workers within each exposure group was 112, 206, and 194 in Groups I, II, and III, respectively. Approximately 44% were current smokers, 20% former smokers, and 35% lifetime nonsmokers, but smoking history (i.e., smoking status, pack-years) did not differ by exposure group. Mean cumulative fiber estimates were 0.45, 1.13, and 6.16 fibers/cc in Groups I, II, and III, respectively.[4]

A follow-up study of this cohort was conducted in 2004–2005 (Rohs et al., 2008) (Table 4-9). This study included 298 workers, of which 280 completed the study interview and pulmonary x-ray. Details of the reasons for non-participation rates are described in Table 4-9. The study interview included information about smoking history and asbestos exposure at the Ohio plant and other work sites.

[4] Calculated from data presented in Table 2 of Lockey et al. (1984).

Table 4-9. Pulmonary radiographic studies of the OH vermiculite processing plant workers

Reference(s)	Inclusion criteria and design details	Results
Lockey et al., 1984; Lockey, 1985	1980, n = 512 (from 530 identified employees with past vermiculite exposure; non-participants included 9 refusals and 9 unavailable due to illness or vacation). Smoking history, work history at the plant, and other asbestos and fiber mineral work history data were collected. Chest exam (rales), nail clubbing, spirometry, forced vital capacity, forced expiratory volume, single-breath carbon monoxide diffusing capacity, and chest x-rays (available for 502 participants)were analyzed. Mean employment duration: 10.2 years[a]	Cumulative fiber exposure related to history of pleuritic chest pain and shortness of breath. No relation between cumulative exposure and spirometry results, forced vital capacity and expiratory volume tests, or carbon monoxide diffusing capacity. Pleural thickening in 10 workers (2%); bilateral, small opacities in 1 (0.2%). Abnormality increased with increasing cumulative exposure.
Rohs et al., 2008	2004–2005, interviews and chest x-rays conducted, n = 298; 280 with interviews and readable chest x-rays (from 431 workers in the 1980 study group of 513[b] who were alive in 2004; 151 living non-participants included 49 refusals, 76 located but did not respond, 8 not located but presumed alive, and 18 missing either x-ray or interview). Age, smoking, asbestos exposure measure (at this plant), and other asbestos exposure data used to compare participants and non-participants. Libby, MT vermiculite ore used in the plant from 1963–1980.	Pleural changes in 80 workers (28.9%). Small opacities (≥1/0) in 8 workers (2.9%). Increasing risk of pleural changes with increasing cumulative exposure: odds ratios (adjusting for date of hire, body mass index) by quartile of cumulative fibers were 1.0 (referent), 2.7, 3.5, and 6.9.

[a]Calculated based on stratified data presented in Table 2 of Lockey et al. (1984).
[b]Rohs et al. (2008) identified one additional eligible worker from the original 530 employees identified with past vermiculite exposure.

The evaluation of each worker included an interview to determine work and health history, spirometry, pulmonary examination, and chest X-ray. Exposure was estimated using the procedure previously described (Lockey, 1985) using the data on fiber levels. Exposure was assumed to occur from 1963 to 1980 in this study, assuming an 8-hour workday and 365 days of exposure per year (J. Lockey, University of Cincinnati, personal communication to R. Benson). Each worker supplied a detailed work history (start and end date for each area within the facility). The exposure reconstruction resulted in a cumulative exposure estimate for each individual. The estimated cumulative exposure for this follow-up study ranged from 0.01 to 19.03 fibers-yr/cc (mean = 2.48). The time from first exposure ranged from 23 to 47 years. Twenty-eight workers reported previous occupational exposure to asbestos. Exposure after work hours was assumed to be zero.

Three board-certified radiologists independently classified the radiographs using ILO criteria (ILO, 2000). Radiologists were blinded to all identifiers. Pleural changes that were considered were localized (pleural plaques) and/or diffuse pleural thickening. Localized (discrete) pleural thickening was defined as thickening with or without calcification, excluding solitary costophrenic angle blunting. Diffuse pleural thickening was pleural thickening, including costophrenic angle blunting, with or without calcification. Interstitial changes were defined as irregular opacities, profusion of 1/0 or greater. A radiographic reading was defined as positive when the median classification from the three independent readings was consistent with pleural change and/or interstitial changes. Radiographs classified as unreadable were not used. Radiographic changes found in the study population are summarized in the Tables 4-10 and 4-11.

Pleural changes were observed in 80 workers (28.9%), and small opacities (≥1/0) were observed in 8 (2.9%). Increasing risk of costophrenic angle blunting (an indicator of pleural effusions) (n = 11), pleural and parenchymal changes (n = 11), or any of these changes (n = 22) were observed with increasing cumulative exposure when assessed by category of workers or by cumulative exposure across all workers. The prevalence of any radiographic change was 2.8% in Group I, 3.9% in Group II, and 5.8% in Group III. Using the cumulative fiber metric, the prevalence of any radiographic change was 2.4% in the <1 fiber/cc-year, 5.0% in 1–10 fibers/cc-year, and 12.5% in the >10 fibers/cc-year groups. The prevalence of pleural changes increased across exposure quartiles from 7.1% in the first quartile to 24.6%, 29.4%, and 54.3% in the second, third, and fourth quartiles, respectively. The range of exposures was estimated as 0.01–0.28, 0.29–0.85, 0.86–2.20, and 2.21–19.03 fiber/cc-years in the first, second, third, and fourth quartiles, respectively. Adjusting for age, date of hire, and body mass index resulted in odds ratios of 2.7, 3.5, and 6.9 for the second, third, and fourth quartiles, respectively (Rohs et al, 2008).

Table 4-10. Prevalence of pleural radiographic changes according to quartiles of cumulative fiber exposure in 280 participants

Exposure quartile	Exposure, fiber-yr/cc, and (mean)	Number of workers	Number of workers with pleural change (%)[b]	Crude OR (95% CI)	Number of workers with parenchymal change (%)
First	0.01 – 0.28 (0.12)	70	5 (7.1)	Reference	0 (0)
Second	0.29 – 0.85 (0.56)	72[a]	17 (24.6)	4.02 (1.39 – 11.60)	0 (0)
Third	0.86 – 2.20 (1.33)	68[a]	20[c] (29.4)	5.42 (1.90 –15.46)	1 (1.5)
Fourth	2.21 – 19.03 (7.93)	70	38 (54.3)	15.44 (5.55 – 42.98)	7 (10)
Total	(2.48)	280	80 (28.6)		8 (2.9)

The 80 workers with pleural radiographic changes include 68 with discrete pleural thickening (85%) and 12 with diffuse pleural thickening (15%)

[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] Significant trend, $p < 0.001$

[c] Typographical error in publication corrected.

Source: Rohs et al. (2008), Table 3

Pleural changes were significantly associated with hire on or before 1973 and age at time of interview ($p<0.001$). Body mass index (BMI), smoking, and sex were not associated with pleural changes (Table 4-11). Body mass index is a potentially important confounder because fat pads can sometime be misclassified as discrete pleural thickening. Hire on or before 1973 and ages at time of interview are each highly correlated with cumulative exposure to fibers. The small number of females (16) in the cohort limits the analysis of the association with sex.

Table 4-11. Prevalence of pleural radiographic changes in 280 participants according to various cofactors

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

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

Modeling of odds ratios with cumulative fiber exposure and including various cofactors (age, hired before 1973, or BMI) with the first exposure quartile as the reference was also conducted. Each model demonstrated the same trend: increasing pleural change with increasing cumulative exposure to fibers. Lack of multicolinearity was demonstrated by the stable results

of the modeling with the exposure-response relationship remaining the same when different models were used with a single cofactor or all cofactors together. There was no evidence of significant interactions using this modeling.

There was potential co-exposure to a number of herbicides, pesticides, and other chemicals in the facility (personal communication to Robert Benson, EPA Region 8, from Ivan Smith, The Scotts Company, June 7, 2007). 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, 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. No quantitative information on exposure to these chemicals is available. However, the addition of the other chemicals to the vermiculite carrier occurred in a different part of the facility after expansion of the vermiculite ore. Industrial hygiene monitoring in these areas showed very low levels of fibers in the air. In addition, none of these other chemicals is volatile. Thus, it is unlikely that workers would be co-exposed by inhalation to these other chemicals. EPA has no information indicating that exposure to these chemicals (when administered as a single entity) causes pleural or parenchymal changes typical of those found in workers employed in the Marysville facility.

This study demonstrates that exposure to Libby Amphibole asbestos can cause radiographic evidence of pleural and parenchymal changes in exposed workers. The prevalence of radiographic changes involving the pleura increased from 2% in 1984 (10/501) to 28.9% in 2004 (80/280). The prevalence of any radiographic change (discrete pleural thickening, diffuse pleural thickening, and/or parenchymal change) was 29.3% (82/280). The increase in prevalence in the follow-up study is most likely due to the additional time between the two studies giving additional time for the changes to become apparent in conventional x-rays. The follow-up study also shows a clear exposure-response relationship for discrete pleural thickening and more extensive radiographic changes (that is, diffuse pleural thickening and parenchymal change) with increasing cumulative exposure to Libby Amphibole asbestos.

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

The studies conducted in the 1980s (Lockey et al., 1984; Lockey 1985) and the follow-up of the cohort (Rohs et al., 2008) indicate that pleural changes can be seen among workers in this plant, with increasing prevalence of changes seen with increasing cumulative exposure.

4.1.4. Community Studies from Other Vermiculite Processing Plants

ATSDR is conducting community evaluations of 28 sites, in addition to Libby, surrounding exfoliation plants that require further action by EPA because of current contamination or evidence (based on a database of invoices) that the plant processed more than 100,000 tons of vermiculite from the Libby, MT mine (Figure 4-1; Table 4-12). These community-level evaluations do not address individual exposures or residential histories; therefore, the evidence in these evaluations pertaining to disease risk is somewhat limited.

Nine of these evaluations included analyses conducted in conjunction with state health departments using death certificate data (Table 4-13). The lung cancer standardized incidence ratios for these evaluations range from 0.74–1.07, and the SMRs range from 0.74–1.1, indicating little evidence of an increased risk of lung cancer among these studies (Table 4-14). As expected from the small number of observations, the standardized incidence ratios for mesothelioma or the category of cancer of the peritoneum, retroperitoneum, and pleura (excluding mesothelioma, but which could reflect some misdiagnoses) are more variable, ranging from approximately 0.5–2.5. Breast and prostate cancer were selected as negative controls (i.e., cancers that have not previously been associated with asbestos exposure) in these evaluations. The patterns observed for these two cancer sites (Table 4-15) were similar to those of lung cancer (Table 4-14). In summary, these studies do not provide evidence of an increased risk of asbestos-related cancers in the communities surrounding plants that processed vermiculite contaminated with Libby Amphibole asbestos. A limitation of these studies, however, is the use of a very broad exposure classification, which would be expected to result in considerable misclassification. As a result, these studies might provide useful information to communities, but more refined study designs are needed to evaluate risk to individuals.

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

The community-based mortality studies around the 28 exfoliation plants that processed vermiculite contaminated with Libby Amphibole asbestos provide little evidence of an increased risk of asbestos-related cancers in the surrounding communities. These studies are quite limited, however, by the broad exposure classification and the inability to limit the analysis to individuals who had resided in the specific areas during the relevant exposure periods. Additional studies

would be needed to more fully examine the potential risks associated with residential exposures from these sources.

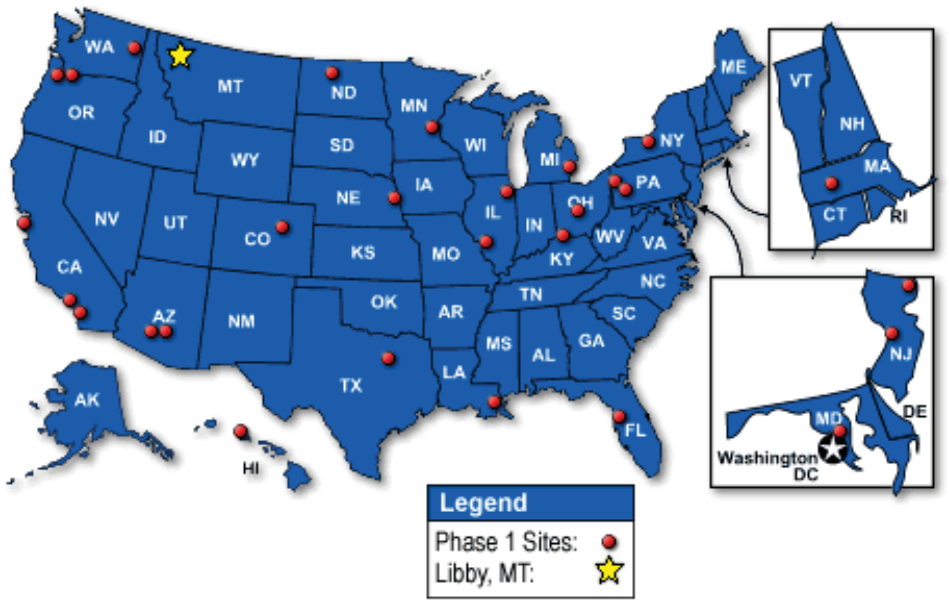


Figure 4-1. Location of 28 sites included in the Phase 1 community evaluations conducted by ATSDR

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

Table 4-10. ATSDR health consultations of 28 sites with potential Libby Amphibole asbestos contamination by status of health data and location (state) of the site

Health data status	Site	Year of report
Health data not included in report, but might be available in the future	Glendale, Arizona	not reported
	Phoenix, Arizona	not reported
	Denver, Colorado	2003
	Tampa, Florida	2005
	Honolulu, Hawaii	2005
	Wilder, Kentucky	2005
	New Orleans, Louisiana	2005
	Beltsville, Maryland	2003
	Easthampton, Massachusetts	2006
	Minneapolis, Minnesota	2003
	Omaha, Nebraska	not reported
	Weesport (Cayuga County), New York[c]	2004[d]
	Portland, Oregon[a]	not reported
	Portland, Oregon[a]	2005
	Ellwood City, Pennsylvania	2006
	New Castle, Pennsylvania	2005
	Dallas, Texas	2005
	Spokane, Washington	2004[d]
Health studies completed	Los Angeles, California	2007
	Newark, California	2005
	Santa Ana, California	2003
	West Chicago, Illinois	2003
	Dearborn, Michigan	2005
	St. Louis, Missouri	2006
	Trenton (Hamilton), New Jersey[b]	2005[d]
	Edgewater, New Jersey[b]	2007
	Marysville, OH	2005

[a]Two separate studies of two different sites in Portland were conducted.
[b]Health data included in a separate report available through the New Jersey Department of Health and Senior Services.
[c]Health data were mentioned, but they were not included in the report.
[d]Publication date obtained from a separate source.

Source: ATSDR (2008).

Table 4-11. Description of study areas in ATSDR health consultations evaluating cancer incidence and mortality[a]

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

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

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

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

Table 4-14. Incidence and mortality results for potential asbestos-related cancers (by cancer site) in communities with ATSDR health consultations evaluating potential Libby Amphibole asbestos contamination

Study area[c]	Incidence[a]				Mortality[b]			
	Observed	Expected[c]	SIR	(95% CI)	Observed	Expected[c]	SMR	(95% CI)
Lung and bronchus								
Los Angeles, CA[d]	100	117.4	0.85	(0.69, 1.04)	210	285.0	0.74	(0.64, 0.84)
Newark, CA[d]	29	27.2	1.07	(0.71, 1.53)	125	124.3	1.01	(0.84, 1.2)
Santa Ana, CA[d]	79	95.4	0.83	(0.66, 1.03)	–	–	–	–
West Chicago, IL	–	–	–	–	95	98.6	0.96	(0.78, 1.18)
Dearborn, MI	757	764.4	0.99	(0.92, 1.06)	1,133	1,261.3	0.90	(0.85, 0.95)
St. Louis, MO	–	–	–	–	319	286.6	1.1	(1.0, 1.2)
Trenton, NJ	496	671.0	0.74	(0.68, 0.81)	976	1,100.3	0.89	(0.83, 0.94)
Edgewater, NJ	35	30.7	1.14	(0.80, 1.59)	51	50	1.02	(0.76, 1.34)
Marysville, OH	–	–	–	–	106	98.1	1.1	(0.9, 1.3)
Mesothelioma								
Los Angeles, CA[d]	1	1.9	0.53	(0.01, 2.96)	–	–	–	–
Newark, CA[d]	1	0.4	2.49	(0.03, 13.9)	–	–	–	–
Santa Ana, CA[d]	4	1.5	2.68	(0.72, 6.87)	–	–	–	–
West Chicago, IL	–	–	–	–	–	–	–	–
Dearborn, MI	8	12.3	0.65	(0.28, 1.28)	–	–	–	–
St. Louis, MO	–	–	–	–	–	–	–	–
Trenton, NJ	6	10.6	0.57	(0.21, 1.24)	–	–	–	–
Edgewater, NJ	1	0.5	2.11	(0.03, 11.7)	–	–	–	–
Marysville, OH	–	–	–	–	–	–	–	–
Peritoneum, retroperitoneum, and pleura (excluding mesothelioma)					**(including mesothelioma)**			
Los Angeles, CA[d]	1	3.1	0.32	(0.00, 1.78)	0	2.1	0.0	–
Newark, CA[d]	3	0.7	4.06	(0.82, 11.9)	0	0.9	0.0	(0, 4.10)
Santa Ana, CA[d]	6	2.7	2.24	(0.82, 4.87)	–	–	–	–
West Chicago, IL	–	–	–	–	1	0.8	1.28	(0.02, 7.12)
Dearborn, MI	16	19.1	0.84	(0.48, 1.36)	9	9.6	0.93	(0.43, 1.77)
St. Louis, MO	–	–	–	–	3	2.3	1.g26 3	(0.3, 3.8)
Trenton, NJ	10	16.7	0.60	(0.29, 1.10)	18	8.3	2.17	(1.29, 3.43)
Edgewater, NJ	1	0.8	1.28	(0.02, 7.13)	0	0.2	0.0	–

Study area[c]	Incidence[a]				Mortality[b]			
	Observed	Expected[c]	SIR	(95% CI)	Observed	Expected[c]	SMR	(95% CI)
Marysville, OH	–	–	–	–	0	0.8	0.0	–

Table 4-14. Incidence and mortality results for potential asbestos-related cancers (by cancer site) in communities with ATSDR health consultations evaluating potential Libby Amphibole asbestos contamination (continued)

Study area[c]	Incidence[a]				Mortality[b]			
	Observed	Expected[c]	SIR	(95% CI)	Observed	Expected[c]	SMR	(95% CI)
Respiratory system and intrathoracic organs								
Los Angeles, CA[d]	111	128.2	0.87	(0.71, 1.04)	217	294.4	0.74	(0.64, 0.84)
Newark, CA[d]	32	30.1	1.06	(0.73, 1.50)	126	128.7	0.98	(0.82, 1.17)
Santa Ana, CA[d]	86	105.0	0.82	(0.66, 1.01)	–	–	–	–
West Chicago, IL	–	–	–	–	100	102.2	0.98	(0.80, 1.19)
Dearborn, MI	831	832.7	1.00	(0.93, 1.07)	1,173	1, 305.1	0.90	(0.85, 0.95)
St. Louis, MO	–	–	–	–	334	296.5	1.1	(1.0, 1.2)
Trenton, NJ	536	732.8	0.73	(0.67, 0.80)	1,008	1,139.1	0.88	(0.83, 0.94)
Edgewater, NJ	42	33.6	1.25	(0.90, 1.69)	53	51.9	1.02	(0.77, 1.34)
Marysville, OH	–	–	–	–	107	101.6	1.0	(0.9, 1.3)
Selected digestive organs								
Los Angeles, CA[d]	101	139.5	0.72	(0.59, 0.88)	155	170.0	0.91	(0.77, 1.07)
Newark, CA[d]	25	27.0	0.92	(0.60, 1.36)	74	63.4	1.17	(0.92, 1.47)
Santa Ana, CA[d]	79	104.0	0.76	(0.60, 0.95)	–	–	–	–
West Chicago, IL	–	–	–	–	70	62.7	1.12	(0.87, 1.41)
Dearborn, MI	899	843.2	1.07	(1.00, 1.14)	819	785.1	1.04	(0.97, 1.12)
St. Louis, MO	–	–	–	–	172	196.7	0.9	(0.7, 1.0)
Trenton, NJ	626	718.1	0.87	(0.80, 0.94)	752	659.8	1.14	(1.06, 1.22)
Edgewater, NJ	51	32.6	1.57	(1.17, 2.06)	27	29.7	0.91	(0.60, 1.32)
Marysville, OH	–	–	–	–	67	66.8	1.0	(0.8, 1.3)

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

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

[c]Expected values have been rounded.
[d]Similar results were observed in the California analyses using alternative methods to calculate standardized risk ratios for incidence and mortality.
CI = confidence interval.
Source: ATSDR (2008).

Table 4-15. Incidence and mortality results for breast cancer and prostate cancer cancers in communities with ATSDR health consultations evaluating potential Libby Amphibole asbestos contamination

Study area[c]	Incidence[a]				Mortality[b]			
	Observed	Expected[c]	SIR	(95% CI)	Observed	Expected[c]	SMR	(95% CI)
Breast cancer (female)								
Los Angeles, CA[d]	104	130.6	0.80	(0.65, 0.97)	109	89.5	1.22	(1.00, 1.47)
Newark, CA[d]	43	34.3	1.25	(0.91, 1.69)	46	38.8	1.18	(0.87, 1.58)
Santa Ana, CA[d]	101	110.2	0.92	(0.75, 1.11)	–	–	–	–
West Chicago, IL	–	–	–	–	44	33.5	1.31	(0.95, 1.76)
Dearborn, MI	764	736.1	1.04	(0.97, 1.11)	401	370.8	1.08	(0.98, 1.19)
St. Louis, MO	–	–	–	–	116	93.1	1.2	(1.0, 1.5)
Trenton, NJ	497	682.2	0.73	(0.67, 0.80)	349	334.4	1.04	(0.94, 1.16)
Edgewater, NJ	30	32.6	0.92	(0.62, 1.31)	24	15.5	1.55	(0.99, 2.30)
Marysville, OH	–	–	–	–	39	34.6	1.1	(0.8, 1.5)
Prostate cancer (male)								
Los Angeles, CA[d]	79	118.1	0.67	(0.53, 0.83)	47	64.5	0.73	(0.54, 0.97)
Newark, CA[d]	24	22.4	1.07	(0.69, 1.59)	17	20.4	0.83	(0.49, 1.34)
Santa Ana, CA[d]	77	88.0	0.87	(0.69, 1.09)	–	–	–	–
West Chicago, IL	–	–	–	–	24	18.14	1.32	(0.85, 1.97)
Dearborn, MI	899	810.3	1.11	(1.04, 1.18)	266	292.9	0.91	(0.80, 1.02)
St. Louis, MO	–	–	–	–	65	66.9	1.0	(0.7, 1.2)
Trenton, NJ	391	674.8	0.58	(0.52, 0.64)	208	225.4	0.92	(0.80, 1.06)
Edgewater, NJ	27	31.7	0.86	(0.56, 1.24)	6	10.4	0.57	(0.21, 1.25)
Marysville, OH	–	–	–	–	28	24.1	1.2	(0.8, 1.7)

[a]All incidence studies used Surveillance, Epidemiology, and End Results (SEER) data as the comparison group except New Jersey, which used New Jersey state rates; incidence period in all analyses was 1986–1995. Incidence data, ICD-10 (International Classification of Diseases) codes: breast cancer, C500:C509 (excluding mesothelioma); prostate cancer, C619 (excluding mesothelioma).
[b]All mortality studies used U.S. rates from the National Center for Health Statistics. Mortality period was 1989–1998 in the Los Angeles and Newark, California analyses, and was 1979–1998 in all analyses. Mortality data, ICD-9 codes: breast cancer, 174; prostate cancer, 185.
[c]Expected values have been rounded.
[d]Similar results were observed in the California analyses using alternative methods to calculate standardized risk ratios for incidence and mortality.

CI = confidence interval.

4.1.5. Case reports

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

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

Laboratory animal studies with exposure to Libby Amphibole or tremolite asbestos show effects similar to those observed in occupationally exposed human populations including pleural pathology, mesothelioma and lung cancer. Tremolite is an amphibole asbestos fiber that is a component of Libby Amphibole asbestos (~6%). Also, in early studies Libby Amphibole asbestos was defined as tremolite. Therefore, laboratory animal studies examining the effect of tremolite exposure have been reviewed and are summarized below to potentially increase understanding of the effects and mechanisms of Libby Amphibole asbestos. Detailed study summaries can be found in Appendix D and summarized in Table 4-16 and 4-17. No inhalation studies have been performed for Libby Amphibole asbestos, but chronic intrapleural injection studies in hamsters demonstrate carcinogenicity following exposure. The chronic inhalation and intrapleural injection laboratory animal studies with tremolite asbestos demonstrated pleural pathology and carcinogenicity in rats. These studies support the epidemiology studies of Libby Amphibole asbestos exposure (Section 4.1), and aid in informing the mechanisms of Libby Amphibole asbestos-induced disease.

4.2.1. 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, 1990a) performed to evaluate the toxicity and carcinogenicity of ingestion of several minerals, including tremolite. The tremolite (Governeur Talc Co, Governeur, New York) used was not fibrous. No significant tumor induction was observed in the animals with oral exposure to

tremolite animals. Although non-neoplastic lesions were observed in many of the aging rats, these were mostly in the stomach and occurred in both controls and exposed animals. The observed lesions included chronic inflammation, ulceration, and necrosis of the stomach (McConnell et al., 1983a). McConnell et al. (1983a) suggested that nonfibrous tremolite could account for the lack of toxicity following exposure in this group of animals. Also, oral studies of asbestos, in general, show decreased toxicity and carcinogenicity as compared to inhalation and implantation/injection studies (Condie, 1983).

4.2.2. Inhalation

There are no laboratory animal studies following inhalation exposure to Libby Amphibole asbestos; however two studies have examined the effect of inhalation exposure to tremolite in Wistar rats (Bernstein et al., 2005; 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. (2003; 2005) exposed Wistar rats to tremolite (100 fibers/cm^3) and chrysotile for 13 consecutive weeks (6 hours per day, 5 days per week) with 1-year follow-up. The results of these inhalation studies produced pronounced inflammation and very high levels of pulmonary fibrosis. Davis et al (1985) also demonstrated an increase in carcinomas and mesotheliomas following exposure to tremolite, with no pulmonary tumors observed in the controls. These results show that Wistar rats exposed to tremolite exhibited increased numbers of pulmonary lesions and possibly tumors.

4.2.3. Intratracheal Instillation Studies

Intratracheal instillation has been used to examine the effect of exposure to Libby Amphibole (Putnam et al., 2008; Smartt et al., 2009; Shannahan et al., 2011a) and tremolite asbestos (Sahu et al., 1975; Blake et al., 2008; Pfau et al., 2008). These studies exposed either C57Bl/6 mice (100 μg/mouse) or WKY rats (0.25 or 1mg/rat) once to Libby Amphibole asbestos and analyzed the results up to 3 mos post-exposure. Putnam et al. (2008) observed non-statistically significant increases in collagen following exposure to Libby Amphibole asbestos, as well as gene expression alterations related to membrane transport, signal transduction, epidermal growth factor signaling, and calcium regulation. Smartt et al. (2009) followed up this study by analyzing specific genes by quantitative RT-PCR for genes involved in collagen accumulation and scar formation (Col1A1, Col1A2, Col3A1). Libby Amphibole asbestos exposure led to increased gene expression of Col1A2 at 1 week post-instillation and Col3A1 at 1 month post exposure. Both studies observed increased inflammation, however, Libby Amphibole asbestos

exposure demonstrated minimal inflammation that did not progress in the time points examined. These studies demonstrate that exposure to Libby Amphibole asbestos may lead to inflammation and fibrosis. Shannahan et al. (2011) exposed two rat models of human cardiovascular disease to Libby Amphibole asbestos to determine if the pre-existing cardiovascular disease in these models would impact the lung injury and inflammation following exposure. Healthy Wistar Kyoto (WKY) rats were compared to spontaneously hypertensive (SH) and spontaneously hypertensive heart failure (SHHF) rats following exposure. All rats (male only) were exposed to 0, 0.25 or 1.0 mg/rat via intratracheal instillation and were examined at 1 d, 1 wk and 1 mo post-exposure. No changes were observed histopathologically, however, changes were observed in markers of homeostasis, inflammation and oxidative stress. While inflammation and cell injury were observed in all strains, no strain-related differences were observed following exposure to Libby Amphibole asbestos (Shannahan et al., 2011). In conclusion, this study showed the potential for population variability related to cardiac disease in response to exposure to Libby Amphibole asbestos, including markers of cellular injury, iron homeostasis and inflammation.

Laboratory animal studies of tremolite intratracheal instillation exposure have been performed in mice in doses ranging from 60 µg to 5 mg. Male Swiss albino mice exposed to tremolite (5mg) via intratracheal instillation demonstrated histological changes (Sahu et al., 1975). Microscopic results following exposure to tremolite showed acute inflammation of the lungs at 7 days post exposure, including macrophage proliferation and phagocytosis similar to that observed with amosite and anthophyllite. Limited progression of fibrotic response was observed at 60 and 90 days post exposure, with no further progression of fibrotic response. Blake et al. (2008) and Pfau et al. (2008) examined the role of asbestos in autoimmunity. Blake et al. (2008) performed in vitro assays with Libby Amphibole asbestos (Section 4.4), and both studies performed the in vivo assays with tremolite. C57BL/6 mice were instilled intratracheally for a total of two doses each of 60-µg saline and wollastonite or Korean tremolite sonicated in sterile PBS, given 1 week apart in the first 2 weeks of a 7-month experiment. Sera from mice exposed to tremolite showed antibody binding colocalized with SSA/Ro52 on the surface of apoptotic blebs (Blake et al., 2008). In Pfau et al. (2008), by 26 weeks, the tremolite-exposed animals had a significantly higher frequency of positive anti-nuclear antibody tests compared to wollastinate and saline. Most of the tests were positive for dsDNA and SSA/Ro52. Serum isotyping showed no major changes in immunoglobulin subclasses (IgG, IgA, IgM), but serum IgG in tremolite-exposed mice decreased overall. Further, IgG immune complex deposition in the kidneys increased, with abnormalities suggestive of glomerulonephritis. No increased proteinuria was observed during the course of the study. Local immunologic response was further studied on the cervical lymph nodes. Although total cell numbers and lymph-node size

were significantly increased following exposure to tremolite, percentages of T- and B-cells did not significantly change.

4.2.4. Injection/ImplantationStudies

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

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

There is one laboratory animal study which examined the effect of tremolite exposure following implantation of fibers in the pleural cavity. Stanton et al. (1981) also examined tremolite and describe a series of studies on various forms of asbestos. Fibers, embedded in hardened gelatin, were placed against the lung pleura. As an intrapleural exposure, results might not be comparable to inhalation exposures, as the dynamics of fiber deposition and pulmonary clearance mechanisms are not accounted for in the study design. Studies using two tremolite asbestos samples from the same lot were described as being in the optimal size range 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 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 that did not lead to mesothelioma production.

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

There are no studies currently available in laboratory animals exposed to Libby Amphibole asbestos by inhalation. However, the chronic intraperitoneal injection study in hamsters (Smith 1978; Smith et al., 1979) demonstrated tumor formation following exposure to tremolite obtained from the Libby, MT mine. No other chronic studies of Libby Amphibole asbestos are available. A recent study in rats examining the impact of pre-existing cardiovascular disease on pulmonary inflammation demonstrated an increase in inflammatory markers following exposure to Libby Amphibole asbestos via intratracheal instillation in SH rats as compared to normal healthy controls exposed to the same dose (Shannahan et al., 2011). More recent studies examined gene expression changes (Putnam et al., 2008; Hillegass et al., 2010) and early protein markers of fibrosis (Smartt et al., 2009) in mice exposed to Libby Amphibole asbestos via intraperitoneal injection. These studies demonstrated an increase in gene and protein expression related to fibrosis following exposure to Libby Amphibole asbestos. 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., 2003; 2005; Davis et al., 1985; Wagner et al., 1982; Roller et al., 1996; 1997; 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 post-exposure), 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 Blake et al. (2008) and Pfau et al. (2008) support human studies demonstrating potential autoimmune effects of asbestos exposure.

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

Species (sex)	Exposure route	Fiber type	Effects*	Reference
LVG:LAK Hamsters (M) (n ~ 60/group)	Intraperitoneal injection (once) 25 mg/0.5 mL 0.9% NaCl solution	Tremolite (sample 60) and tremolite + vermiculite (sample 63)	Pleural adhesions (fibrosis): examined10 animals/group at ~3 mo post exposure: Sample 60: 10/10; Sample 63: 10/10; Control: 0/10 Mesothelioma: Sample 60: 5 /66; Sample 63: 5/64; Control: 0/60	Smith, 1978 (W.R. Grace study)
C57Bl/6 mice (M, F) (n = 7/group)	Intratracheal instillation (once) 1 wk, 1 mo, 3 mo 100 µg of sample in 30 µL saline	Libby Amphibole asbestos (Six Mix) and crocidolite	Altered gene expression in mice exposed to both samples; increase in collagen in exposed animals	Putnam et al., 2008
C57Bl/6 mice (M, F) (n = 7/group)	Intratracheal instillation (once) 1 wk, 1 mo, 3 mo 100 µg of sample in 30 µL saline	Libby Amphibole asbestos (Six Mix) and crocidolite	Collagen gene expression and protein levels increased following exposure to both forms of asbestos (~ 1 mo post exposure).	Smartt et al., 2009
Wistar Kyoto rats (M) (n = 12/group) Spontaneously Hypertensive (SH) (n = 6/group) SH Heart Failure (SHHF) (n = 6/group)	Intratracheal instillation (once) 1 d, 1 wk, 1 mo 0.25 or 1.0 mg/rat	Libby Amphibole asbestos (Six Mix)	Strain-related differences observed in biomarkers of inflammation following exposure to Libby Amphibole asbestos. No differences were observed in histopathology.	Shannahan et al., 2011

*When available, results are shown as number of animals with tumors/total number of animals examined.

Table 4-17. In vivo data following exposure to tremolite asbestos

Species (sex)	Exposure route	Fiber type	Effects*	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)	Offspring from exposed mothers were smaller at weaning and throughout life; No toxicity or increase in neoplasia in tremolite rats as compared to controls.	McConnell et al., 1983a
Wistar rats (M) (n = 48)	Inhalation 10 mg/m^3 (7 h each day, 5 days per week, total of 224 days)	South Korean tremolite and brucite	Increased fibrosis (19/39) and carcinogenesis (18/39).	Davis et al., 1985
AF/Han rats (n = 33 – 36/group)	Intraperitoneal injection 10 mg/2 mL PBS; single exposure	Tremolite (Six samples)	All six fibers could induce mesothelioma: California: 36/36* Swansea: 35/36* Korea: 32/36* Italy: 24/36 Carr Brae: 4/33 Shinness: 2/36 * asbestiform types led to mesothelioma in most if not all exposed animals in this study	Davis et al., 1991
Hamsters (n ≤ 35/group)	Intrapleural injection 10 or 25 mg	Four types of tremolite (Sample FD-14; 275; 31; 72)	Sample FD-14: 0/35 Sample 275: 0/34 (10 mg); 0/31 (25 mg)Samples 31: 3/41 (10 mg); 12/28 (25 mg) Sample 72: 4/13 (10 mg); 13/20 (25 mg)	Smith et al., 1979
Sprague-Dawley and Wistar rats (n = 32 Wistar rats (Sample A); 48 Sprague-Dawley rats (Samples B and C))	Intrapleural injection 20 mg/rat	Tremolite (Three samples)	No tumors following exposure to Sample 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)	Sample 1: 21/28 pleural sarcomas Sample 2: 22/28 pleural sarcomas	Stanton et al., 1981

Table 4-17. In vivo data following exposure to tremolite asbestos				
Species (sex)	**Exposure route**	**Fiber type**	**Effects***	**Reference**
Wistar rats (F) (n = 40/group)	Intraperitoneal injection 1 × 3.3 and 1 × 15 mg, lifetime observation	Tremolite	Limited details in text. Increase in mesothelioma following exposure to tremolite: 3.3 mg sample: 9/29; 15 mg sample: 30/37	Roller et al., 1996, 1997
Wistar rats (M) (n = 56)	Inhalation (flow-past nose only) 100 fibers/cm^3 longer than 20 µm, 5 days, follow-up 1 yr later	Tremolite	Tremolite had a pronounced inflammatory response with rapid granuloma development (1day post exposure); Slight interstitial fibrosis observed at 90 and 180 days post-exposure.	Bernstein et al., 2003, 2005
C57Bl/6 mice (F) (n = 10/group)	Intratracheal instillation Two doses of 60 µg each given 1 wk apart in the first and second week of a 7-mo experiment	Tremolite and wollastonite	Tremolite-exposed mice demonstrated increased IgG immune complex deposition in the kidneys, increased size of local lymph nodes, and increased total cell count.	Pfau et al., 2008

*When available, results are shown as number of animals with tumors/total number of animals examined.

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

Tables 4-16 and 4-17 summarize the studies described in this section, with full study details available in Appendix F. Limited in vivo studies have been performed exposing laboratory animals to Libby Amphibole asbestos. One intrapleural injection study using tremolite from the Libby, MT area is included in this section under Libby Amphibole asbestos since earlier terminology for Libby Amphibole asbestos was often tremolite (Smith, 1978). Hamsters in this study exposed to Libby Amphibole asbestos developed fibrosis and mesothelioma following exposure. Subchronic studies in mice (Putnam et al., 2008; Smartt et al., 2008) demonstrated gene and protein expression changes related to fibrosis production following exposure to Libby Amphibole asbestos. Finally, a short-term study in a rat model for human cardiovascular disease demonstrated an increase in inflammatory markers following exposure to Libby Amphibole asbestos (Shannahan et al., 2011).

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

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 Blake et al. (2008) and Pfau et al. (2008) support human studies demonstrating potential autoimmune effects of asbestos exposure.

4.3. OTHER DURATION OR ENDPOINT-SPECIFIC STUDIES

4.3.1. Immunological

Two epidemiology studies have examined the potential role of Libby Amphibole asbestos and autoimmunityNoonan et al. (2006) used the data from the community health screening to examine self-reported history of autoimmune diseases (rheumatoid arthritis, scleroderma, or lupus) in relation to the asbestos exposure pathways described in the pulmonary analyses (Section 4.1, Table 4-8). To provide more specificity in the self-reported history of these diseases, a follow-up questionnaire was mailed to participants to confirm the initial report and obtain clarifying information regarding the type of disease, whether the condition had been diagnosed by a physician, and whether the participant was currently taking medication for the

disease. Responses were obtained from 208 (42%) of those individuals who had reported these conditions. Of these 208 responses, 129 repeated the initial report of the diagnosis of rheumatoid arthritis, and 161 repeated the initial report of the diagnosis of rheumatoid arthritis, scleroderma, or lupus. Among people aged 65 and over (n = 34 rheumatoid arthritis cases, determined using responses from the follow-up questionnaire), a two- to three-fold increase in risk was observed in association with past work in mining and milling operations, asbestos exposure in the military, use of vermiculite in gardening, and frequent playing on vermiculite piles when young. Furthermore, this increase was observed in individuals exhibiting two measures of pulmonary effects—restricted forced vital capacity and presence of parenchymal abnormalities. Restricted forced vital capacity, playing on vermiculite piles, and other dust or vermiculite exposures were also associated with rheumatoid arthritis in the group younger than 65 (n = 95 cases). The definition of restricted forced vital capacity used in the analysis by Noonan et al. (2006). (FVC <80% of predicted values and a ratio of FEV1 to FVC that is ≥70% predicted, differs from the definition used in the ATSDR report of the community health screening (ATSDR, 2001). In the ATSDR report, a moderate-to-severe restricted forced vital capacity is defined as an FVC <70%. For all participants, an increased risk of rheumatoid arthritis was observed with increasing number of exposure pathways. RRs of 1.0, 1.02, 1.79, 2.51, and 3.98 were observed for 0 (referent), 1, 2–3, 4–5, and 6 or more pathways, respectively (trend $p < 0.001$, adjusting for restrictive spirometry, parenchymal abnormalities, and smoking history). Although the information gathered in the follow-up questionnaire and repeated reports of certain diagnoses decreased the false-positive reports of disease, considerable misclassification (over-reporting and under-reporting) is likely, given the relatively low confirmation rate in other studies—particularly for rheumatoid arthritis (Rasch, 2003; Karlson, 2003; Ling, 2000).

Another study examined serological measures of autoantibodies in 50 residents of Libby, MT, and a comparison group of residents of Missoula, Montana (Pfau et al., 2005; Table 4-18). The Libby residents were recruited for a study of genetic susceptibility to asbestos-related lung disease, and the Missoula residents were participants in a study of immune function. The Libby sample exhibited an increased prevalence (22%) of high-titer (≥1:320) antinuclear antibodies when compared to the Missoula sample (6%), and similar increases were seen in the Libby sample for rheumatoid factor, anti-RNP, anti-Scl-60, anti-Sm, anti-Ro (SSA), and anti-La (SSB) antibodies. Although neither sample was randomly selected from the community residents, an individual's interest in participating in a gene and lung disease study likely would not be influenced by the presence of autoimmune disease or autoantibodies in that individual.

Table 4-18. Pulmonary radiographic, and other health studies in the Libby, MT community

1

Reference(s)	Inclusion criteria and design details	Results
Autoimmune Disease		
Noonan et al., 2006	Nested case-control study among 7,307 participants in 2000–2001 community health screening. Conducted interviews, gathered self-reported history of rheumatoid arthritis, scleroderma, or lupus. Follow-up questionnaire mailed to participants concerning self-report of "physician-diagnosis" of these diseases and medication use.	Association with work in Libby mining/milling operations (ages 65 and older): Rheumatoid arthritis OR: 3.2 (95% CI = 1.3, 8.0) Rheumatoid arthritis, lupus, scleroderma OR: 2.1 (95% CI = 0.90, 4.1) Risk increased with increasing number of asbestos exposure pathways.
Pfau et al., 2005	Libby residents (n = 50) recruited for study of genetic susceptibility to asbestos-related lung disease. Missoula, Montana comparison group (n = 50), recruited for study of immune function; age and sex-matched to Libby participants. Serum samples obtained; IgA levels, prevalence of antinuclear, anti-dsDNA antibodies, anti-RF antibodies, and anti-Sm, RNP, SS-A, SS-B, and Scl-70 antibodies determined.	Increased prevalence of high titer (≥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-Ro (SSA) and anti-La (SSB) antibodies observed in Libby sample.

2

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

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

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

In vitro analysis of fibers depends on the characteristics of the fibers and cell types used for the studies. Therefore, in reviewing the literature it is important to pay attention to cell types used, particularly related to the ability to internalize fibers and produce an oxidative stress response. Results from in vitro studies have demonstrated potential biological mechanisms of oxidative stress and inflammation in response to exposure to Libby Amphibole and tremolite

asbestos. These studies are summarized below and in Tables 4-19 and 4-20, with detailed study descriptions available in Appendix D.

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

4.4.1. Inflammation and Immune Function

Hamilton et al., (2004) showed an increase in TH1 and TH2 cytokines following exposure to both asbestos and particulate matter, suggesting a similar effect of exposure to both materials on immune function. Analysis of these results is limited, as the use of primary cells in culture that led to an extremely variable response. Two studies by Blake et al. (2007, 2008) further examined the effect of Libby Amphibole asbestos on immune response in murine macrophages. These studies demonstrated that Libby Amphibole asbestos was internalized, and this internalization resulted in an increase in ROS. These studies also showed a variable cytotoxic response, as Libby Amphibole asbestos 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 Libby Amphibole asbestos exposed-cells. An increase (relative to controls) in autoantibody formation following exposure to Libby Amphibole asbestos also was 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 (Wagner et al., 1982; Okayasu et al, 1999).

Mechanisms of oxidative stress following exposure to Libby Amphibole asbestos were also studied in human mesothelial cells (Hillegass et al. 2010). Gene expression changes following exposure to 15×10^6 $\mu m^2/cm^2$ Libby Amphibole asbestos[6] as compared to the non-pathogenic control (75×10^6 $\mu m^2/cm^2$ glass beads) in the human mesothelial cell line LP9/TERT-1 for 8 and 24 hrs. 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 one gene related to reactive oxygen species processing. Oxidative

[6] 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 non-toxic (15×10^6 $\mu m^2/cm^2$) or the toxic dose (75×10^6 $\mu m^2/cm^2$).

stress was observed as both dose- and time-dependent in cells exposed to Libby Amphibole asbestos but was increased following exposure to the higher dose of Libby Amphibole asbestos (statistical analysis not possible). GSH levels were transiently depleted following 2–8 hrs exposure to the higher dose of Libby Amphibole asbestos, with a gradual recovery up to 48hrs in LP9/TERT-1 cells (HKNM-2 not analyzed). These studies demonstrate that Libby Amphibole asbestos 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.

Gene expression alterations of interleukin-8 (IL-8), cyclooxygenase-2 (COX-2), heme oxygenase (HO)-1 as well as other stress-responsive genes as compared to amosite (Research Triangle Institute) was observed in primary human airway epithelial cells (HAEC) following exposure to Libby Amphibole asbestos. Comparisons were made with both fractionated (aerodynamic diameter $\leq$2.5μm) and unfractionated fiber samples (Duncan et al., 2010). Crocidolite (CRO) 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 (AM), AM2.5 (fractionated), Libby Amphibole asbestos (LA), or LA 2.5 (fractionated) for 2 or 24 hours in cell culture. Cytotoxicity was determined by measurement of lactate dehydrogenase (LDH) from the maximum dose (26.4 μg/cm^2) of both amosite and Libby Amphibole asbestos samples, with less than 10% LDH present following exposure to all four samples. Minimal increases in gene expression of IL-8, COX-2 or HO-1 were observed at 2 h post-exposure to all five fiber types; at 24h post-exposure, however, a dose response was observed following exposure to all fiber types with the results showing a pro-inflammatory gene expression response (Duncan et al., 2010). These results support a limited cytotoxicity of both amosite and Libby Amphibole asbestos under these concentrations and time frames.

4.4.2. Genotoxicity

ROS production and genotoxicity (micronuclei induction) following exposure to Libby Amphibole asbestos has been demonstrated in XRCC1-deficient human lung epithelial H460 cells (Pietruska et al., 2010). XRCC1 is involved in the repair mechanisms for oxidative DNA damage, particularly single strand breaks. Micronuclei induction was measured following treatment of cells by controls (positive, hydrogen peroxide; negative, paclitaxel) and by 5μg/cm^2 fibers or TiO_2 particles for 24 hrs. Spontaneous micronuclei induction was increased in XRCC1-deficient cells in a dose-dependent manner following exposure to crocidolite and Libby Amphibole asbestos as compared to control. These results support a potential genotoxic effect of exposure to both crocidolite and Libby Amphibole asbestos.

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

Okayasu et al. (1999) analyzed the mutagenicity of Metsovo tremolite, erionite, and the man-made ceramic (RCF-1) fiber. Human-hamster hybrid A(L) cells contain a full set of hamster chromosomes and a single copy of human chromosome 11. Mutagenesis of the CD59 locus on this chromosome is quantifiable by antibody complement-mediated cytotoxicity assay. The authors state that this is a highly sensitive mutagenicity assay, and previous studies have demonstrated mutagenicity of both crocidolite and chrysotile (Hei et al., 1992). The cytotoxicity analysis for mutagenicity was performed by exposing 1×10^5 A(L) cells to a range of concentrations of fibers as measured by weight (0–400 μg/mL or 0–80 $\mu g/cm^2$) for 24 hours at

37°C. CD59 mutant induction showed a dose-dependent increase in mutation induction for erionite and tremolite, but RCF-1 did not.

4.4.3. Cytotoxicity and Cellular Proliferation

Wagner et al. (1982) examined the in vitro cytotoxicity of three forms of tremolite used in their in vivo studies. LDH and BGL were measured in the medium following incubation of unactivated primary murine macrophages to 50, 100, and 150 μg/mL of each sample for 18 hours. The Korean tremolite (Sample C) produced results similar to the positive control: increased toxicity of primary murine macrophages, increased cytoxicity of Chinese hamster ovary (CHO) cells, and increased formation of giant cells from the A549 cell line. The tremolite sample from Greenland (Sample B) did result in increased toxicity over controls; although to a lesser degree (statistics are not given). Although differential toxicity of these samples was noted on a mass basis, data were not normalized for fiber content or size. The inference is that differential results may be due, at least in part, to differential fiber counts.

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

Summary

The review of these studies clearly highlights the need for more controlled studies examining Libby Amphibole asbestos in comparison to other forms of asbestos and for examining multiple endpoints, including ROS production, DNA damage, and pro-inflammatory

gene expression alterations, to improve understanding of mechanisms involved in cancer and other health effects. These results suggest that Libby Amphibole asbestos may act through similar mechanisms as other forms of asbestos, but data gaps still remain to determine specific mechanisms involved in Libby Amphibole asbestos-induced disease. Studies that examined cellular response to tremolite also found that tremolite exposure may lead to increased ROS production, toxicity, and genotoxicity (Wagner et al., 1982; Okayasu et al, 1999). As with the in vivo studies, the definition of fibers and how the exposures were measured varies among studies.

Table 4-19. In vitro data following exposure to Libby Amphibole asbestos				
Test system	**Fiber type**	**Dose/exposure duration**	**Effects**	**Reference**
Primary human alveolar macrophages and lymphocytes	Libby Amphibole asbestos or crocidolite	0, 25, 50 µg/mL 24 h	Upregulated TH1 and TH2 cytokines (IFNgamma, IL-4, IL-13)	Hamilton et al., 2004
Murine macrophages (primary and RAW264.7)[a]	Libby Amphibole asbestos and crocidolite	Internalization: 0, 5, 62.5 µg/cm^2 3–24 h	Internalized Libby Amphibole asbestos fibers were mostly less than 2 µm in length.	Blake et al., 2007
		Oxidative stress: 0, 6.25, 32.5, 62.5 µg/cm^2 3, 7, 12, and 24 h	Increased ROS over control (wollastonite) and crocidolite Decreased GSH	
		Cell viability: 0, 6.25, 32.5, 62.5 µg/cm^2 3, 7, 12, and 24 h	No effect was observed on cell viability	
		DNA damage: 0, 6.25, 32.5, 62.5 µg/cm^2 3, 7, 12, and 24 h-	No increase in DNA damage and adduct formation.	
Murine macrophages (primary and RAW264.7)	Libby Amphibole asbestos or crocidolite	0, 62.5 µg/cm^2 0–72 h	Time-course dose response for apoptosis; Redistribution of autoantigen on cell surface	Blake et al., 2008
Human lung epithelial cells (wild-type and XRCC1-deficient)	Libby Amphibole asbestos or crocidolite	5 µg/cm^2 24 h	Dose-dependent increase in micronuclei in both cell types, but increased in the XRCC1-deficient cells as compared to wild-type	Pietruska et al., 2010
Human mesothelial cells (LP9/TERT-1 and HKNM-2)	Libby amphibole asbestos or crocidolite	0, 15×10^6 µm^2/cm^2 (non-toxic) and 75×10^6 µm^2/ cm^2 (toxic) for 8 or 24 h	Alterations in genes related to oxidative stress, particularly SOD2	Hillegass et al., 2010
Primary human airway epithelial cells (HAECs)	Libby Amphibole asbestos (fractionated and unfractionated), amosite (fractionated and unfractionated) , crocidolite	0, 2.64, 13.2 or 26.4 µg/cm^2 2, 4 or 24 h	Increases in pro-inflammatory gene expression and ROS production	Duncan et al., 2010

[a]All results for RAW264.7. Data not shown for primary cells though authors state similar response to RAW264.7.

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

Table 4-12. In vitro data following exposure to tremolite asbestos				
Test system/species	**Fiber type**	**Dose/exposure duration**	**Effects**	**Reference**
Primary murine macrophages	Sample A (flake-like from California talc deposits); Sample B (medium-sized fibrous from Greenland); Sample C (fine-fiber material from S. Korea); Positive Control (crocidolite)	0, 50, 100, and 150 µg/mL 18 h	LDH and BGL levels increased following exposure to Sample C (longer, thinner fibers) and crocidolite (positive control). Sample C led to the greatest increases in giant cell formation and cytotoxicity of samples tested. Sample B also led to some increased cytotoxicity.	Wagner et al., 1982
TA98, TA100, TA102 *S. typhimurium*	Metsovo tremolite	TA98, TA100, and TA102: 0–500 µg/per plate 2 days	No significant revertants were observed in any of the three Salmonella strains tested.	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

A[L] cells (hamster hybrid cells containing human chromosome 11)	Tremolite, erionite, RCF-1	0–400 µg/mL 24 h	No significant increase in HPRT mutations for these three fibers; Dose-dependent induction of mutations in CD59 did occur for erionite and tremolite.	Okayasu et al., 1999

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

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4.5. SYNTHESIS OF MAJOR NONCANCER EFFECTS

The non-cancer health effects observed following inhalation exposure to Libby Amphibole asbestos include pleural thickening and asbestosis. Recent studies have also examined non-cancer health effects following exposure to Libby Amphibole asbestos in other systems, including autoimmune effects and cardiovascular disease.

4.5.1. Pleural Thickening

Pleural thickening includes two distinct biological lesions, discrete pleural plaques in the parietal pleura and diffuse pleural thickening of the visceral pleura. Although the visceral and parietal pleura provide a continuous lining for the interior of the thoracic cage, wrapping around the lobes of the lung, they are distinct (Jones, 2002; Broaddus et al., 2011). Differences lie primarily in the submesothelial layers, the existence of stomata in the parietal pleura and greater innervations of the parietal pleura (Jones, 2002.) Although discrete pleural plaques may extend to impact a large surface, these deposits lie between the pleural membrane and the thoracic cavity, and fusing of discrete pleural plaques do not constitute a diagnosis of diffuse pleural thickening, since this diagnosis specifically refers to thickening of the visceral pleura (ATS 2004, ILO B-Reader standards). There are reports of discrete plaques in the visceral pleura, which may be localized thickening of this tissue. It should also be noted that extensive thickening of the visceral pleura may be accompanied by fusing between the parietal and visceral surfaces of the pleural membrane where there are discrete plaques. Thickening of the visceral pleura is more often localized to lobes of the lung with pronounced parenchymal changes and it has been hypothesized that the inflammatory and fibrogenic processes within the lung parenchyma may influence the fibrogenic process in the visceral pleura.

In clinical settings there are difficulties in distinguishing between these two lesions in part due to lack of radiographic film diagnostic specificity as well as the ILO definitions for diffuse pleural thickening of the visceral pleura which may result in some variability in reporting of discrete pleural plaques. There are two classifications for pleural thickening in current guidelines (ILO, 2000). Diffuse pleural thickening is currently only determined where there is thickening along significant extent of the chest wall, and this thickening is "in the presence of and in continuity with, an obliterated costophrenic angle [7]" (ILO, 2000). Although previous

[7] **Obliteration of the costophrenic angle (CA):** The costophrenic angle is measured as the angle between the ribcage and the diaphragm on a posterior anterior viewed radiograph (the costophrenic recess, Figure 5-1). When CA blunting or obliteration is noted on a radiograph it is recorded as present or absent (ILO, 2000). Obliteration of the CA may occur in the absence of other radiographic signs. However, where it occurs in conjunction with pleural thickening, it may be used to define the type of pleural thickening.

classification schemes attempted to distinguish between thickening of the parietal pleura and diffuse thickening of the visceral pleura, the ILO states" reading standard x-rays cannot always distinguish between thickening of the visceral or parietal pleura" (ILO, 2000). Thus, all other pleural thickening is now defined as localized pleural thickening (i.e. where there is no costophrenic angle obliteration). Localized pleural thickening on the chest wall, and diffuse pleural thickening may be graded indicating thickness, and the extent of the chest wall impacted, however these data are not always provided in study reports, therefore regardless of extent of the pleural thickening, only presence or absence may be noted.

4.5.2. Asbestosis

Asbestosis is the most severe nonmalignant disease associated with exposure to asbestos fibers. Asbestosis is the interstitial pneumonitis and fibrosis caused by inhalation of asbestos fibers and becomes evident only after an appreciable latency period. Asbestosis is characterized by a diffuse increase of collagen in the alveolar walls (fibrosis) and the presence of asbestos fibers, either free or coated with a proteinaceous material and iron (asbestos bodies). The mildest form of asbestosis involves the alveolated walls of respiratory bronchioles and the alveolar ducts. More severe grades involve greater proportions of the acinus until the whole acinar structure is involved and some alveoli are completely obliterated (ATS, 2004). A profusion of irregular opacities at the level of 1/0 is used as the boundary between normal and abnormal. Asbestosis is associated with dyspnea, bibasilar rales, and changes in pulmonary function: a restrictive pattern, mixed restrictive-obstructive pattern, and/or decreased diffusing capacity (ATS, 2004). In one of the earliest studies conducted, about 50% of the asbestos workers presented with a FVC below 80% of predicted (ATS, 2004).

Radiographic evidence of small opacities in the lung is direct evidence of scarring of the lung tissue and as the fibrotic scaring of lung tissue consistent with mineral dust and mineral fiber toxicity. The scarring of the parenchymal tissue of the lung contributes to measured changes in pulmonary function, including obstructive pulmonary deficits from narrowing airways, restrictive pulmonary deficits from impacting the elasticity of the lung as well as decrements in gas exchange. However, although data across the mineral fiber literature strongly support a finding of functional deficits where small opacities are visible on radiographs, the data also indicate that deficits in pulmonary function (consistent with interstitial fibrosis) are seen before these changes are detected by radiographic examination. Thus changes in lung function may occur before the fibrotic lesions can be detected on standard radiographs (ATS, 2004 and Brodikin et al., 1994). For example, decreased CO_2 diffusion is a sign of reduced gas exchange in the pulmonary region of the lung and is observed in workers exposed to other types of asbestos even when small opacities are absent on radiographs. Similarly, obstructive deficits in

lung function may be observed without radiographic signs for fibrotic lesions. As decreased diffusion and obstructive deficits are mechanistically linked to changes in the parenchymal tissue these data suggest radiographs may not be sensitive enough to protect against adverse effects from parenchymal effects of asbestos exposure.

4.5.3. Other noncancer health effects (cardiovascular toxicity, autoimmune effects)

There is limited available research available on noncancer health effects occurring outside the respiratory system. Two such effects (cardiovascular toxicity and autoimmunity) have been examined following Libby Amphibole asbestos exposures and thus, are discussed briefly here. Recent studies have explored the role of asbestos exposure in cardiovascular disease (Larson et al., 2010). Mechanistic studies have examined the potential role of iron and the associated inflammation for both the respiratory and cardiovascular disease (Shannahan et al., 2011). Limited studies have examined a causal association between asbestos exposure and autoimmune disease (reviewed in Bunderson-Schelvan et al., 2011), but limitations in the scope and number of these studies makes it difficult to reach conclusions as to the role of asbestos exposure in autoimmunity.

4.5.4. Libby Amphibole asbestos summary of non-cancer health effects

The studies in humans summarized in Section 4.1 have documented an increase in mortality from non-malignant respiratory disease and in radiographic changes in the pleura and parenchyma among employees of the Libby vermiculite mining operations (Amandus et al., 1987a, b, c; McDonald et al., 2004, 1986a, b; Sullivan 2007; Larson et al. 2010a). Additional studies (Lockey et al., 1984; Rohs et al., 2008) have documented an increase in radiographic changes in the pleura and parenchyma among employees of a manufacturing facility in Marysville, Ohio that used Libby vermiculite ore contaminated with Libby Amphibole asbestos. These studies used ILO diagnostic criteria and demonstrated that the increases in prevalence of adverse effects in the lung and pleural cavity are positively associated with increased cumulative exposure to Libby Amphibole asbestos. Finally, additional studies have documented an increase in pleural abnormalities (Peipins et al., 2003; Muravov et al., 2005) and progressive loss of lung function (Whitehouse, 2004) among residents of Libby, Montana. Two studies (Pfau et al, 2005; Noonan et al., 2006) conducted among residents of Libby, Montana, support the hypothesis that auto-immunity may also be associated with exposure to Libby Amphibole asbestos. Larson et al. (2010a) also showed that Libby Amphibole may increase mortality from cardiovascular toxicity in residents of Libby.

Although experimental data in animals and data on toxicity mechanisms are limited for Libby Amphibole asbestos, the existing data are consistent with the non-cancer health effects observed in both Libby workers and community members. Pleural fibrosis was increased in hamsters after intrapleural injections of Libby Amphibole asbestos (Smith, 1978). More recent studies have demonstrated increased collagen deposition consistent with fibrosis following intratracheal instillation of Libby Amphibole asbestos fibers in mice (Putnam et al., 2008; Smartt et al., 2009). Pulmonary fibrosis, inflammation, and granulomas were observed after tremolite inhalation exposure in Wistar rats (Bernstein et al., 2003, 2005) and intratracheal instillation in albino Swiss mice (Sahu et al., 1975). Davis et al. (1985) also reported pulmonary effects after inhalation exposure in Wistar rats including increases in peribronchiolar fibrosis, alveolar wall thickening, and interstitial fibrosis. A recent study by Shannahan et al. (2011) examined the effect of exposure to Libby Amphibole asbestos in rats with pre-existing cardiovascular disease, and found strain-related differences for biomarkers of inflammation following exposure to Libby Amphibole asbestos. This short-term study only examined animals for 1 month post-exposure, so the long-term effect of altered inflammation is unknown. Limited in vitro studies have demonstrated oxidative stress following Libby Amphibole asbestos exposures in various cell types (Blake et al., 2007; Pietruska et al., 2010; Hillegass et al., 2010; Duncan et al. 2010). Libby Amphibole asbestos fibers increased intracellular ROS in both murine macrophages and human epithelial cells (Blake et al., 2007; Duncan et al., 2010). Surface iron, inflammatory marker gene expression were increased following exposure to Libby Amphibole asbestos in human epithelial cells (Duncan et al., 2010; Pietruska et al., 2010; Shannahan et al., 2011). Tremolite studies demonstrate cytotoxic in various cell culture systems.

4.5.5. Mode-of-Action Information (non-cancer)

The precise mechanisms causing toxic injury from inhalation exposure to asbestos or other mineral fibers have not been established. However, nearly all-durable mineral fibers with dimensional characteristics that allow penetration to the terminal bronchioles and alveoli of the lung have the capacity to induce pathologic response in the lung and pleural cavity (ATSDR, 2001; Witschi and Last, 1996). The physical-chemical attributes of mineral fibers are important in determining the type of toxicity observed. Fiber dimension (width and length), density and other characteristics such as chemical composition, surface area, solubility in physiological fluids, and durability all play important roles in both the type of toxicity observed and the biologically significant dose. Fibrosis results from a sequence of events following lung injury which includes inflammatory cell migration, edema, cellular proliferation and accumulation of collagen. There is currently insufficient evidence to determine the non-cancer mode of action for

Libby Amphibole asbestos. However, current support for mechanisms (i.e., chronic inflammation, cytotoxicity and cellular proliferation) involved in potential non-cancer health effects following exposure to Libby Amphibole asbestos are described below.

4.5.5.1. *Chronic Inflammation*

Chronic pulmonary inflammation has been observed following inhalation exposure to fibers, which is often followed by fibrosis at the site of inflammation if the fibers persist (Oberdorster, 1994). 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. As described in Section 3, fibers that are deposited in the lung may be taken up by alveolar macrophages. Once engulfed by the macrophage, small fibers may remain in place or be translocated across the bronchiole or alveolar membrane to the interstitial and pleural space. Longer fibers that are not easily engulfed by the macrophages may remain in the alveoli for an extended period of time. Further, longer fibers partially engulfed by macrophages may lead to increased release of inflammatory mediators (i.e., frustrated phagocytosis) (Gwinn and Vallyathan 2006). It is believed that these macrophages release mediators (lymphokines and growth factors) that attract immunocompetent cells or stimulate collagen production. Thus the mediators of the disease may be an on-going inflammatory response as a result of the prolonged "residence time" of the fibers within the lung parenchyma. This increased inflammatory response may be involved in the pathogenesis of pleural fibrosis and asbestosis.

Laboratory animal studies of general asbestos exposure generally demonstrate inflammatory changes in the lung and pleura followed by cellular proliferation; the level of this effect is believed to be dependent on various fiber characteristics (McConnell et al., 1999). The inflammatory response to fibers has been studied in depth for other types of asbestos (crocidolite, chrysotile) but not for Libby Amphibole asbestos or tremolite (reviewed in Mossman et al., 2007). Although limited, the data described here for Libby Amphibole asbestos, and to a greater extent for tremolite, suggest a similar response in the lung and pleura. In vivo exposure to tremolite led to an increase in inflammation for all studies where it was measured. This increase appeared in some cases to depend on fiber size and morphology (Smith et al., 1979; Davis et al., 1991). Bernstein et al. (2003, 2005) observed that exposure to tremolite led to pronounced inflammation as soon as 1 day after inhalation exposure in male Wistar rats. Inflammation also occurred in male albino Swiss mice in an acute-duration study that did not lead to fibrosis or carcinogenesis, possibly due to the short study duration (150 days) (Sahu et al., 1975). In vitro analysis of Libby Amphibole asbestos showed increases in inflammatory cytokines (Hamilton et

al., 2004) and in pro-inflammatory gene expression (Duncan et al., 2010).

Inflammation is observed in animal studies for Libby Amphibole asbestos and tremolite and is relevant to humans based on similar responses in other asbestos-exposed cohorts analyzed (Musk et al., 2008; Hein et al., 2007; Levin et al., 1998). Therefore, the evidence described above suggests chronic inflammation is observed following Libby Amphibole and tremolite asbestos exposure; however, the role of inflammation in the non-cancer health effects (e.g., pleural thickening) following exposure to Libby Amphibole asbestos is unknown.

4.5.5.2. *Cytotoxicity and Cellular Proliferation*

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

Although slightly increased compared to controls, cytotoxicity in murine macrophage cells exposed to Libby Amphibole asbestos was decreased compared to other fiber types (Blake et al., 2008). Cytotoxicity was slightly, but statistically significantly, increased compared to an unexposed control at 24 hours post exposure to Libby Amphibole asbestos, while crocidolite exposure resulted in even higher levels of cytotoxicity. No other in vitro study examined cytotoxicity following exposure to Libby Amphibole asbestos, although an increase in apoptosis was demonstrated in this same cell system (Blake et al., 2008). Recent studies in mice exposed to Libby Amphibole asbestos demonstrated increased collagen deposition and collagen gene expression, markers of fibrosis (Putnam et al., 2008; Smartt et al., 2009). Tremolite and Libby Amphibole asbestos exposure led to increases in both fibrosis in all but one animal study, supporting a role for proliferation in response to these fibers. Taken together with studies on other asbestos fibers, these data suggest that a cytotoxicity and cell proliferation may play a role in the non-cancer health effects following exposure to Libby Amphibole asbestos.

4.6. EVALUATION OF CARCINOGENICITY

4.6.1. Summary of Overall Weight of Evidence

Under the U.S. EPA Guidelines for Carcinogen Risk Assessment (U.S. EPA, 2005a) Libby Amphibole asbestos is "carcinogenic to humans" following inhalation exposure based on

epidemiologic evidence that shows a convincing association between exposure to Libby Amphibole asbestos fibers and an increased incidence of lung cancer and mesothelioma and subsequent mortality (McDonald et al., 1986a, 2004; Amandus and Wheeler, 1987; Sullivan, 2007, Larson et al., 2010b, Moolgavkar et al., 2010). These results are further supported by animal studies that demonstrate the carcinogenic potential of Libby Amphibole asbestos fibers and tremolite fibers in rodent bioassays. As a durable mineral fiber of respirable size, this conclusion is consistent with the extensive published literature that documents the carcinogenicity of amphibole fibers.

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

Libby, MT workers have been the subject of multiple mortality studies demonstrating an increased cancer mortality in relation to estimated fiber exposure. Occupational studies conducted in the 1980s (Amandus and Wheeler, 1987; McDonald et al., 1986a) as well as the extended follow-up studies published in more recent years (Sullivan et al., 2007; McDonald et al., 2004; Larson et al., 2010b) and additional analyses of the extended follow-up (Moolgavkar et al., 2010) provide evidence of an increased risk of lung cancer mortality and of mesothelioma mortality among the workers exposed to Libby amphibole asbestos in the Libby vermiculite mining and processing operations. Positive exposure-response relationships are shown in each study. Although a plateauing of the increased risk of lung cancer (relative risks of 1.4 and 1.5) in the two highest exposure categories (23.0–99 and ≥ 100 fibers/cc-yrs) was seen in Sullivan (2007). This type of pattern is commonly seen in occupational cohort mortality studies (Stayner et al., 2003) and does not diminish the weight of these results in supporting the determination of the carcinogenicity of Libby Amphibole asbestos. This association is also supported by the case series of 11 mesothelioma patients among residents in or around Libby, MT and among family members of workers in the mining operations (Whitehouse et al., 2008).

Although experimental data in animals and data on toxicity mechanisms are limited for Libby Amphibole asbestos, tumors were observed in tissues similar to those in humans (mesotheliomas, lung cancer) indicating the existing data are consistent with the cancer effects observed in humans exposed to Libby amphibole asbestos. Smith (1978) reported increased incidence of mesotheliomas in hamsters after intrapleural injections of Libby Amphibole asbestos. Additionally, studies in laboratory animals (rats and hamsters) exposed to tremolite via inhalation (Bernstein et al., 2005, 2003; Davis et al., 1985), intrapleural injection (Smith et al., 1979; Wagner et al., 1982; Davis et al., 1991, Roller et al., 1997, 1996) or implantation (Stanton et al., 1981) have shown increases in mesotheliomas and lung cancers. Tremolite from various sources was used and varied in fiber content and in potency (Section 4.2.1.2). Although

McConnell et al. (1983a) observed no increase in carcinogenicity following oral exposure to nonfibrous tremolite, the ability of this study to inform the carcinogenic potential of fibrous tremolite through inhalation is unclear, and these study results contribute little weight to the evaluation of the carcinogenicity of fibrous Libby Amphibole asbestos.

The available mechanistic information suggests Libby Amphibole asbestos induces effects that may play a role in carcinogenicity (Section 4.3.2). Several in vitro studies have demonstrated oxidative stress and genotoxicity following Libby Amphibole asbestos exposures in various cell types (Blake et al., 2007; Pietruska et al., 2010; Hillegass et al., 2010; Duncan et al. 2010). Libby Amphibole asbestos increased intracellular ROS in both murine macrophages and human epithelial cells (Blake et al., 2007; Duncan et al., 2010). Additionally, surface iron, inflammatory marker gene expression and aneugenic micronuclei were increased following exposure to Libby Amphibole asbestos in human epithelial cells (Duncan et al., 2010; Pietruska et al., 2010). Tremolite studies demonstrate cytotoxic and clastogenic effects (micronucleus induction and chromosomal aberrations) of the fibers in various cell culture systems.

In summary, the epidemiologic data demonstrate an association between exposure to Libby Amphibole asbestos and increased cancer incidence. Supporting evidence of carcinogenicity was observed in laboratory animal studies exposed to Libby Amphibole asbestos or tremolite following multiple routes of exposure in multiple species (see Table 4-20, 4-31). Overall, the available evidence supports the conclusion that Libby Amphibole asbestos is carcinogenic to humans.

4.6.2. Mode–of-Action Information

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

EPA guidance provides a framework for analyzing the potential mode(s) of action by which physical, chemical, and biological information is evaluated to identify key events in an agent's carcinogenicity (U.S. EPA, 2005). Agents can work through more than one mode of action (MOA), and MOA can differ for various endpoints (e.g., lung cancer versus mesothelioma). Reasonably, the analysis of a MOA would start with some knowledge of an agent's biological activity that leads to cellular transformation resulting in carcinogenicity. Although early steps in the process often can be identified, carcinogenicity is a complex process resulting from multiple changes in cell function. Due to the limited data available specific to Libby Amphibole asbestos, the mode of action of Libby Amphibole asbestos for lung cancer and mesothelioma following inhalation exposure is unknown.

Research on various types of mineral fibers supports the role of multiple potential events following exposure to asbestos in general (i.e., chronic inflammation, generation of reactive

oxygen species (ROS), direct genotoxicity, and cytotoxicity and cellular proliferation) in the carcinogenic response to mineral fibers. It is possible that these events are relevant to both the non-cancer and cancer effects following exposure to Libby Amphibole asbestos. However, mechanistic information of these effects following exposure to Libby Amphibole asbestos and/or tremolite is restricted to a limited number of laboratory animal and in vitro studies. These effects are described below, including discussion of the data limitations for reaching a conclusion regarding the mode of action for Libby Amphibole asbestos. Multiple key events for one particular MOA have not been identified; therefore the mode of action for Libby Amphibole asbestos carcinogenicity cannot be established.

4.6.2.1.1. Chronic inflammation

As described in Section 4.5.1.1, chronic pulmonary inflammation has been observed following inhalation exposure to fibers, which is often followed by fibrosis at the site of inflammation if the fibers persist (Oberdorster, 1994). Chronic inflammation is hypothesized to lead to a carcinogenic response through the production of reactive oxygen species and increased cellular proliferation (Hannahan and Weinberg 2011). Although limited, the data described in Section 4.5.1.1 suggest an increase in inflammatory response following exposure to Libby Amphibole and tremolite asbestos similar to that observed for other durable mineral fibers (reviewed in Mossman et al., 2007). Whether this inflammatory response then leads to cancer is unknown. Studies examining other types of asbestos (crocidolite, chrysotile, and amosite) have demonstrated an increase in chronic inflammation as well as respiratory cancer related to exposure (reviewed in Kamp and Weitzman, 1999). Chronic inflammation has also been linked to genotoxicity and mutagenicity following exposure to some particles and fibers (Driscoll et al., 1995, 1996, 1997). The evidence described above suggests chronic inflammation is observed following Libby Amphibole and tremolite asbestos exposure; however, the role of inflammation and whether it leads to lung cancer or mesothelioma following exposure to Libby Amphibole asbestos is unknown.

4.6.2.1.2. Reactive oxygen and nitrogen species production

Fiber exposure has been shown to lead to increases in ROS (reviewed in Kamp et al., 1992). Fibers can directly lead to the production of ROS by iron-catalyzed generation through the Fenton reaction. ROS are also produced following phagocytosis of fibers. ROS production following exposure to asbestos has been shown to be associated with DNA damage, chronic inflammation, and lipid peroxidation. As described in Section 4.3.2.1.1, chronic inflammation may lead to increased proliferation and DNA damage, which in turn may lead to tumor

formation. The hydroxyl radical produced as part of the ROS production following fiber exposure has been shown to directly interact with DNA (Leanderson et al., 1988).

ROS production has been measured in response to both Libby Amphibole asbestos and tremolite exposure. The study of Libby Amphibole asbestos (Blake et al., 2007) demonstrated an increase in superoxide anion. Blake et al. (2007) also demonstrated that total superoxide dismutase was inhibited following exposure to Libby Amphibole asbestos, along with a decrease in intracellular glutathione, both of which are associated with increased levels of ROS. These results are supported by a recent study in human mesothelial cells (Hillegass et al., 2010). Increased ROS production was also observed in human airway epithelial cells following exposure to Libby Amphibole asbestos (Duncan et al., 2010). This increase in ROS and decrease in glutathione are a common effect following exposure to asbestos fibers and particulate matter. Limited studies, however, have examined the specific type of ROS produced following exposure to each type of asbestos. Although ROS production is relevant to humans, based on similar human responses as compared to animals, information on the specifics of ROS production following exposure to Libby Amphibole asbestos is limited to the available data described here. Therefore, the role of ROS production in lung cancer and mesothelioma following exposure to Libby Amphibole asbestos is unknown.

4.6.2.1.3. Genotoxicity/mutagenicity

Genotoxicity and, more specifically, mutagenicity, are associated with tumor formation through alterations in genetic material. 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 direct 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 likely to be 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).

One in vitro study examined genotoxicity of Libby Amphibole asbestos by measuring DNA adduct formation following exposure via murine macrophages (primary and immortalized) (Blake et al., 2007). The data showed no increase in adduct formation as compared to unexposed controls. A second study observed increases in micronuclei induction in both normal human lung epithelial cells and XRCC1-deficient cells for both Libby Amphibole and crocidolite asbestos (Pietruska et al. 2010). Two studies of tremolite examined genotoxicity. The first found no significant increase in revertants in the Ames assay (Athanasiou et al., 1992), which is similar to results obtained for other forms of asbestos. This study did find, however, that tremolite exposure led to a dose-dependent increase in chromosome number and micronuclei formation, which has also been described for other asbestos fibers (as reviewed in Hei et al., 2007; Jaurand, 1999). 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 Libby Amphibole asbestos 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 Libby Amphibole asbestos- 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 Libby Amphibole asbestos is unknown.

4.6.2.1.4. 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 affording genotoxic effects an opportunity to multiply. Increased cell proliferative regeneration is also a hallmark of tumor clonal expansion and generally occurs in response to increased apoptosis. As described in Section 4.5.1.2, increased cytotoxicity and cellular proliferation has been observed in in vitro studies following exposure to Libby Amphibole asbestos and tremolite. Tremolite and Libby Amphibole asbestos exposure led to increases in both fibrosis and tumorigenicity in all but one animal study, supporting a possible role for proliferation in response to these fibers. Taken together with studies on other asbestos fibers, these data suggest that a cytotoxicity and cell proliferation may play a role in tumor formation. However, there is limited data to demonstrate that increased cytotoxicity and cellular

proliferation following exposure to Libby Amphibole asbestos leads to lung cancer or mesothelioma.

Summary. Data for Libby Amphibole asbestos and tremolite provide limited evidence that suggest chronic inflammation, ROS, genotoxicity, and cytotoxicity and cellular proliferation may play a role in the carcinogenicity of Libby Amphibole asbestos. However, data are inadequate to establish how these effects may lead to lung cancer or mesothelioma following exposure to Libby Amphibole asbestos.

4.6.2.2. *Application of the Age-Dependent Adjustment Factors (ADAFs)*

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

4.7. SUSCEPTIBLE POPULATIONS

Certain populations may be more susceptible to adverse health effects from exposure to Libby Amphibole asbestos. Because the adverse health effects resulting from exposure to Libby Amphibole asbestos have been, for the most part, 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 non-occupational exposure in other age groups, in other genders (i.e., females), and in different race 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 the ability to distinguish true differences from chance variation in effect estimates is related to the sample size and statistical power, which, in most cases, is quite limited in these studies. In addition, genetic polymorphisms, preexisting health conditions, and differences in nutritional status may alter an individual's response to Libby Amphibole asbestos. 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 Libby Amphibole asbestos. Where data are available, each of these factors is discussed below with respect to increased susceptibility to non-cancer effects and cancer from exposure to Libby Amphibole asbestos, and where information specific to Libby Amphibole asbestos is not available, the general literature on the toxicity of mineral fibers is briefly referenced.

There are also factors which may influence one's exposure potential to asbestos based on lifestage or other defined population. For example, children spend more hours outside and may engage in activities which impact exposure level compared to adults (NRC, 1993; US EPA 2006.) Since lifestage and activity patterns which increase exposure potential may increase the potential for health effects from exposure, these factors define those 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 Libby amphibole asbestos.

4.7.1. Influence of Different Lifestages on Susceptibility

Individuals at different lifestages differ from one another physiologically, anatomically, and biochemically. Individuals in early and later lifestages 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 (ILSI, 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 lifestages might respond differently and thus potentially be more susceptible to adverse healtheffects of Libby Amphibole asbestos exposure.

4.7.1.1. *Lifestage Susceptibility*

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

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

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

For exposure to other types of asbestos, studies have reported non-cancer outcomes in early lifestages. Those in the very young include reports of stillbirth (Haque et al., 1996, 1998) and death among infants (age 1-27 months) due to sudden infant death syndrome and bronchopulmonary dysplasia (Haque and Kanz, 1988). These studies found higher levels of asbestos in the lungs of those who died compared to controls. In the infant study, the authors

speculate that either there was a pre-existing abnormal lung physiology in these children that may contribute to a reduced ability to clear fibers from the lung, or that the children could have an increased exposure to asbestos (Haque and Kanz, 1988). Those in older children include reports of pleural and diaphragmatic calcifications (Epler et al., 1980) and altered immune and respiratory conditions (Shtol et al., 2000).

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

It is possible that early lifestage exposure may increase the risk of non-cancer outcomes in adulthood compared to adult exposure. For instance, one man exposed to Libby amphibole when he was 18-19 years old was diagnosed with asbestosis at 65 years old (Wright et al., 2002). After tremolite exposure during childhood, there is one study of altered immunity in adulthood (Zerva et al., 1989) and a case report of asbestosis in adulthood (Voisin et al., 1994). Another study also reported an increased risk of asbestosis in after childhood exposure to asbestos from parental occupational exposure to asbestos (Kilburn et al., 1985).To address the potential for increased susceptibility to cancer from early lifetime exposures, one needs to consider if there is evidence of differential health effects such as increased potency from early lifetime exposure; decreased latency based on the age of exposure or cancers observed with early lifetime exposures not seen with adult exposures. There are no published reports that can directly answer these questions for exposure to Libby amphibole asbestos.

While cancers in adults have been documented following exposure to Libby Amphibole asbestos, similar reports describing childhood cancers resulting from this exposure have not been identified. Few cancers occurring in children have been documented in children exposed to any form of asbestos. Examples of cases include a 17-year-old exposed to chrysotile and tremolite (Andrion et al., 1994) and a 3-year-old exposed to chrysotile (Lieben and Pistawka, 1967), both of whom developed mesothelioma. However, childhood mesothelioma, in particular, may have an etiology that is different from that of the disease that is seen in adults (Cooper et al., 1989).

No cancer bioassays have been performed in juvenile animals exposed to Libby Amphibole asbestos.

There are several case reports of individuals who were exposed to Libby amphibole asbestos as children who were later diagnosed with mesothelioma (Whitehouse et al., 2008). Of the 11 cases described by Whitehouse et al. (2008), 2 reported potential exposure scenarios that were limited to childhood, and both of these were diagnosed at a relatively young age at diagnosis (48, compared with 52 to 82 years of age for the other 9 cases). Although these case studies support the link between exposure to Libby amphibole asbestos and mesothelioma, it is unclear if children are more susceptible than adults.

Case reports of exposure to tremolite during childhood, and subsequent diagnosis of mesothelioma in adulthood (Magee et al., 1986; Rey et al., 1993; Sakellariou et al., 1996; Schneider et al., 1998; Senyigit et al., 2000), support the limited data summarized above for Libby Amphibole asbestos. Additional case studies of mesothelioma after childhood exposure to other types of asbestos are available (Anderson et al., 1976; Ascoli et al., 2003; Cazzadori et al., 1992; Inase et al., 1991; Kane et al., 1990; Li et al., 1978, 1989; Magnani et al., 2001; Martensson et al., 1984; Roguin et al., 1994; Rom et al., 2001; Schneider et al, 1995, 1996a, 1996b; Wagner et al., 1960; Wassermann et al., 1980; Yano et al., 2009). These studies, however, do not clarify whether exposure during childhood yields different adverse health effects compared with exposure during adulthood.

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

Studies of exposure to other types of asbestos have attempted to determine if exposure to asbestos in early life results in an increased risk of developing cancer. An early study in the United Kingdom described occupational exposure to chrysotile, crocidolite, and amosite for a group of 900 women. First exposure from ages 15–24 years led to a higher relative mortality risk for lung and pleural cancer compared with women who were first exposed at older ages (SMR 30 based on 12 observed and 0.4 expected, SMR 8 based on 4 observed and 0.5 expected, and SMR 6.7 based on 6 observed and 0.9 expected in the first exposure at ages 15-24, 25-34, and ≥35 years, respectively) (Newhouse et al., 1972). A study by Hansen et al. (1998) in Wittenoom, Western Australia examined 27 individuals diagnosed with mesothelioma who had been environmentally exposed to crocidolite (i.e., residents of the town but not directly employed in the area's crocidolite mining and milling industry); 11 of these subjects were children

<15 years old at the time of exposure. One-third of all the subjects were less than 40 years old when diagnosed, but the authors found no increase in mesothelioma mortality rates when analyzed by age at first exposure. However, risk was significantly increased based on time from first exposure, duration of exposure, and cumulative exposure (Hansen et al., 1998). Additional studies of this cohort found that the mesothelioma mortality rate was lower for those first exposed (based on age residence in the area began) to crocidolite at ages <15 years (n = 24; mesothelioma mortality rate 47 per 100,000 person-years) compared with those first exposed at ages ≥15 years (n = 43; mesothelioma mortality rate 112 per 100,000 person-years) (Reid et al., 2007). The hazard ratio for age at first residential exposure of ≥15 years compared with <15 years was 3.83 (95% CI 2.19, 6.71), adjusting for cumulative exposure, gender, and an interaction term for gender and cumulative exposure.

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

Later lifestage is generally defined as ≥65 years old. Because pulmonary function (volume and rate of breathing) decreases with age, increased deposition of fibers in the lung from exposures in later lifestages is unlikely. Clearance of fibers from the lung might be reduced, however, as older adults have a less effective cough reflex and strength and the cilia are less able to move mucus up and out of the airway (U.S. EPA, 2005). Older adults could be more susceptible to the effects of Libby Amphibole asbestos due to the gradual age-related decline in physiological processes. Additionally, decreased immune function, increased genetic damage, and decreased DNA repair capacity can result in increased susceptibility with age (U.S. EPA, 2005). 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 Libby amphibole asbestos on these processes are not available.

Due to the natural increase of non-cancer health effects among older adults, it is likely that older individuals exposed to Libby amphibole at some point in their lives will have elevated rates of disease. Radiographic tests among those exposed to Libby amphibole show that older age is one of the factors most associated with pleural or interstitial abnormalities (Amandus et al., 1987b; ATSDR, 2001; Horton et al., 2006; Lockey et al., 1984; McDonald et al., 1986b; Muravov et al., 2005; Peipins et al., 2003; Rohs et al., 2008). However, abnormal radiographs

are more common with age (Pinsky et al., 2006). In workers 65-years-old and over at the time of screening, an increased risk of systemic autoimmune disease and rheumatoid arthritis was observed among mine workers, as well as those who were exposed to asbestos in the military (Noonan et al., 2006). However, systemic autoimmune disease, rheumatoid arthritis, and systemic lupus erythematosus are more common in those aged 45-64 compared to those aged 17-44 years or those 65 years old and older (Noonan et al., 2006).

While these results show more non-cancer effects among older individuals exposed to Libby amphibole, the available studies do not assess the timing of the exposure in relation to these outcomes. This data is necessary to evaluate if older individuals are more susceptible than younger individuals. Therefore, no conclusions can be drawn about differential risk of non-cancer after later lifestage 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 Libby Amphibole asbestos. It should be noted that observed health effects among individuals exposed to Libby Amphibole asbestos are likely to increase with increasing age due to the long latency period for the exposure-response for asbestos and lung cancer and other chronic diseases. However this type of observation would not directly address the question of whether exposures at older ages have a stronger or weaker effect compared with exposures at younger ages.

4.7.2. Influence of Gender on Susceptibility

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

Most occupational studies for Libby Amphibole asbestos have examined the effects of exposure only in men (Amandus and Wheeler, 1987; Amandus et al., 1987a, 1988; McDonald et al., 1986a, 1986b, 2004; Sullivan, 2007; Moolkavkar et al., 2010). There is limited information specifically on women exposed to Libby Amphibole asbestos. In the Libby, MT community studies, no gender-related trends in mortality due to lung or digestive cancer were observed

(ATSDR, 2000). These limited data do not provide a basis for drawing conclusions regarding gender-related differences in adverse health effects from Libby Amphibole asbestos.

4.7.3. Influence of Race or Ethnicity on Susceptibility

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

Of the occupational and residential studies for Libby Amphibole asbestos, the vast majority of subjects with known race were white, precluding the ability to conduct an analysis of racial and ethnicity-related differences in the mortality risks within the Libby worker cohort. In a study of occupational exposure to chrysotile asbestos in a textile factor, lung cancer mortality risk in relation to exposure was lower in non-white males (0.84, 95% CI = 0.52–1.27) compared to white males (2.34, 95% CI = 1.94–2.79), although a statistically significant increase in SMR was observed for non-white males at high exposure levels (≥120 fiber-years/mL) (Hein et al., 2007). This observed difference could be due to a lower prevalence of smoking among non-white compared with white males (Hein et al., 2007).

4.7.4. Influence of Genetic Polymorphisms on Susceptibility

XRCC1 is a DNA damage repair gene. A recent study demonstrated that XRCC1-deficient cells exposed to Libby Amphibole or crocidolite asbestos demonstrated increased levels of micronuclei induction (Pietruska et al., 2010). Two other studies examined XRCC1 polymorphisms in relation to disease risk with other types of asbestos exposure. Zhao et al. (2005) found no association between XRCC1 polymorphisms and asbestosis in asbestos-exposed workers. A study, by Dianzani et al. (2006), however, did find an association between XRCC1 and asbestos-induced lung disease in a population exposed to asbestos

pollution. Further work is necessary, with clear definitions of patient populations and their exposure levels, so that these studies and others can be compared to determine if XRCC1 polymorphisms increase susceptibility to adverse health effects following exposure to Libby amphibole asbestos.

SODs are free radical scavengers that dismutate superoxide anion to oxygen and hydrogen peroxide. SODs are expressed in most cell types exposed to oxygen. Several common forms of SODs occur and are named by the protein cofactor: copper/zinc, manganese, iron, or nickel. A recent study observed no significant alterations in levels of intracellular SOD following a 3 hr exposure to Libby Amphibole asbestos in mice (Blake et al., 2007). Other studies in humans and mice have examined SOD expression in relation to other types of asbestos exposure. Manganese superoxide dismutase (MnSOD) activity was elevated in biopsies of human asbestos-associated malignant mesothelioma, although no genotypic differences were found to be related to this change in activity (Hirvonen et al., 2002). Other studies have focused on the role of extracellular superoxide dismutase (EcSOD) and asbestos-induced pulmonary disease (Fattman et al., 2006; Gao et al., 2008; Kliment et al., 2008; Tan et al., 2004). These studies have suggested a protective effect of ECSOD, with mice that lack this form of SOD having increased sensitivity to asbestos-induced lung injury (Fattman et al., 2006).

No studies that examine the role of cell-cycle control genes were found. Additionally, no information on other genetic polymorphisms in relation to disease risk among those exposed to Libby Amphibole asbestos was identified in the available literature.

Familial studies showing unusually high incidence of mesothelioma suggest that genetic factors might play a role in the etiology of mesothelioma (Huncharek, 2002; Roushdy-Hammady et al., 2001; Ugolini et al., 2007). Whether a genetic factor or a common environmental element leads to the similar responses in these families is difficult to determine. Increased interest in the role of genetic factors in asbestos-related health outcomes has led to several analytical studies on specific genetic polymorphisms. A review of 24 published reports (19 studies) discusses the current state of knowledge regarding genetic susceptibility associated with asbestos-related diseases (in particular, malignant pleural mesothelioma). Results from several studies demonstrated an association between asbestosis-related diseases and GSTM1-null polymorphism, whereas results for other polymorphisms were conflicting (Neri et al., 2008). Some polymorphisms discussed in Neri et al. (2008) are in genes for N-acetyl-transferase 2 (NAT2); glutathione-s-transferases (GSTs); SOD; CYP1A1, CYP2D6; neurofibromatous 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 (Kleymenova et al., 1997; Vaslet et al., 2002; 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 (Bianchi et al., 1995; Cheng et al., 1999; Mayall et al., 1999). 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 et al., 1999).

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 exposure in humans (Bocchetta et al., 2000; Carbone et al., 2007; Cristaudo et al., 2005; Foddis et al., 2002; Mayall et al., 1999; Kroczynska et al., 2006). Co-exposure to asbestos and SV40 has been associated with p53-related effects in vitro (Mayall et al., 1999; Bocchetta et al., 2000; Foddis et al. 2002), 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 Libby Amphibole asbestos.

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 Libby Amphibole asbestos. For example, individuals with chronic obstructive pulmonary disease have increased inhalation volume (Phalen et al., 2006) and increased fine particle deposition (Bennett et al., 1997; Kim and Kang, 1997; Phalen et al., 2006) 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 et al., 2001; Brown and Bennett, 2004). For people exposed to Libby Amphibole asbestos, an increased risk for interstitial lung abnormalities was observed for those with a history of pneumonia (Peipins et al., 2003). In another study, bronchial asthma was examined as a potential confounding variable for asbestos-related effects on pulmonary function, although no confounding was observed (Whitehouse, 2004).

4.7.6. Influence of Lifestyle Factors on Susceptibility

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

The Libby occupational exposure studies (Amandus et al., 1987a, Amandus and Wheeler, 1987; Larson et al., 2010; McDonald et al., 2004; 2002; 1986a,b; Sullivan, 2007) did not examine the potential interaction between smoking, Libby Amphibole asbestos exposure, and lung cancer risk. However, epidemiological (Lee, 2001; Savastano et al., 2004; Reif and Heeren, 1999) and laboratory studies (Jaurand et al., 1983; Jung et al., 2000; Valavanidis et al., 1996, 2009; Lohani et al., 2002) have examined the potential synergistic effect of asbestos and cigarette smoke co-exposure in lung cancer. A synergistic interaction between the ROS from cigarette smoke and asbestos fibers might contribute to increases in lung cancer in asbestos mine workers (Kamp et al., 1992; Jackson et al., 1987). Research has suggested that asbestos fibers might also enhance the delivery of multiple carcinogens in cigarette smoke, and that cigarette smoking decreases the clearance mechanisms in the lungs and could, therefore, lead to an increase in fiber presence in the lungs (Nelson and Kelsey, 2002). For lung cancer, a synergistic relationship between cigarette smoking and asbestos exposure has been demonstrated (Hammond et al., 1979; Selikoff and Hammond, 1979, Wraith and Mengersen, 2008). Smoking likely causes genetic alterations associated with lung cancer (Landi et al., 2008) that might increase the carcinogenic risk from exposure to asbestos. Benzo(a)pyrene, a component of tobacco, also has been observed to enhance the carcinogenic effects of asbestos (DiPaolo et al., 1983; Kimizuka et al., 1987; Loli et al., 2004; Mossman et al., 1983, 1984; Reiss et al., 1983).

4.7.7. Susceptible Populations Summary

A very limited amount of information is available on exposure to Libby Amphibole asbestos early in life that could lead to increased risk of asbestos-induced disease later in life. Due to the long latency period of some diseases in relation to asbestos exposure in general, however, adverse effects may be more likely to be observed with an increase in age. This assumption requires further investigation. The number of women who have been occupationally exposed to Libby Amphibole asbestos is very small, and health risks have not been evaluated

specifically for this group. Differences between men and women in residential sources and types of exposure (e.g., types of activities done in the household) also preclude the possibility of drawing conclusions regarding the relative susceptibility of women compared with men to health effects of exposure to Libby Amphibole asbestos. Similarly, sufficient data are not available to draw conclusions regarding racial or ethnic variation in susceptibility to diseases caused by exposure to Libby Amphibole asbestos. In addition, the potential modifying effects of genetic polymorphisms, pre-existing health conditions, nutritional status, and other lifestyle factors have not been studied, specifically as related to exposure of Libby amphibole asbestos and health outcomes.

5. EXPOSURE-RESPONSE ASSESSMENT

5.1. ORAL REFERENCE DOSE (RfD)

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

5.2. INHALATION REFERENCE CONCENTRATION (RfC)

5.2.1. Choice of Principal Study and Critical Effect

Studies in humans have shown several health effects on the lung and pleura (a thin tissue surrounding the lung and lining the chest cavity) such as pleural thickening and fibrosis of the lung and pleura as well as potential autoimmune or cardiovascular disease following inhalation exposure to Libby Amphibole asbestos (see Section 4.5). There are no studies in laboratory animals by the inhalation route of exposure suitable for derivation of an RfC since the available animal studies lack adequate dose-response information and are of a short-term duration.

Table 5-1. Summary of rationale for identifying candidate principal studies on Libby Amphibole asbestos for RfC development.

Attribute	Preferred Characteristics for Candidate Principal Studies for the Libby Amphibole Asbestos RfC
Relevance of exposure paradigm	Subchronic or chronic studies over studies of acute exposure duration as most relevant environmental exposure scenarios are expected to address chronic exposure scenarios (potentially including both continuous exposure from ambient conditions and episodic activity-related exposures). Measures of cumulative exposure rather than mean or peak exposure; cumulative exposure is a widely used metric to address asbestos risk. It is consistent with the expectation that toxic responses will reflect accumulative effect of asbestos inhaled and deposited in tissues over time as opposed to shorter term patterns of exposure to asbestos concentrations. Data on exposure concentrations and durations are preferred to address associations with time since first exposure (TSFE), peak exposure, or average intensity. Relatively lower exposure intensities which may represent conditions more similar to environmental exposures.
Study design characteristics	Sufficient follow-up time for outcomes to develop (which can depend on the health outcome being addressed). Study size and participation rates that are adequate to detect and quantify health outcomes being studied; with no indications of bias in study population selection. Use of a study design or analytic approach which adequately addresses the relevant sources of potential confounding, including age, sex, smoking, and exposure to other risk factors (such as non-Libby asbestos).

Measurement of exposure	Exposure estimates should supported by appropriate measurement techniques. Exposure estimates supported by methods that measure fiber exposures for Libby Amphibole asbestos; fiber concentration data based upon phase contrast microscopy (PCM). 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.
Measurement of effect(s)	Emphasis is placed on the more sensitive health outcome endpoints that are available (e.g, generally morbidity findings will be more sensitive than mortality findings). An RfC is intended to be a level at which no category of adverse health outcome would occur. Pleural and parenchymal changes assessed using good quality radiographs, evaluated by ≥1 certified B reader according to International Labour Organization (ILO) standards. Evaluation of radiographs should not be influenced by knowledge of exposure status

Quantitatively, study characteristics preferred for RfC derivation include adequate exposure-response information, ideally with analyses based on estimates including assignment of quantitative exposure estimates to distinguish exposure levels in the study subjects. The evidence for effects on the lung and pleura in humans includes both cohort studies of exposed workers as well as population studies drawn from the Libby community (including former workers). Pleural and lung anomalies have been reported in population studies of individuals exposed in and around Libby, MT (Weill et al., 2010; Peipins et al., 2003; Peipins et al., 2004; Whitehouse 2004; Muravov et al., 2005). However, these morbidity studies based on community/worker populations were not considered as candidate principal studies because quantitative exposure estimates are not available and the studies cannot support derivation of an RfC. Increased respiratory symptoms and bloody phlegm have also been associated with the number of potential pathways of exposure to Libby Amphibole asbestos in the community among individuals under 18 years of age (Vinikoor et al., 2010). Additionally, two studies examined autoimmune effects in community members living in Libby, MT; Noonan et al. (2006) included former vermiculite facility workers, while Pfau et al. (2005) do not specify if former workers were included. These studies (Vinikoor et al. 2010; Noonan et al. 2006; Pfau et al. 2005) do not quantify exposure, and therefore cannot be used for RfC derivation.

Five cohort mortality studies of Libby miners identified increased risk of mortality from non-cancer causes (McDonald et al., 1986a; Amandus et al., 1987b; McDonald et al., 2004; Sullivan, 2007; Larson et al., 2010a). These studies were not considered because mortality is not a preferred endpoint for deriving a reference value. Studies with more sensitive endpoints (i.e. morbidity studies) are preferred to mortality studies. Several morbidity studies examined the quantitative association between exposure to Libby Amphibole asbestos and lesions in the lung or surrounding pleura in exposed human populations; two are studies in Libby miners (Amandus

et al., 1987b; McDonald et al., 1986b) and two are studies in workers from the Marysville facility (Lockey et al., 1984; Rohs et al., 2008). Rohs et al. (2008) was a follow-up study to Lockey et al. (1984) in of the same cohort and reported a higher prevalence of adverse effects following the longer time from first exposure. These four studies, all of which demonstrate an association between Libby Amphibole asbestos exposure and increased risk of effects on the lung and pleura were considered for selection as the principal study to serve as the basis for the derivation of the RfC.

All four candidate principal studies (Rohs et al., 2008; Amandus et al., 1987b; McDonald et al., 1986b; Lockey et al., 1984) have adequate reporting of the studied populations, methods of analysis, statistical analyses, and results. Each of the four candidate studies have shown non-malignant respiratory effects, specifically pleural thickening (localized and/or diffuse) and asbestosis (parenchymal changes and pulmonary fibrosis) in exposed individuals based on guidelines from the International Labour Organization (ILO) for classification of radiographs (ILO, 1971; ILO, 1980; ILO, 2000). Characteristics of these four studies are summarized in Table 5-2. See Sections 4.1.2.2 and 4.1.3 for detailed information for each study.

These candidate studies were then evaluated in terms of quality attributes that would support their use as a principal study in derivation of an RfC. In selecting among potential candidate principal studies, there were several factors, summarized in Table 5-1, that were considered.

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

Cohort and Reference	Study Population	Outcome assessment	Radiographic endpoints evaluated	Exposure assessment	Exposure characteristics
Libby Worker Cohort					
McDonald et al., 1986b	244 employees, comprising 164 "current" workers (as of July 1, 1983) and 80 "past" workers Age at exam (years): "current" "past" <39 80 1 40-59 69 30 >60 15 49 No job tenure information; (10.7 as reported by Armstrong et al., 1988)	Radiographs taken at time of cohort assembly (1983) Films independently read by 3 experienced readers using 1980 ILO standards Film quality: Good: 56% Fair: 36% Poor: 7% Unreadable: 0.4%	1) Parenchymal changes (small opacities $\geq$ 1/0) 2) Pleural changes (Pleural thickening of chest wall, Pleural calcification)	Individual work histories and exposure levels for specific work locations were used to estimate cumulative exposures for cohort members. 1935-1967: Exposure estimated based on professional judgment. For mill locations only (1950-1967) exposure estimated using dust to fiber conversion and interviews with plant employees 1968-1982: Air samples analyzed for fibers by PCM analysis	Mean cumulative exposure "current" 40.1 f/cc-yr "past " 118.9 f/cc-yr Exposure Categories: <10 f/cc-yrs (n=92) 10-20f/cc-yrs (n=64) 20-100 f/cc-yrs (n=53) 100-200 f/cc-yrs (n=16) >200 f/cc-yrs (n=19)
Amandus et al., 1987b	184 men employed 1975-1982, with at least 5 years job tenure Mean (SD), years: Age at exam: 44 (12) Job tenure: 14 (8)	Company radiographs Source year: 1981-82 (72.8%) 1976-1980 (26.6%) <1975 (1 worker) Films independently read by 3 certified B-readers using 1980 ILO standards Film quality (by reader): Acceptable: 60.9, 60.9, 29.3% Poor: 16.3, 14.7, 22.8% Unreadable: None	1) Parenchymal changes (small opacities $\geq$ 1/0) 2) Pleural changes (Pleural thickening at any site withoug costophrenic angle obliteration, pleural calcification, pleural thickening of chest wall only)	Individual work histories and exposure levels for specific work locations were used to estimate cumulative exposures for cohort members. 1935-1967: Exposure estimated based on professional judgment. For mill locations only (1950-1967), exposure estimated using dust to fiber conversion and interviews with plant employees.	Exposure Categories: 0-15 f/cc-yrs (n=63) 16-30 f/cc-yrs (n=29) 31-85 f/cc-yrs (n=44) >86 f/cc-yrs (n=48)

				1968-1982: Air samples analyzed for fibers by PCM analysis	
OM Scott plant Cohort, Marysville, OH*					
Lockey et al., 1984	512 plant employees Mean (range), years: Age at exam: 37.5 (19-66) Mean (SE), years: Job tenure by exposure group and smoking status (NS=non-smoker, EX=former smoker, CS=current smoker) Low, NS: 6.6 (1.1) Low, EX: 11.3 (1.6) Low, CS: 10.5 (1.2) Medium, NS: 8.4 (1.0) Medium, EX: 13.3 (8.9) Medium, CS: 8.9 (0.7) High, NS: 12.2 (0.9) High, EX:13.0 (1.1) High, CS: 10.7 (0.9)	Posterior-anterior chest radiographs taken in 1980 Films independently read by 2 certified B-readers using modification of 1971 ILO standards	1) Parenchymal changes (only one small opacity recorded (grade 1/1), unclear if opacities graded 1/0 or 0/1 would have been reported) 2) Pleural changes (Discrete pleural plaque, Pleural thickening, Pleural calcification) 3) costophrenic angle blunting only	Individual work histories and exposure levels for specific work locations were used to estimate cumulative exposures for cohort members. 1957-1971: Exposure estimated based on interviews with plant employees and post-1972 air measurements. Some workplace exposure control measures were taken prior to 1972. 1972-1980: Air samples analyzed for fibers by PCM analysis. Some jobs do not have measurements associated with them especiallyprior to industrial hygiene measures.	Exposure Categories: < 1 f/cc-yrs (n=247) 1-10 f/cc-yrs (n=190) 10-20f/cc-yrs (n=42)
Rohs et al., 2008	280 plant employees (follow-up of cohort described in Lockey et al., 1984) Mean (SD), range (years): Age: 59.1 (10.5), 44-87 Mean (SD), median (years): Years since first exposure No pleural changes (n=200): 32.1 (5.5), 31.0	Posterior-anterior chest radiographs taken 2002-2005 Films independently read by 3 certified B-readers using 2000 ILO standards 7 employees had unreadable films and are not included in the	1) Parenchymal changes (small opacities, profusion score >1/0) 2) Pleural changes (Localized pleural thickening {thickening excluding costophrenic angle blunting}, Diffuse pleural thickening {thickening with costophrenic angle	Exposure assessment from Lockey et al. (1984) with change in start date to 1963.	Exposure Categories: 0.005-0.24 f/cc-yrs (n=70) 0.25-0.74 f/cc-yrs (n=72) 0.75-1.91 f/cc-yrs (n=68) 1.92-19.03 f/cc-yrs (n=70)

	Pleural changes present (n=80): 36.8 (4.9), 37.9	cohort of 280 participants	blunting}, Pleural calcification)		

*In addition to the exposure information used by Lockey et al. (1984) and Rohs et al. (2008), the University of Cincinnati augmented and refined these exposure estimates using additional exposure data, which included industrial hygiene measurements not previously available and estimates of exposure after 2000.

The two radiographic studies of workers from Libby, MT (Amandus et al., 1987b; McDonald et al., 1986b) were conducted by different research groups, and focused on different subsets of the cohort of vermiculite facility workers. Since both groups utilized the same exposure measurements and employment records, similar but not identical job exposure matrices (JEMs) and subsequent exposure estimates, were developed. For example, different numbers of occupation locations were used, and different approaches for estimating exposure where more than one sample was available for a given location, task or time period. McDonald et al. (1986b) examined radiographic changes among men and women employed by the company at the time of the study, and among former male employees still residing in the area. Logistic regression analysis was used to examine the relationship between cumulative Libby Amphibole asbestos exposure and radiographic abnormalities, controlling for age and smoking. Positive exposure response relationships were found with cumulative exposure for asbestosis and pleural anomalies. The study by Amandus et al. (1987b) was conducted in the same base population, but consisted of current employees only. In contrast to McDonald et al. (1986b), where the x-rays used were performed specifically for the study, Amandus et al. (1987) used company radiographs. Among the 184 participants, prevalence of radiographic abnormalities was 4% for pleural calcification, 10% for small opacities and 13% for pleural thickening. Logistic regression analysis was used to examine the relationship between cumulative Libby Amphibole asbestos exposure and radiographic abnormalities, controlling for age; a separate model was constructed restricting to current and former smokers for comparison. A positive exposure response relationship was found for cumulative exposure and asbestosis. Multivariate analyses did not find a significant relationship between cumulative exposure and pleural anomalies.

The two remaining candidate studies are in workers from the Marysville plant; the study by Rohs et al. (2008) is a follow-up of the earlier study by Lockey et al. (1984). As with the previously described studies, there was variability in the quality of exposure assessment over time for the cohort (Rohs et al., 2008; Lockey, 1985; Lockey et al., 1984). The first measurements of in-plant exposure began in 1972, and earlier exposures were estimated assuming the mean fiber value for a given department, for the years in which fiber measurements became available, as late as 1980 for some tasks (Lockey, 1980). To examine the association between cumulative Libby Amphibole asbestos exposure and radiographic abnormalities, each participant with radiographic abnormality was pair-matched by age with a participant without radiographic abnormalities. The follow-up study by Rohs et al. (2008) examined radiographic abnormality in a subset of the cohort defined by Lockey et al. (1984). Data collection took place in 2002-2005. Some of the original participants were deceased (16%), while others were not included due to refusal (12.8%), non-response (16.2%), or because they were not located (1.9%). Participants provided a new chest radiograph, which was read according to 2000 ILO standards.

The association between quartiles of cumulative Libby Amphibole asbestos exposure and pleural changes was assessed using logistic regression; several covariates were investigated, including age at exam, smoking history, body mass index (BMI), sex and year of hire (pre-1973 versus 1973 and later).

5.2.1.1. *Evaluation of Exposure in Candidate Studies*

Each of the studies provided estimates of cumulative Libby Amphibole asbestos exposure (in fibers-yr/cc), rather than mean or peak exposure. However, there were differences in exposure intensity. In contrast to vermiculite facility workers in Libby, MT, the workers at the OM Scott Plant in Marysville, OH, were generally exposed at lower levels (see Table 5-2), and were primarily exposed in the workplace. Because of showering and changing into civilian clothes at the end of the work shift for most employees, non-occupational exposure in the Marysville workers was minimal. Despite the uncertainty in the magnitude of pre-1972 exposures (discussed below), the available data indicate worker exposures in the Marysville plant did not generally include the high intensity exposures observed for the Libby worker cohort, with Rohs et al. (2008) reporting a mean exposure of 2.48 fiber/cc-year. The lower intensity exposures for the Marysville cohort, and corresponding lower cumulative exposures, are an advantage of this study considering there are uncertainties inherent in exposure-response data and extrapolating from the high intensity occupation exposures to lower level exposures often seen in community and environmental exposures.

5.2.1.2. *Evaluation of Study Populations in Candidate Studies*

The candidate principal studies differed in the study populations, in terms of follow-up time, study participation, and available information. In comparing the studies of Libby miners, an advantage of the McDonald et al. (1986b) study is the inclusion of both current and former workers—these former workers likely have longer time since first exposure and may have higher exposure intensities and durations compared to current workers. However, there is a potential for differential participation. All current employees were included in the McDonald et al. (1986b) study, while 80 of 110 eligible former employees agreed to provide chest radiographs. Although exact participation rates are not given, Amandus et al. (1987b) report that radiographs were unavailable for >50% of workers who were employed <5 years, or who ceased employment prior to 1975. Among Marysville workers, there were very few employees who declined to participate in the earlier study by Lockey et al. (1984), where 512 out of 530 employees were included, but there is potential for selection bias in the follow-up by Rohs et al. (2008), where only 280 employees out of the original cohort were evaluated. If non-participants from either cohort had different incidence rates compared to participants, the prevalence of radiographic

changes may be under- or overestimated. Rohs et al. (2008) state that employees hired in 1973 or earlier (when exposure estimates were more uncertain) were more likely to participate compared to employees hired after 1973, and while the range of cumulative Libby Amphibole asbestos exposure was similar between participants and non-participants, participants did have higher mean cumulative exposure estimates.

The studies by McDonald et al. (1986b) and Rohs et al. (2008) had the longest follow-up times—the first included former workers as well as current workers, while the second was a follow-up conducted 24 years after the original study by Lockey et al. (1984). In terms of information available for statistical analysis, both studies of Libby miners and the follow-up study by Rohs et al. (2008), used age rather than time since first exposure (TSFE) in logistic regression models. Lockey et al. (1984) matched cases and non-cases on age. TSFE is preferable, since it gives more information about latency between exposure and outcome development; while age and TSFE are related, they are not perfectly correlated, in that there is a range of ages for a given date of hire. Both studies of Libby miners also evaluated smoking as a potential confounder of the association between Libby Amphibole asbestos exposure and radiographic changes. Lockey et al. (1984) only matched on age, but the follow-up examination by Rohs et al. (2008) included information on several important covariates including gender, prior exposure to asbestos, body mass index (BMI) and smoking history.

5.2.1.3. *Evaluation of Exposure Assessment in Candidate Studies*

The two studies in Libby miners (McDonald et al., 1986b; Amandus et al., 1987b) used similar exposure estimation, based on the same fiber measurements and work records. However, there is considerable uncertainty in exposure estimates in earlier years. Exposure during this time was estimated using dust to fiber conversion and information from employee interviews. McDonald et al. (1986b) used a factor of 4.6 for dust to fiber conversion, while Amandus et al. (1987a) used a factor of 4. However, Table V in Amandus et al. (1987a) showed that different comparisons of dust versus fiber levels in the Libby workplace showed potential values of that factor in the range of 1.2 to 11.5. Additionally, only duration of employment—not job category—was known for 69% of the whole cohort of vermiculite facility workers hired from 1935 to 1959. Without knowledge of the job category, the same exposure concentration was assigned to most of these workers, resulting in particularly large measurement error for workers hired prior to 1960. Another source of uncertainty in exposure estimates for this cohort is possible community/non-occupational exposures. Members of the Libby worker cohort may have lived in Libby prior to/after employment, and resided in Libby and surrounding areas during employment. In both cases there may have been community exposures to Libby Amphibole asbestos which are not captured in occupational-based cumulative exposure metrics.

This is not likely to be a major source of concern for the workers in the study since estimated occupational exposures were at high levels, but is a source of uncertainty in estimating the exposure-response relationship.

Exposure assessment also changed over time in the Marysville cohort (Lockey, 1985; Rohs et al., 2008). Fiber concentration measurements were not available prior to 1972, and since industrial hygiene measurements were implemented in the Marysville plant in the 1970's, exposure levels during prior years are unknown. EPA collaborated with a research team at the University of Cincinnati to update the exposure reconstruction for all workers who participated in the Lockey et al. (1984) and Rohs et al. (2008) studies, taking into account additional industrial hygiene data that were not previously available. As discussed in detail in Appendix F, exposure estimates for each worker in the Marysville plant were developed based on available industrial hygiene data from the plant. Figure 5-1 shows the measured or estimated average concentration of Libby Amphibole (PCM f/cc) in air of each department from 1957 to 2000.

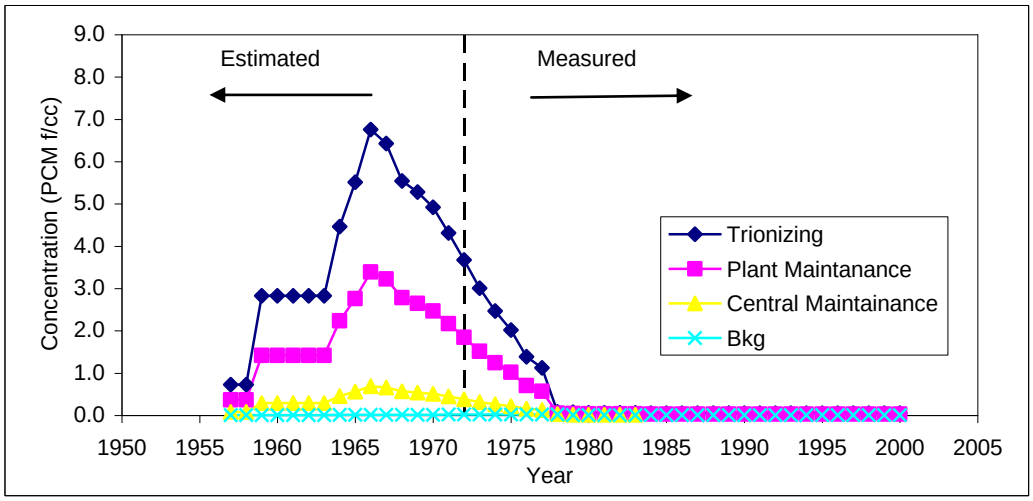

FIGURE 5-1. Estimated and measured exposure concentrations in Marysville facility

Trionizing is a term used in the Marysville facility and includes unloading of rail cars containing vermiculite ore (track), using conveyers to move the vermiculite ore into the expander furnaces, separation of the expanded vermiculite from sand, blending in of lawn care chemicals, and drying and packaging of the final product.

Using available data on the year of hire and the departments in which each person worked, the authors estimated the cumulative exposure (CE, f-yrs/cc) for each worker for each year since the date of hire. Information obtained and recorded for each worker included:

- Gender
- Body mass index (2000s only)
- Smoking history

- Date and age at time of health examination (1980 and/or 2000s)
- Occurrence of adverse effects at the time of examination, including presence or absence of a) localized pleural thickening, b) diffuse pleural thickening, c) parenchymal change. Pleural and parenchymal changes were detected by conventional radiographs
- Date of start and end of employment
- Exposure to Libby Amphibole asbestos in the Marysville facility by year
- Presence or absence of known exposure to asbestos at other locations

The updated exposure reconstruction utilized 914 industrial hygiene measurements for fibers, which represented a substantial increase from the 180 industrial hygiene measurements for fibers available in Lockey et al. (1984) and Rohs et al. (2008). Additionally, the reconstruction included exposure after 1980, as the additional industrial hygiene data showed that fibers were still present in the facility after 1980 in contrast to the previous assumption of zero fibers present after 1980 (Lockey et al., 1984; Rohs et al, 2008), and assigned the beginning of exposure to Libby Amphibole asbestos as 1959 in contrast to 1957 (Lockey et al., 1984) or 1963 (Rohs et al., 2008). The assignment of the start of exposure was based on interviews with plant personnel. The exposure reconstruction procedure took into account each worker's job history, including extensive overtime for some workers, and is described in detail in Appendix F.

5.2.1.4. *Evaluation of Outcome Assessment in Candidate Studies*

In all four candidate studies, outcomes were assessed using chest radiographs independently evaluated by ≥1 reader. However, there were differences in the standards used for evaluation of radiographic changes, as well as timing and quality of the radiographs. The two studies in Libby miners (McDonald et al., 1986b; Amandus et al., 1987b) used similar outcome assessment procedures, with radiographs evaluated by 3 readers according to 1980 ILO standards. Two different sets of standards were used to evaluate radiographs in the Marysville cohort. The first study used modified 1971 ILO standards (modifications not stipulated) (Lockey et al., 1984), while the follow-up study used the updated 2000 ILO standards (Rohs et al., 2008).

Radiograph quality may also impact outcome assessment. In McDonald et al. (1986b), which used radiographs taken in 1983 specifically for the study, 7% of films were classed as poor quality (some technical defect impairing the pneumoconiosis classification) and 0.4% as unreadable. Amandus et al. (1987b), which used company radiographs taken over a wide time period (<1975 to 1982) report that the proportion of films rated as poor ranged from 14.7% to 22.8% depending on the reader. In the Marysville cohort, radiographic quality was better—Lockey et al. (1984) state that "radiographs that could not be interpreted because of poor quality

were repeated" while Rohs et al. (2008) note that only 7 out of 298 radiographs taken were considered unreadable.

5.2.1.5. *Selection of Principal Study*

Of the four candidate principal studies, the two studies of pleural and parenchymal changes among Libby miners (Amandus et al., 1987b; McDonald et al., 1986b) were considered, but compared to the studies among Marysville workers (Rohs et al., 2008; Lockey et al., 1984), were not preferred due to the higher levels of exposure (particularly for earlier years, when only dust level measurements were available and when exposure predictions have greater uncertainty), and limitations in the quality of the radiographs used for outcome assessment.

The Marysville cohort (as defined in Rohs et al., 2008 and Lockey et al., 1984) was selected as the principal study for the derivation of the RfC based on increased risk of pleural and parenchymal effects, at lower cumulative exposure levels (compared to the Libby worker cohort), the examination of longer time from first exposure (considering time from first exposure is an important factor in the development of the health effect), information on more covariates, use of more recent 2000 ILO diagnostic criteria, and the availability of detailed exposure and health outcome information for each worker.

5.2.1.6. *Selection of Critical Effect*

The pleural and parenchymal effects observed in exposed individuals in the Marysville cohort (Rohs et al., 2008; Lockey et al., 1984) included increased prevalence of pleural thickening (characterized as either discrete pleural thickening or diffuse pleural thickening) and parenchymal changes (small opacities). These effects were determined using conventional radiographs (Rohs et al., 2008). In clinical settings there are difficulties in distinguishing between these two lesions in part due to lack of radiographic film diagnostic specificity as well as the ILO definitions for diffuse pleural thickening of the visceral pleura which may result in some variability in reporting of discrete pleural plaques. There are two classifications for pleural thickening in current guidelines (ILO, 2000). Diffuse pleural thickening is currently only determined where there is thickening along significant extent of the chest wall, and this thickening is "in the presence of and in continuity with, an obliterated costophrenic angle" (ILO, 2000). Although previous classification schemes attempted to distinguish between thickening of the parietal pleura and diffuse thickening of the visceral pleura, the ILO states" reading standard x-rays cannot always distinguish between thickening of the visceral or parietal pleura" (ILO, 2000). Thus, all other pleural thickening is now defined as localized pleural thickening (i.e. where there is no costophrenic angle obliteration). Localized pleural thickening on the chest wall, and diffuse pleural thickening may be graded indicating thickness, and the extent of the

chest wall impacted, however these data are not always provided in study reports, therefore regardless of extent of the pleural thickening, only presence or absence may be noted.

The radiographic changes occur in different anatomical locations. Localized pleural thickening may include plaques in the parietal pleura, or thickening of the visceral pleura, where this thickening does not impact the costophrenic angle (angle between the diaphragm and chest wall as viewed on a radiograph). Diffuse pleural thickening is designated when thickening of the visceral pleura extends to blunt/obliterate the costophrenic angle. Pleural thickening does not progress to parenchymal changes. The data on the radiographic changes are presented in Table 5-3, Figure 5-2 and Figure 5-3. For the purposes of illustration, the data are presented in groups of 50 individuals each, representing approximate quintiles after exclusion of workers with other previous asbestos exposure. Figures 5-2 and 5-3 present the cumulative prevalence of radiographic changes; Figure 5-2 shows the mean cumulative human equivalent exposure expressed on a normal scale, while in Figure 5-3 exposure is expressed on a log scale to provide a better visual image at the low end of the distribution.

Table 5-3. Mean cumulative human equivalent exposures and prevalence of health outcomes found in Marysville workers (Rohs et al., 2008)

Mean Cumulative Human Equivalent Exposure, fibers-yr/cc (range)	Localized Pleural Thickening	Diffuse Pleural Thickening	Parenchymal Change
0.061 (0.001-0.121)	3/50	0/50	0/50
0.156 (0.123-0.197)	8/50	0/50	0/50
0.282 (0.198-0.420)	12/50	2/50	1/51
1.037 (0.421-2.460)	17/50	1/50	1/50
13.140 (2.475-34.165)	19/52*	7/52	5/52
Total	59/252	10/252	7/252

* Includes 3 workers with both discrete pleural and parenchymal changes (small opacities viewed on the radiograph).

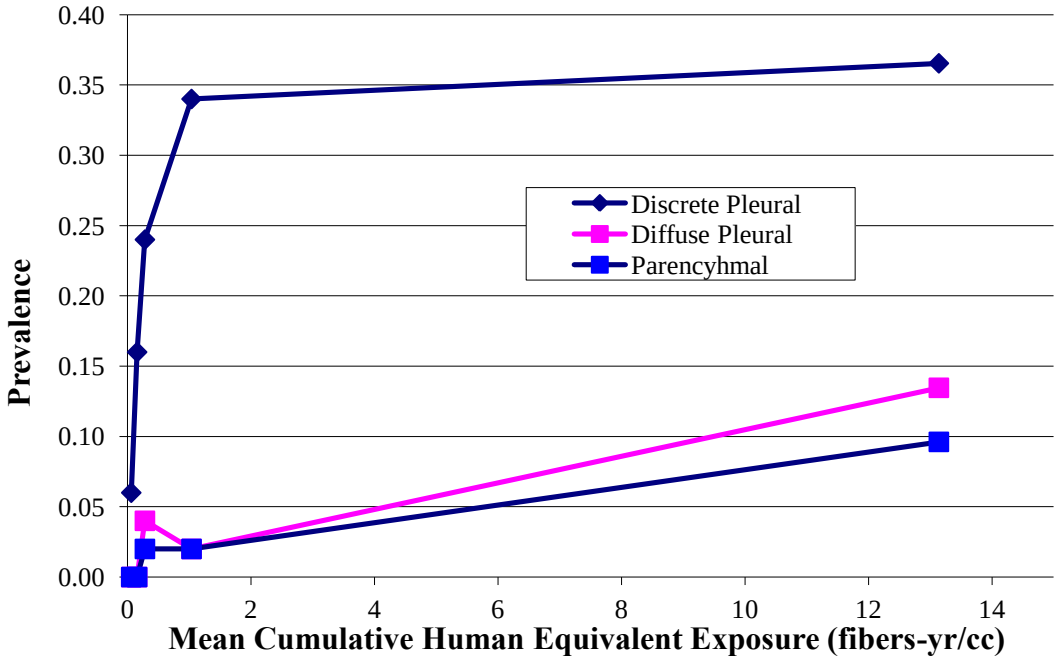

Figure 5-2. Prevalence of radiographic change versus mean cumulative human equivalent exposure

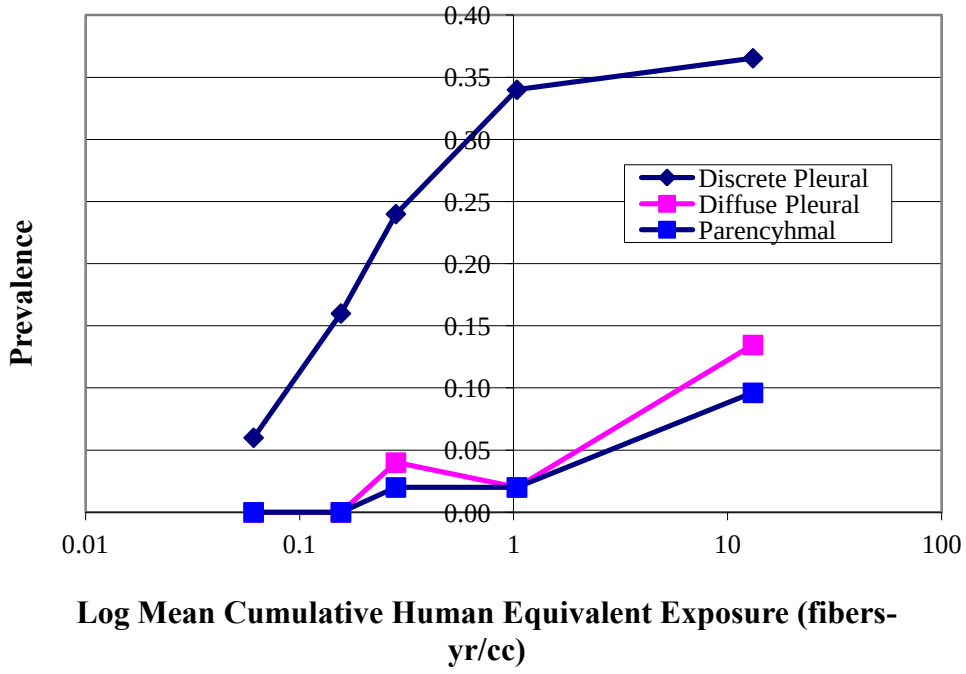

Figure 5-3. Prevalence of radiographic change versus mean cumulative human equivalent exposure

EPA selected localized pleural thickening (characterized by Lockey et al., 1984 and Rohs et al., 2008 as discrete pleural thickening) as the critical effect due to its higher prevalence relative to the other outcomes, minimal adversity (compared with other effects), and specificity for durable mineral fiber exposure. EPA considers localized pleural thickening to be an adverse effect and is attributed to exposure to Libby Amphibole asbestos.

Pleural thickening in general is associated with decreased pulmonary function (Miller et al., 1994, Wang et al., 2001 and Petrovic et al., 2004) and this association is strengthened as the severity of the pleural thickening increases (Lilis et al., 1991) (see Section 4.5). Thickening of the parietal pleura (all sites) is an accepted marker of mineral fiber exposures, and the most sensitive of the endpoints detected by standard radiographs, both in terms of exposure levels and time. The available information is largely in agreement that where multiple and bilateral parietal plaques are observed that this is a distinctive marker of exposure to asbestos and other durable mineral fibers (e.g., erionite) (ATS 2004, Broaddus et al., 2011). Therefore, localized pleural thickening is a sensitive and fairly specific biological effect of mineral fiber exposure.

The radiographic classification of localized pleural thickening may include both parietal plaques and diffuse visceral thickening (without costophrenic angle involvement) (ILO, 2000). These lesions are distinct and may contribute independently to observed health effects. Parietal plaques are known to induce chronic constricting chest pain which increases in severity as the extent of the plaques increases. Pleural thickening in general is associated with reduced lung function parameters with increased effect correlating with increased severity of the pleural thickening (Lilis et al., 1991; Miller et al., 1994; Wang et al., 2001; Petrovic et al., 2004). Specifically, lung function impairment has been demonstrated in several studies where pleural thickening without costophrenic angle involvement has been studied (Broderick et al., 1992; Kilburn and Warshaw, 1991; Garcia-Closas et al., 1995). Although there is some evidence from HRTC studies that parietal plaques alone may not directly impair lung function, the studies were small, and may not have included severe plaques. There is clear evidence from HRTC studies that the presence and extent of visceral thickening does impair lung function (Swartz et al., 1993; Copley et al., 2001). Thus the radiographic classification of localized pleural thickening (ILO, 2000) defines radiographic anomalies which are associated with chronic chest pain, decreased lung volume and decreased measures of lung function.

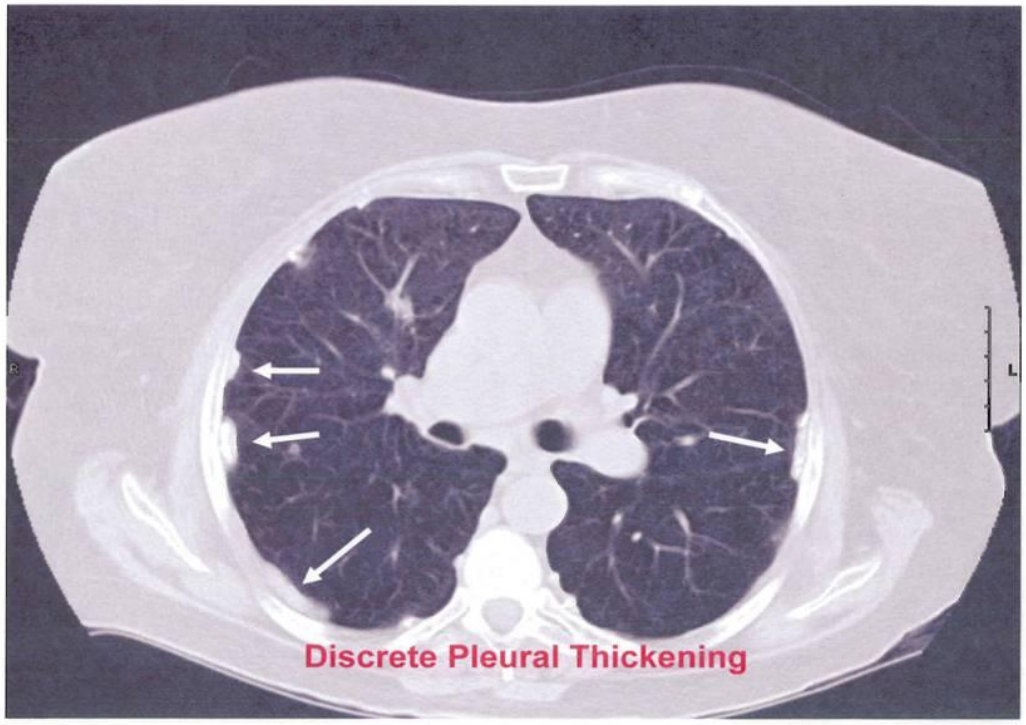

Figure 5-4. HRCT Scan of an individual with localized pleural thickening (arrows), Source: Dr. Brad Black, Card Clinic, Libby, MT

5.2.2. Methods of Analysis

5.2.2.1. *Exposure data and choice of exposure metric*

In brief, the starting point for exposure reconstruction was the measured or estimated concentration of Libby Amphibole asbestos in air (fibers/cc) of each department from 1957-2000. The distribution of exposure by department is summarized in Figure 5-1. Using available data on the year of hire and the departments in which each person worked, the cumulative exposure (fibers-yrs/cc) for each worker for each year since the date of hire was estimated. Each worker's cumulative exposure was then adjusted to a cumulative human equivalent exposure for continuous exposure (CHEEC; fibers-yr/cc) to represent exposure 24 hours/day and 365 days/year (assuming that any exposure off site was zero). Adjustments for different inhalation rates in working versus nonworking time periods were incorporated in this analysis. These calculations are somewhat more involved than the usual conversions to equivalent continuous exposure concentrations that EPA makes in the analysis of occupational studies. Conversions for non-cancer effects are usually made using an adjustment factor of 240 days/365 days x 10 m^3/20

m^3 (U.S. EPA 1994). However, the adjustment factor in this assessment takes into account the extensive seasonal overtime for some job classes at the Marysville facility, as well as other annual periods when work hours were reduced (Appendix F). The estimated CHEEC was used to represent Libby Amphibole asbestos exposure in all subsequent analyses, as it combines aspects of both intensity of exposure and duration of exposure. (Note: the University of Cincinnati coined the term CHEEC, in its report. However, the calculated value is similar to what EPA usually calls continuous human equivalent exposure (HEC, U.S. EPA, 1994b). For Libby Amphibole asbestos the exposure metric is calculated as cumulative exposure (fibers-yr/cc).

It is anticipated that there is some biological latency period between exposure to Libby Amphibole asbestos and development of localized pleural thickening—that is, exposure in the most recent past may not contribute to thickening. Because localized pleural thickening does not generally occur immediately after exposure, and requires some time to develop to the state that it can be detected on a conventional chest x-ray, exposures that occur close to the time of x-ray may not contribute to the occurrence of observable disease, and may tend to obscure the exposure-response relationship. Accordingly, a lagged exposure (i.e. cumulative exposure discounting the most recent time period) may be the most appropriate measure to use. Therefore, exposure estimates with various lags were investigated (lags of 0, 5, 10, 15 and 20 years). For example, a CE value based on lag of 5 years excludes all exposures that occurred within 5 years of the date of x-ray. The values are designated as CE0, CE5, CE10, CE15, and CE20. Looking at prevalence of the outcome for various categories of time elapsed since first exposure the first localized pleural thickening was detected ~10 years after the first exposure.

5.2.2.2. *Datasets for Modeling Analyses*

The individual health outcome data for all workers who participated in the Lockey et al. (1984) and the follow-up by Rohs et al. (2008) studies was used for exposure-response modeling. To avoid any bias from previous occupational exposure to asbestos, only the data from those who did not report any previous occupational exposure to asbestos were used. The data from Lockey et al. (1984) and Rohs et al. (2008) were combined for the full cohort to provide a greater range in time from first exposure. Outcome assessments, i.e. chest x-rays, were performed at two different time points, 1980 and 2002-2005. While the evaluation approaches were generally similar (independent readings by 3 certified B-readers), it is important to note that x-ray readings were performed by different individuals, under a different reading protocol in 1980 (modified 1971 ILO standards) compared to 2000s (2000 ILO standards), leading to some uncertainty in statistical analyses that combine these datasets. An additional consideration is body composition—in some cases, difficulty in distinguishing fat pads from true pleural thickening

may lead to misclassification of the outcome. BMI measurements are available for the latter study but not for the 1980 evaluation; the effect of BMI was investigated and is discussed below.

The consensus read of the x-rays from three B-readers was used in both studies. Because the ILO criteria were updated in 2000, the reader forms from Lockey et al. (1984) showing pleural changes were evaluated for consistency with the ILO 2000 criteria. No change in diagnosis was found. In addition, no change in x-ray or film quality was found that would reduce confidence in the Lockey et al. (1984) data.

The full data set of the exposure-response relationship for localized pleural thickening was as follows:

1. The data from Lockey et al., (1984), n = 513 and Rohs et al. (2008), n = 280 were combined, n = 793
2. All workers who reported exposure to asbestos at other locations were excluded (n = 793 – 105 = 688).
3. For workers who were x-rayed in both Lockey et al. (1984) and Rohs et al. (2008), one of the observations was excluded so that there were no repeat observations for individual workers. For workers who were negative for localized pleural thickening in Lockey et al., the 1984 study data were excluded and the Rohs et al. (2008) data were retained. For workers who were positive for localized pleural thickening in Lockey et al. and also in Rohs et al., the 1984 study data were retained. One worker was positive in 1984 and negative in 2008. The 2008 study data were retained for this worker. (n = 688 – 252 = 436).
4. Two workers from Lockey et al. (1984) were excluded because the start day and the x-ray date were the same. (n = 436 – 2 = 434).

The Marysville cohort data comprise 434 workers who were not previously exposed to asbestos and had at least one valid x-ray observation. Because the concentration of Libby Amphibole in workplace air was estimated rather than measured for all years prior to 1972, this data set was stratified into two sub-sets: 1) workers hired in 1972 or after (for whom all exposure values are measured), and 2) workers hired before 1972 (for whom some of the exposure values are estimated). Distribution of cases and time since first exposure (T) at each outcome assessment are shown in Table 5-4. Due to the differences in exposure assessment (estimated prior to 1972, measured thereafter), the cohort is stratified by date of first exposure.

TABLE 5-4. DISTRIBUTION OF CASES AND TIME FROM FIRST EXPOSURE (T) FOR MARYSVILLE WORKERS

	All participants*		First exposed before 1972		First exposed 1972 or later	
	Cases/Total	Range of T	Cases/Total	Range of T	Cases/Total	Range of T
Examined 1980 (Lockey et al., 1984)	5/434	0.42-23.43	4/236	8.76-23.43	1/198	0.42-8.42
Examined 2002-2005 (Rohs et al., 2008)	59/252	23.15-47.38	47/133	31.09-47.38	12/119	23.15-32.65

*The 252 individuals examined in 2002-2005 were also examined in 1980. Note that there were originally 513 individuals in the Lockey et al. (1984) cohort; of these, 77 had previous asbestos exposure and were excluded (n=436). Two individuals were excluded because their x-ray date was the same as their employment start date (n=434). These exclusions are also reflected in the Roh et al. (2008) cohort.

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

The best measured exposure data are considered to be those from 1972 and later. Due to the longer follow-up time and additional covariate information, the most informative outcome data come from the 2002-2005 examination. Based on these considerations, the sub-cohort which includes data from workers from in the 2002-2005 examination, and who began work in 1972 or later (12/119 cases) (Rohs et al., 2008), was chosen as the preferred analysis to develop a point of departure (POD) for localized pleural thickening to serve as the basis for the RfC. Additionally, sample POD estimates based on statistical analyses of results from the full cohort (Lockey et al., 1984 and Rohs et al., 2008 combined) were included for comparison.

5.2.2.3. *Statistical Modeling of the Sub-cohort*

EPA performed analyses of study results for the sub-cohort whose exposures began on or after 1/1/1972 when workplace PCM measurements were available, reducing uncertainties associated with exposure assessment. The most sensitive endpoint for exposure to Libby Amphibole asbestos was identified as localized pleural thickening. Epidemiologic methods were used to analyze the exposure-response data and benchmark dose (BMD) methodology was used to estimate PODs. In this approach, the available data are fit to a set of mathematical exposure-response models to determine an appropriate empirical representation of the data. A recommended model form is then determined; commonly this is the model with the best fit as

measured by Akaike's Information Criterion (AIC) value among these model forms judged to provide an appropriate and statistically adequate representation of the data. For inhalation data the benchmark concentration (BMC) is defined as the exposure level, calculated from the best-fit model, which results in a specified benchmark response (BMR). The RfC is derived from the lower 95% confidence limit of the BMC, referred to as the BMCL, which accounts for statistical uncertainty in the model fit to the data. All analyses were performed using SAS® statistical software v. 9.1. BMCLs were obtained by the profile likelihood method as recommended by Crump and Howe (1985) using the NLMIXED procedure in SAS (Wheeler, 2005) (See Appendix E for details).

For models where a background parameter is included, a 1% risk of localized pleural thickening was assumed. Previous studies have reported a range of estimates of the prevalence of localized pleural thickening. In two studies of persons not previously exposed to asbestos, Anderson et al (1979) and Castellan et al (1985) report estimated prevalence estimates of 1.2% (4/326) and 0.2% (3/1422), respectively. In cross-sectional studies, which may include persons with occupational exposure to asbestos, Rogan reported localized pleural thickening prevalence estimates of 1.2% in the NHANES I (1971-1975; Rogan, 1987) and 3.9% in the NHANES II (Rogan, 2000). Among military populations, two studies have reported an estimated prevalence of 2.3% (Miller, 1996; Bohnker, 2005). Based on these reports, the 1% background rate was chosen as representing the prevalence among persons without occupational exposure to asbestos.

EPA selected a BMR of 10% extra risk for the prevalence of localized pleural thickening. In the absence of information to indicate otherwise, this response level was considered appropriate for derivation of the RfC under the assumption that this level of localized pleural thickening is minimally adverse (U.S. EPA, 2000). In this particular case, only workers who did not report any previous occupational exposure to asbestos were included in the analyses and the study by Rohs et al. (2008) can readily detect a 10% increase in prevalence of localized pleural thickening, a highly specific response to exposure to asbestos and other mineral fibers.

For the Marysville cohort, however, individual exposure and health outcome results are available and a more comprehensive analysis is possible. This type of analysis has more statistical power since it benefits from individual information on each study subject and allows for consideration of potential confounders.

5.2.2.3.1. Statistical model evaluation and selection

Dichotomous statistical models describing the probability of individual response as a function of cumulative exposure (represented by CHEEC in units of fibers-yr/cc) were used. In order to investigate the key explanatory variables for analysis, a forward selection process was used to evaluate the association of each of the potential covariates with risk of localized pleural

thickening, controlling for Libby Amphibole asbestos exposure. Covariates considered for inclusion in the model were: time since first exposure (T), age at x-ray, gender, smoking history and BMI. This initial modeling was done using a standard logistic regression model, as is commonly applied in analysis of epidemiological data. The base model was a logistic regression model with cumulative Libby Amphibole asbestos exposure (natural log transformed) as the independent variable. This model provided an adequate fit to the data (Hosmer-Lemeshow p-value of 0.7073), and the exposure variable was statistically significantly associated with the outcome (beta [SE] = 0.5398 [0.2374] increase in log odds for every unit increase in CHEEC, p-value=0.0230). Covariates were evaluated according to whether inclusion of the covariate improved model fit as assessed by the AIC, and statistical significance of the covariate. When controlling for Libby Amphibole asbestos exposure, inclusion of each of the covariates increased the AIC for the model, and none were associated with odds of localized pleural thickening: T: p-value=0.9350; age at x-ray: p-value=0.6822; gender: p-value=0.7734; smoking: p-value=0.1905; BMI: p-value=0.3206. Therefore, only cumulative Libby Amphibole asbestos exposure (CHEEC) was included in further analyses.

The candidate models (see Table 5-5 for model forms) were: logistic (with CHEEC considered as continuous and continuous with a natural logarithm transformation), probit (with CHEEC considered as continuous and continuous with a natural logarithm transformation), 3-parameter log-logistic, dichotomous Hill, and dichotomous Michaelis-Menten models (with only CHEEC for the latter three models). These are statistical models used to evaluate dichotomous data, and were considered appropriate here given the supralinear nature of the observed relationship between Libby Amphibole asbestos exposure and prevalence of localized pleural thickening. Further details of these analyses are included in Appendix E. All of the candidate models had adequate fit as assessed by the Hosmer-Lemeshow test (a form of the Pearson chi-squared goodness-of-fit statistic). Models were compared using the AIC—values were quite similar among the candidate models, ranging from 75.7 to 78.3 (Table 5-5). The model with the lowest AIC was the 3-parameter log-logistic model (AIC=75.7). For models from the set of candidate models with AICs within 2 units of the lowest AIC, BMC_{10} and $BMCL_{10}$ estimates were similar (within a factor of 3 of the values from the lowest-AIC model); thus based on the AIC the 3-parameter log-logistic model was selected.

Different exposure lags (0, 5, 10, 15 and 20 years) were then investigated for this model. The AIC values did not vary much for lags of 0 to 15 years (AIC ranging from 75.1 to 75.7), but the 10-year lagged exposure provided the lowest AIC and was selected as the preferred exposure metric. There was a larger decrease in model fit when using the 20-year lagged exposure (AIC of 77.00). In addition, there were cases of localized pleural thickening in the full cohort with

fewer than 20 years since first exposure; therefore, using such a long lag (which necessitates the assumption that these are background cases) was not judged to be appropriate.

The 3-parameter log-logistic model using the 10-year lagged exposure had a p-value for fit of 0.74 and an AIC value of 75.1, and the exposure variable was statistically significantly associated with odds of localized pleural thickening (beta [SE]=0.6524 [0.2741] per fibers-yr/cc, p-value=0.0189) (Figure 5-5). This model yielded a BMC_{10} of 0.2543 fibers-yr/cc and a corresponding $BMCL_{10}$ of 0.0757 fibers-yr/cc for a 10% increase in prevalence of localized pleural thickening. This $BMCL_{10}$ of 0.0757 fibers-yr/cc is the preferred POD estimate to support development of an RfC for Libby Amphibole asbestos.

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

Model	Exposure Metric	Form	AIC	Hosmer-Lemeshow GOF p-value	BMD	BMDL
Logistic	CHEEC	P(CE)=1/[1+exp(-a-b*CE)]	78.3	0.7442	0.5715	0.2547
Logistic	ln(CHEEC)	P(CE)=1/[1+exp(-a-b*ln(CE))]	76.2	0.7073	0.2490	0.0558
Probit model	CHEEC	P(CE)=Φ(a+b*CE)	77.9	0.7726	1.5267	00.9185
Probit model	ln(CHEEC)	P(CE)=Φ(a+b*ln(CE))	76.6	0.6650	0.2276	0.0472
3-parameter log-logistic	ln(CHEEC	P(CE)=bkg+(1 – bkg) / [1 + exp(-a – b*ln(CE))]	75.7	0.7339	0.3447	0.0956
CE, lag 5			75.3	0.5519	0.2980	0.0887
CE, lag 10*			**75.1**	**0.6833**	**0.2543**	**0.0757**
CE, lag 15			75.4	0.4226	0.1993	0.0536
CE, lag 20			7777.0	0.6363	0.1258	0.0196
Dichotomous Hill†	ln(CHEEC)	P(CE) = bkg + (Plateau – bkg)*CE^b / [exp(-a)+CE^b]	77.7	0.6724	0.3295	0.0961
Michaelis-Menten±	ln(CHEEC)	P(CE) = bkg + (Plateau – bkg)*CE / [exp(-a)+CE]	75.8	0.5413	0.3330	0.1342

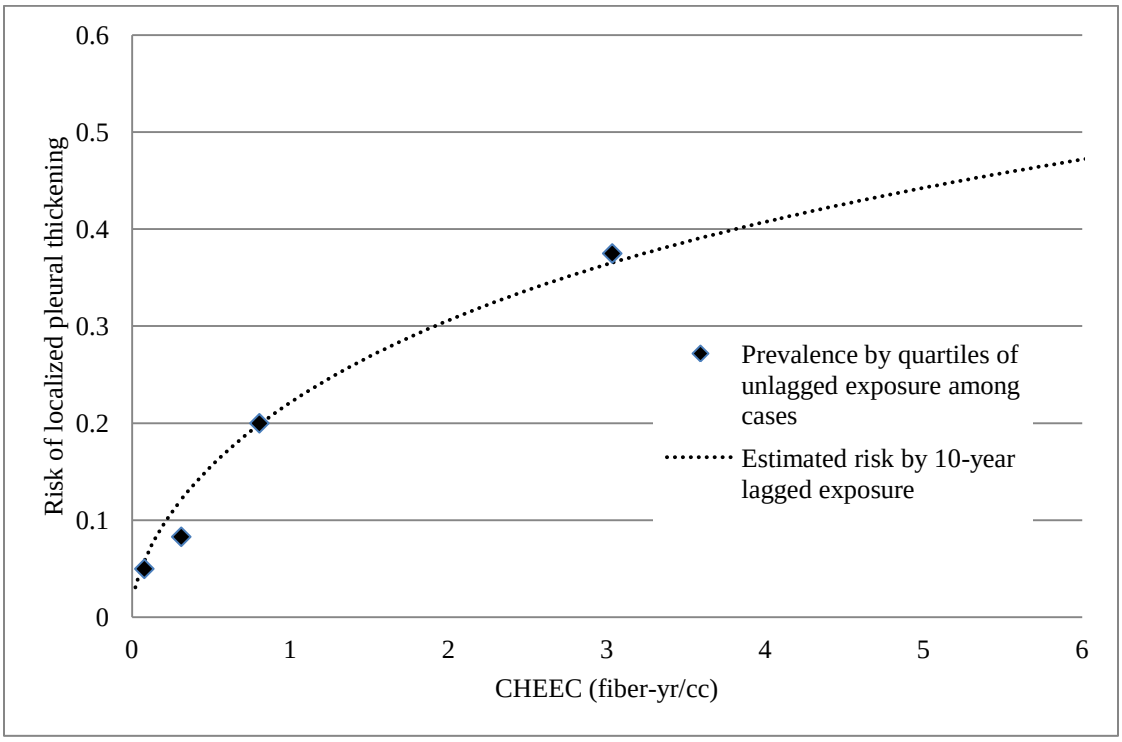

Figure 5-5. Graph of observed prevalence of localized pleural thickening and estimated probability of localized pleural thickening calculated using the 3-parameter log-logistic model with 10-year lagged exposure.

5.2.3. RfC Derivation—Including Application of Uncertainty Factors (UFs)

The derivation of the RfC from the morbidity studies of the Marysville cohort (Rohs et al., 2008; Lockey et al., 1984) was calculated from a POD ($BMCL_{10}$) of 0.076 fibers-yr/cc for localized pleural thickening by adjusting to 70 years of exposure, lagged by 10 years (non-occupational, lifetime exposure), and dividing by a total uncertainty factor of 100. The RfC is 1 x 10^{-5} fibers/cc for continuous exposure (rounded to one significant digit) was derived as follows:

$$RfC = POD \div UF$$
$$RfC = POD_{ADJ} \div UF$$
$$RfC = [0.076 \text{ fibers-yr/cc } (1/(70\text{-}10 \text{ years})] \div 100$$
$$RfC = 1.2 \text{ x } 10\text{-}5 \text{ fibers/cc, rounded to } 1 \text{ x } 10\text{-}5 \text{ fibers/cc}$$

A total uncertainty factor of 100 was applied in the derivation of the RfC. The rationale for the individual uncertainty factors are below.

An UF value of 1 was applied for extrapolation from animals to humans (interspecies extrapolation, UF_A) because the critical effect used as the basis for the RfC was observed in humans.

An UF value of 10 was applied for interindividual variability to account for human-to-human variability in susceptibility (intraspecies extrapolation, UF_H) in the absence of quantitative information to assess the toxicokinetics and toxicodynamics of Libby Amphibole asbestos in humans. Only adults sufficiently healthy for full time employment were included in the principal study; and the study population was primarily male.

An UF value of 1 was applied for LOAEL-to-NOAEL extrapolation (UF_L) because the current approach is to address this factor as one of the considerations in selecting a BMR for modeling. In this case, a BMR of 10% increase in the incidence of localized pleural thickening was selected under an assumption that it represents a minimally biologically significant change.

An UF value of 1 was applied for extrapolation to chronic exposure (subchronic to chronic exposure extrapolation, UF_S) as the exposure in the facility was long term (from approximately 13 weeks to more than 44 years, with more than 90% of the workers having a duration of exposure of more than 6 years).

An UF value of 10 was applied to account for deficiencies in the database (UF_D) based on lack of data on effects other than in the respiratory system, limitations of the principal study design, other observed effects (cardiovascular disease and autoimmune effects) that have not been well-studied, and uncertainties in time from first exposure.

Lack of data on effects other than in the respiratory system: There are no data in laboratory animals or humans on general systemic effects, developmental and reproductive effects, neurotoxicity, or developmental neurotoxicity for Libby Amphibole asbestos. The lack of studies could reflect reasonable judgments made by some (ATSDR, 2001; ATS, 2004) that other effects are not expected at exposures that would be protective of effects in the respiratory tract or that general systemic effects would not be expected. However, it is known that inhaled asbestos fibers migrate out of the lung and into other tissues lending uncertainty to any assumptions that other effects would not be expected.

Limitations of principal study design: The human study used to derive the POD was conducted in a relatively small population of workers with no previous occupational exposure to asbestos with a large range in duration of exposure (from approximately 13 weeks to more than 44 years); although, the study is sufficient to detect a 10% increase in the prevalence of an adverse effect. The study was conducted more than 20 years after the facility stopped using ore

from Libby. However, the study used a cross-sectional design and may be negatively biased since individuals with more severe disease could have left employment or may have died and not been included in the follow-up study resulting in an underestimation of toxicity. Additionally, it is known that high-resolution computer tomography (HRCT) can identify mineral fiber-related lesions in the respiratory tract, which cannot be identified by standard radiographs. Thus the technology employed for determining the prevalence of radiographic changes in the Marysville cohort may underestimate the actual prevalence of localized pleural thickening.

Other observed effects that have not been well-studied but for which there is evidence of association with exposure to Libby Amphibole asbestos: Two studies have found a possible increased prevalence of autoimmune disease and biological markers for autoimmune disease in Libby residents (Pfau et al., 2005 Noonan et al., 2006) although these studies do not indicate whether the autoimmune effects would be observed at exposures lower than that observed for localized pleural thickening. Subsequent animal studies have indicated that exposure to Libby amphibole asbestos does induce autoantibodies in mice (Blake et al., 2008). It is unknown if autoimmune effects are secondary to the chronic inflammatory response expected from exposure to mineral fibers. However, one study of individuals in a community exposed to tremolite found changes in immune parameters in exposed individuals without localized pleural thickening and that additional immune markers, including autoantibodies, increased in individuals with localized pleural thickening (Zerva et al., 1989). A mortality analysis for the Libby worker cohort also found associations between occupational exposures to Libby Amphibole asbestos and mortality due to cardiovascular disease (Larson et al., 2010a).

Time from first exposure: The data for the sub-cohort of workers exposed post 1972 allowed for assessing prevalence of localized pleural thickening approximately 30 years after first exposure. However, there is evidence to indicate that the prevalence of localized pleural thickening is likely to continue to increase more than 30 years after first exposure (Paris, 2009, 2008; Jakobsson et al., 1995; Hillerdal 1994; Ehrlich et al., 1992; Järvholm, B, 1992; Lilis et al. 1991; Merchant, 1990; McDonald et al 1986b). Therefore, a POD established at 30 years time from first exposure may underestimate the actual prevalence of localized pleural thickening 70 years from first exposure. Since the full-cohort model includes time from first exposure as a variable, one approach to address this uncertainty is to use this model to extrapolate to later time points. This modeling shows a non-linear increase in prevalence of localized pleural thickening with time from first exposure. However, this approach is problematic because there are no data available with time from first exposure greater than 47 years in the cohort. Therefore, while the likelihood of increased prevalence of localized pleural thickening beyond 30 years is supported by statistical analysis of the full cohort, this modeling does not allow accurate estimation of the

size of such an effect. Thus, the use of a POD established 30 years from first exposure does represent uncertainty with respect to assessing the potential effects for a lifetime of exposure.

The RfC was developed based on fiber counts employing PCM following NIOSH counting rules where the minimum detectable fiber diameter is 0.25 µm, fiber length is > 5 µm and the aspect ratio is ≥ 3. For use at other sites, the fiber dimensions at the site can be attained using PCM or TEM where they are reported as phase contrast microscope equivalents [PCMe]. The RfC is for continuous lifetime exposure (24 hours/day, 365 days/year, with exposure beginning at birth and continuing for 70 years). See Table 5-6 for guidance on using the RfC for other exposure scenarios—the RfCs in this table are estimated using the POD divided by the total uncertainty factor of 100, pro-rated over a range of exposure durations. The RfC can be applied at other sites where vermiculite ore from Libby, MT was used.

TABLE 5-6. Exposure concentrations (RfCs) for various exposure durations*

Age at First Exposure	Age at Examination For Health Effect	1 yr	2 yrs	5 yrs	10 yrs	20 yrs	30 yrs	40 yrs	50 yrs	60 yrs
0	70	7.6E-04	3.8E-04	1.5E-04	7.6E-05	3.8E-05	2.5E-05	1.9E-05	1.5E-05	1.3E-05
10	70	7.6E-04	3.8E-04	1.5E-04	7.6E-05	3.8E-05	2.5E-05	1.9E-05	1.5E-05	
20	70	7.6E-04	3.8E-04	1.5E-04	7.6E-05	3.8E-05	2.5E-05	1.9E-05		
30	70	7.6E-04	3.8E-04	1.5E-04	7.6E-05	3.8E-05	2.5E-05			
40	70	7.6E-04	3.8E-04	1.5E-04	7.6E-05	3.8E-05				
50	70	7.6E-04	3.8E-04	1.5E-04	7.6E-05					

*Because the presence of localized pleural thickening is not dependent on time from first exposure in the model used, the RfC is a linear function of duration of exposure. The equation is RfC_D = POD/(Duration x UF). The POD is 0.076 fibers-cc/yr, duration is years and excludes any exposure after age 60, and UF is 100.

5.2.4. Alternative Analyses of the Full Marysville Cohort

Modeling of the full cohort was also conducted utilizing the full dataset for localized pleural thickening from the Marysville cohort. Since the full cohort includes data combined from Lockey et al. (1984) and Rohs et al. (2008), there were individuals who had more than one observation. As noted in Section 5.2.2.2, for those workers x-rayed in both 1980 (Lockey et al.,

1984) and 20042-2005 (Rohs et al., 2008), one of the observations was excluded so that there are no repeat observations for individual workers.

Time from first exposure to x-ray (T) is an important variable in understanding the full Marysville dataset, as can be seen by the much higher prevalence of localized pleural thickening in the 2000s compared to the 1980 assessment, an increase which cannot be fully explained by the increases in cumulative exposure occurring with continued exposure. Consequently, in looking at the full cohort, T is a strong predictor of localized pleural thickening. In contrast, for the sub-cohort analysis above, T is not predictive of localized pleural thickening risk when CHEEC is in the model; one reason is that in the sub-cohort the range of T is much smaller and all the values of T well exceed the minimal time since first exposure until the observation of thickening of about 10 years suggested by the data (23.15-32.62 years); in addition, there is less measurement error in the exposure for this group. One consideration in interpreting these results is that T does not represent time from first exposure to an event (or a detectable event), rather it is time from first exposure to the detection of an event. As such, it cannot be construed as an indicator of biological latency. Secondly, there is an element of time encompassed in the cumulative exposure metric—CHEEC reflects duration of exposure as well as intensity. Therefore, in some sense adding the T variable is 'double-counting' time. Finally, given the occurrence of higher exposures in earlier years (i.e., for individuals having large values of T), there is confounding between inference about the quantitative effect of time since first exposure and estimated cumulative exposure.

A similar approach as described in Section 5.2.2.3 was used to evaluate candidate models for the full cohort. Details are provided in Appendix E. However, since time since first exposure (T) was an important covariate for these analyses, further efforts were needed to develop a model incorporating T along with exposure. The logistic and probit models including CHEEC as a continuous exposure had inadequate model fit as evaluated using the Hosmer-Lemeshow test (p-values of 0.003 for both) and so were not considered for further analysis. The remaining candidate models (logistic and probit with the natural logarithm of CHEEC, 3-parameter log-logistic, dichotomous Hill, and dichotomous Michaelis-Menten) had adequate fit. Among these models, the AIC values ranged from 327.9 (Michaelis-Menten) to 346.8 (logistic with the natural logarithm of CHEEC). Based on these results, the Michaelis-Menten model was selected for further evaluation and different approaches were investigated to represent T along with cumulative Libby Amphibole asbestos exposure using this model form.

The approach taken to incorporate T was through modification of the plateau term in the Michaelis-Menten model to allow the plateau for the exposure-response relationship to change for different values of T. After investigating various forms for the plateau (described in

Appendix E), the lowest AIC resulted when the plateau term took the form: Plateau = Background + (1-background)* $\Phi(T|m,s)$, where $\Phi(T|m,s)$ represents the cumulative normal probability distribution function. Different exposure lags were then investigated for this model—as seen for the sub-cohort, the AIC values were quite similar for lags of 0-15 years (AICs ranging from 277.72 to 278.04. However, the 20-year lagged exposure had an increased AIC of 280.60 and was not judged an appropriate choice. The 10-year lagged exposure resulted in the lowest AIC, and was thus chosen as the preferred exposure metric. In order to estimate a BMC_{10} and corresponding $BMCL_{10}$ for this model form, a fixed value of T must be specified.

A first analysis need for this model is to provide results based on the full cohort for comparison with the estimated BMC_{10} and $BMCL_{10}$ values developed above for the sub-cohort with exposure data starting in 1972 (Section 5.1.2.3.1). For this need, a value of T=30 years was selected in order to provide a suitable comparison to modeling results for the sub-cohort, where the mean time since first exposure was 28 years. The BMC_{10} was 0.1384 fibers-yr/cc, with a corresponding $BMCL_{10}$ of 0.0541 fibers-yr/cc. These values, and particularly the $BMCL_{10}$, are in the same range as those estimated using the preferred analysis with the sub-cohort (BMC_{10} and $BMCL_{10}$ of 0.2543 and 0.0757 fibers-yr/cc, respectively). This analysis thus provides confirmation of the reasonableness of the modeling results developed using the sub-cohort database.

One alternative analysis using the full cohort model, with a time since first exposure value of T=40 years was conducted. A $BMCL_{10}$ of 0.0134 fibers-yr/cc was calculated with the Cumulative Normal Michaelis-Menten model. The $BMCL_{10}$ with T = 40 years is used because it is near the upper end of the range of T values available in the data set (Tmax = 47.375 years). This POD combined with a lag time of 5 years (used because Larson et al. (2010b) showed that discrete pleural thickening could be observed much earlier than previously thought) and a total uncertainty factor of 100 was used to derive an alternative RfC of 3.8×10^{-6} fibers/cc or rounding to one significant digit, 4×10^{-6} fibers/cc. See Appendix E for details. This alternative RfC is an order of magnitude lower compared to both the preferred sub-cohort analysis and the full cohort analysis with a fixed T of 30 years.

Another alternative analysis based on projection of risks using the full cohort model for a "lifetime" time since first exposure of T = 70 years. Note that none of the workers had a T>50 years; therefore this modeling represents a statistical extrapolation beyond available data. A $BMCL_{10}$ of 0.0041 fibers-yr/cc was calculated with the Cumulative Normal Michaelis-Menten model. This POD combined with a lag time of 5 years and a total uncertainty factor of 30 was used to derive an alternative RfC of 2.1×10^{-6} fibers/cc or rounding to one significant digit, 2×10^{-6} fibers/cc. See Appendix E for details.

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

Because of the greater certainty in the exposure reconstruction in the sub-cohort based on the data set where industrial hygiene data were collected in the facility (that is, workers hired in 1972 and later and examined for health effects in 2004), the RfC of 1×10^{-5} fibers/cc for Libby Amphibole asbestos is based on the preferred sub-cohort analysis.

5.2.5. Previous RfC Derivation

There is no previous RfC derivation for Libby Amphibole asbestos.

5.3. UNCERTAINTIES IN THE INHALATION REFERENCE CONCENTRATION (RfC)

Uncertainty in the exposure reconstruction

As in all epidemiological studies there are uncertainties in the exposure reconstruction. In this case there is some uncertainty 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 errors in this process could affect assigned Libby Amphibole asbestos exposure estimates. As stated previously, exposure measurements started in the Marysville plant in 1972; exposures prior to this time were estimated by University of Cincinnati scientists, based on focus group interviews with 15 long-term former workers. Exposure estimates for the period prior to 1972 thus can be considered as semi-quantitative rather than directly based on industrial hygiene data. The University of Cincinnati analysis assumed that early exposure levels in the plant are twice those measured in 1972 (Appendix F). The greater uncertainty of the pre-1972 exposure estimates led to EPA's decision to focus the analysis on the post-1972 group of workers rather than the full cohort. Although it is generally true that the use of more data is an advantage for statistical analyses because it allows

for the computation of more statistically precise effect estimates, this increased precision may be offset by a negative impact on the accuracy of the effect estimate if an increase in sample size is accompanied by greater exposure misclassification or other biases.

While the uncertainties related to a lack of quantitative measurements are not relevant to the sub-cohort analysis, it is important to recognize that exposure assessment post-1972 also has some limitations. The main source of uncertainty is the lack of exposure measurements for certain occupations/tasks (including polyform, warehouse, blender, feeder, resin, screen/mill, and track jobs) before industrial hygiene improvements that started in 1974 (Appendix F; Lockey, 1980). For some of these occupations, post-1974 measurements are quite high, suggesting that industrial hygiene measures were not immediately implemented.

There is uncertainty 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 the first usage of Libby ore in 1959 (see Appendix C). There is also uncertainty in the post-1972 data regarding asbestos content in other ore sources (Virginia, South Carolina and South Africa). Libby Amphibole asbestos was not used in the facility after 1980. However, industrial hygiene measurements 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 between different kinds of asbestos. Analysis of the bulk ores from Virginia and South Africa showed the presence of only a few or no amphibole fibers. No information is available to evaluate the nature of the fibers in these post 1980 samples. Lockey (1980, Figure 2, Tables 8-9) shows contradictory results on asbestos content in ore from Africa and asbestos content in South Carolina material comparable to Libby; recent retesting by the University of Cincinnati indicates that levels of these other ores were present at levels just above the limit of detection (Appendix C). University of Cincinnati was not able to obtain South Carolina material, but this material was used only for a relatively short time.

Accordingly, post-1980 exposure was included in the calculation of cumulative exposure to fibers and assumes that these fibers cause the same health effect. However, because the concentration of fibers in the workplace was near background after 1980, this exposure makes only a small contribution to an individual's cumulative exposure estimate.

There was potential co-exposure to other chemicals in the Marysville facility. These other chemicals were used after expansion of vermiculite ore in another area of the facility. Industrial hygiene data showed very low levels of fibers in these areas. In addition, none of these chemicals are volatile. The most likely route of exposure to these chemicals is through

dermal contact. It is unlikely that any co-exposure to these particular chemicals would alter the exposure-response relationship of Libby Amphibole asbestos in the respiratory system.

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

Uncertainty in the radiographic assessment of localized pleural thickening

There is some uncertainty associated with ascertainment of the health outcome. Conventional radiographs were used to determine the health outcome. Discrete pleural thickening may be difficult to detect, particularly if the affected areas are small in size, and fat deposits or other anatomical features (musculature, fractures) may be mistaken for pleural plaques (Gilmartin 1979). Thus, outcome misclassification may be present in the Marysville data. For example, one of the workers had a positive X-ray at 1980 scan, but a negative X-ray at 2000s scan (excluding this worker from the analysis did not change results). However, uncertainty in the prevalence of localized pleural thickening in each individual is considered minimal due to the use of a team of highly qualified chest radiologists evaluating the radiographic films and the use of consensus diagnosis.

Body mass index (BMI) was investigated as a potential explanatory variable because fat pads can sometimes be misdiagnosed as pleural thickening. BMI was not measured in the 1980 examination, but was available for most participants of the 2000s examination. To address whether fat deposits may affect outcome classification, EPA considered the effect of adding BMI as a covariate in the model. However, BMI did not display an association with odds of localized pleural thickening in this population (See Appendix E). While these covariates were not associated with risk of localized pleural thickening in the sub-cohort after adjusting for exposure, it was not possible to evaluate this relationship in the full cohort. In general, smoking rates have

declined between 1980 and 2000s and BMIs have probably increased, so one can't necessarily assume the relationships will be the same for the two examination periods.

In terms of the technology used for outcome assessment, high-resolution computed tomography (HRCT) can detect mineral fiber-related lesions in the respiratory tract, which cannot be identified by standard radiographs. Thus the technology employed for determining the prevalence of radiographic changes in the Marysville cohort may underestimate the actual prevalence of localized pleural thickening.

Uncertainty due to time from first exposure

There is some uncertainty associated with the length of follow-up of the Marysville cohort. The observed range of time since first exposure to x-ray in the full cohort is 0.4-47 years, and 23.2-32.7 years in the recommended sub-cohort. It is anticipated that the prevalence of localized pleural thickening in the study population – and in the post 1972 exposure cohort – may continue to show some increase with passage of time. In this case, the modeling approach may not accurately reflect the exposure-response relationship that would be seen with a longer follow-up time. However, a recent study by Larson et al. (2010b) examined serial radiographs conducted on a group of Libby vermiculite workers with pleural or parenchymal changes. They found that among those workers with localized pleural thickening, all cases were identified within 30 years, and that the median time from hire to the first detection of localized pleural thickening was 8.6 years. Although the workers included in the Marysville sub-cohort had generally higher exposures and earlier start dates (mostly prior to 1972) compared to the full worker population, these findings indicate that the range of follow-up time in the sub-cohort is likely sufficient to support the dose response modeling developed in this assessment. Note that the likelihood that prevalence of localized pleural thickening may further beyond 30 years after first exposure is a principal rationale cited for the selection of a database UF of 10 in this assessment.

Modeling of the full cohort (see Appendix E) showed that time from first exposure was the most significant explanatory variable. However, modeling of the sub-cohort hired in 1972 or later showed that time from first exposure was not a significant explanatory variable. The range of time from first exposure in the sub-cohort is much shorter (23 – 32.65 years versus 0.42 – 47.38 years). Therefore, it is likely that the prevalence of localized pleural thickening would increase if the individuals hired in 1972 or later were examined in the future.

Uncertainty in background rate of localized pleural thickening

In the derivation of the RfC, a background rate of 1% for localized pleural thickening was used. However, there is a range of estimates (0.02% to 3.9%) of prevalence of localized pleural thickening in studies looking at the background rate in populations not known to be occupationally exposed to asbestos. In populations where efforts were made to exclude individuals with prior exposure to asbestos, rates of 1.2% (4/326) and 0.2% (3/1422) were reported by Anderson et al. (1979) and by Castellan et al. (1985). Higher rates of localized pleural thickening are reported from cross sectional studies of the general population and individuals with military service. Using chest x-rays collected in NHANES I (1971-1975), Rogan et al. (1987) reported a background rate of 1.2%; a similar assessment using chest x-rays collected in NHANES II (1976-1980) found a background rate of 3.9% (Rogan et al. 2000). Miller et al. (1996) reported a background rate of 2.3% in inpatients and outpatients at a Veteran's Administration medical center, while Bohnker et al. (2005) reported a background rate of 2.3% based on data collected from the U.S. Navy Asbestos Medical Surveillance Program. One reason estimated background rates vary in the published literature is due to differing age structure of the study populations, as localized pleural thickening prevalence in influenced by age. The mean age of the Marysville sub-cohort at the time of x-ray is 52 years (median is 50 years). However, in statistical modeling of the Marysville sub-cohort, uncertainty in the background rate of localized pleural thickening is very low. Both the fixed and estimated values are in the range of estimates above and the difference in the POD when the background rate is fixed at 1% versus when it is estimated (estimated background rate of 3.76%) is less than 3%. As discussed in Section 4.1, there is a range of estimates (0.2% to 3.9%) in the background rate of localized pleural thickening. In the modeling, the background rate was set at 1% and not estimated. This is expected to have an insignificant effect on the value of the RfC.

Uncertainty in Model Functional Form and Lagged Exposure

A number of model forms were explored in the initial stages of analysis (Appendix E), before selecting the log-logistic model. The log-logistic model is widely used for epidemiologic data, and is easily interpreted. In this application the ratio of the BMC to the BMCL (0.2543/0.0757 = 3.4) was reasonable given the size of the available dataset, indicating acceptable statistical precision in the BMC estimate. In addition, BMCs and BMCLs estimated from other candidate models for the post 1972 exposure sub-cohort were in a similar range to the selected model. Finally, the complementary analysis with the full cohort (utilizing a 30 year time since first exposure value which was selected to be consistent with time since first exposure values within the sub-cohort) provided similar results to the sub-cohort analysis. A second model-based uncertainty is the choice of lag for cumulative exposure. The RfC derivation is

based on the exposure lagged by 10 years, since this lag yielded the lowest AIC. However, if other lags (with similar AICs) are used, the difference in POD may fluctuate to be approximately 8% higher or approximately 40% lower. However, as the RfC is rounded to one significant digit, the choice of lag does not affect the estimated RfC.

5.4. CANCER EXPOSURE-RESPONSE ASSESSMENT

5.4.1. Overview of Methodological Approach

The objective of this human health assessment is to derive a cancer estimate for inhalation exposure to Libby Amphibole asbestos. The inhalation unit risk (IUR) is defined as an upper-bound excess lifetime cancer risk estimated to result from continuous exposure to an agent at a concentration of 1 µg/L in water, or 1 µg/m^3 in air. However, current health standards for asbestos are given in fibers/cc of air as counted by phase contrast microscopy (PCM), since they are based on health effects observed in occupational cohorts and this is the standard for measuring fibers in an occupational environment (U.S. EPA, 1988; OSHA, 2008). Similarly, when examining the available health effects data for Libby Amphibole asbestos, the best available exposure metric available at this time is fibers/cc counted by PCM (Section 4.1.1.2). Therefore, for Libby Amphibole asbestos the IUR represents the lifetime risk of mortality from either mesothelioma or lung cancer in the general U.S. population from chronic inhalation exposure to Libby Amphibole asbestos at a concentration of 1 fiber/cc of air.

IURs are based on human data when appropriate epidemiologic studies are available. The general approach to developing an IUR from human epidemiologic data is to quantitatively evaluate the exposure-response relationship for that agent to derive a specific estimate of its cancer potency in the studied population. For this assessment, the first step was to identify the most appropriate data set available, which in this case can be used to quantitatively estimate the effects of Libby Amphibole asbestos exposure on cancer mortality. Once the relevant data describing a well-defined group of individuals along with their exposures and health outcomes was collected, an appropriate statistical model was selected that adequately fit the data, and then individual-level exposures were modeled using a variety of possible exposure metrics (Section 5.4.2). The available epidemiologic data allowed for modeling of the effects of estimated ambient occupational exposures to Libby Amphibole asbestos on the observed mortality risk in workers. Exposure-response modeling was conducted for each cancer mortality endpoint individually, and in some cases, the statistical model and the specific metric of exposure used for each cancer endpoint may have been different. For example, the exposure metric that best describes the exposure-response relationship for mortality from mesothelioma attributable to occupational exposure to Libby Amphibole asbestos was found to be different from the exposure

metric that best describes mortality from lung cancer (Section 5.4.3). Potential covariates that may also be important predictors of cancer mortality are included in the statistical models. These models were then statistically evaluated to determine which exposure metric representing estimated ambient occupational exposures provided the best statistical fit to the epidemiologic data.

This cancer potency estimate derived from the epidemiologic data is then applied to the general U.S. population to determine the exposure level that would be expected to result in 1% extra cancer mortality risk over a lifetime of continuous exposure. For epidemiologic studies, which may be based on larger numbers of individual observations, smaller response levels that are closer to the background response levels are considered appropriate. Extra risk is defined as equaling $(R_x - R_o) / (1 - R_o)$, where R_x is the lifetime cancer mortality risk in the exposed population, and R_o is the lifetime cancer mortality risk in an unexposed population (i.e., the background risk). For example, if the expected lifetime risk of lung cancer mortality in the unexposed general U.S. population is 5%, then this human health assessment seeks to estimate the level of exposure to Libby Amphibole asbestos that would be expected to result in a lifetime risk of lung cancer mortality of 5.95%; this lifetime risk of mortality is equivalent to a 1% extra risk $(0.0595 - 0.05) / (1 - 0.05) = 0.01$. For mesothelioma mortality, an absolute risk was considered, rather than extra risk, because mesothelioma is very rare in the general population (Hillerdal, 1983).

A life-table analysis (see Appendix G for details) was used to compute the 95% lower boundon the lifetime exposure to Libby Amphibole asbestos that corresponds to a 1% extra risk of cancer mortality in the general U.S. population using age-specific mortality statistics and the exposure-response relationships for each cancer endpoint as estimated in the studied population. This lower bound on the level of exposure serves as the point of departure (POD) for extrapolation to lower exposures and for deriving the unit risk. Details of this analysis are presented in Section 5.4.4. A cancer-specific unit risk was obtained by dividing the extra risk (1%) by the POD. The cancer-specific unit risk estimates for mortality from either mesothelioma or lung cancer were then statistically combined to derive the final IUR (Section 5.4.5). Uncertainties in this cancer assessment are described in detail in Section 5.4.6.

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

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

The available sources of data included the cohort of workers employed at the vermiculite mining and milling operation in and around Libby, MT. This cohort has been the subject of

several epidemiologic analyses (Amandus and Wheeler, 1987; Amandus et al., 1987a, 1987b; McDonald et al., 1986; Sullivan, 2007; Larson et al., 2010a; Moolgavkar et al., 2010; and described in detail in Section 4.1). There have also been published reports on cases of mesothelioma in the Libby, MT area (Whitehouse et al., 2008) and mortality data published by the Agency for Toxic Substances and Disease Registry (ATSDR) (2000). However, published mortality data on Libby, MT residents (Whitehouse et al., 2008; ATSDR, 2000) could not be used in exposure-response modeling due to lack of quantitative exposure data.

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

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

5.4.2.1. *Description of the Libby Worker Cohort*

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

According to Sullivan (2007), nearly all of these study subjects were workers at the Libby, MT vermiculite mine, mill, and processing plant. Although the mine was several miles from Libby, MT, some of the study subjects worked in the town (see Section 4.1.1.1). Workers may have also been assigned jobs as truck drivers, or jobs working in the screening plant, railroad loading dock, expansion plants, or an office. Individuals' demographic and work history data were abstracted from company personnel and pay records. A database created by NIOSH in the 1980s contained demographic data and work history starting from September 1935, and vital status at the end of 1981 for 1,881 workers. NIOSH compared these data with company records on microfilm, and work history data were re-abstracted to ensure data quality. One person was removed from the cohort because company records stated that he was hired, but never worked (Sullivan 2007). Nine workers with Social Security numbers listed in company records were excluded because demographic and work history data were not available, leaving 1,871 workers in the cohort available for epidemiologic analysis. Table 5-7 shows the demographic and exposure characteristics of this cohort.

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

Table 5-7. Demographic 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
Mean year of birth	1,929
Mean year of hire	1,959
Mean age at hire (years)	30.2
Mean person-years of follow-up (no lag)	35.9
Total person-years of follow-up (no lag)	67,101
Mean employment duration (years)	3.7
Mean cumulative exposure (fibers/cc-years)	96.0
Median cumulative exposure (fibers/cc-years)	9.8

Basic demographic information on the occupational cohort members was largely complete. However, when data were missing, they were imputed by NIOSH based on the following assumptions regarding gender, race, and date of birth. Seven workers with unknown gender were assumed to be male because 96% of the workforce was male and NIOSH review of names did not challenge that assumption (Sullivan, 2007). Workers of unknown race (n = 935) were assumed to be white because workers at this facility were known to be primarily white, and U.S. Census Bureau data indicate that 90-95% of the local population identify themselves as white (Sullivan, 2007). For four workers with unknown birth dates, date of birth was estimated by subtracting the mean age at hire for the cohort from the worker's hire date. The potential impact of this imputation procedure on the analytic results is discussed in Section 5.4.6.

5.4.2.2. *Description of Cancer Endpoints*

This human health assessment of Libby Amphibole asbestos focuses on two cancer endpoints: mesothelioma and lung cancer. The endpoint for both mesothelioma and lung cancer was mortality, not incidence. Incidence data are not available for the Libby worker cohort. However, there is evidence that other cancer endpoints may also be associated with exposure to

asbestos. The International Agency for Research on Cancer (IARC) concluded that there was sufficient evidence in humans that other types of asbestos (chrysotile, crocidolite, amosite, tremolite, actinolite, and anthophyllite) were causally associated with mesothelioma and lung cancer, as well as cancer of the larynx and the ovary (Straif et al., 2009). Among the entire Libby worker cohort, only 2 deaths were found to be due to laryngeal cancer, and there were no deaths from ovarian cancer among the 84 female workers. The EPA did not evaluate these other outcomes as part of this assessment. The limited number of female workers in this cohort is discussed later as a source of uncertainty in the derived estimates (Section 5.4.6).

Mesothelioma did not have a distinct ICD code prior to introduction of the 10th revision (ICD-10) which was not implemented until 1999. Therefore, for deaths in the Libby worker cohort occurring from 1979 to 1998, death certificates were obtained if the NDI identified the death as being from one of the possible mesothelioma codes identified by Marsh et al. (2001), or from respiratory cancer, nonmalignant respiratory disease, digestive cancer, or unspecified cancer. Death certificates (1940-1998) were reviewed by the NIOSH principal investigator (Sullivan, 2007) to identify any mention of mesothelioma on the death certificate, as is the standard procedure for assessing mesothelioma mortality and as has been used in other analyses of Libby worker cohort mesothelioma mortality (McDonald et al., 2004; Larson et al., 2010a). In total, 18 mesothelioma deaths occurring from 1979 to 2006 were identified by NIOSH using these methods (which serves as the basis for this assessment); 19 mesothelioma deaths were identified by Larson et al. (2010a) for the same cohort from death certificates for all causes of death rather than the more targeted set of causes indentified by Marsh et al. (2001) or Sullivan (2007).

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

Mortality records (and death certificates) may not always reflect the true cause of death for various reasons (e.g., misdiagnosis, improper recording on the death certificate, or miscoding of the cause of death). For mesothelioma, the undercounting of cases (underascertainment) is a particular concern given the limitations of the ICD classification systems used prior to 1999 (detection rates varied from 12% from ICD-9 codes alone to 83% from manual inspection of

death certificates [Davis et al., 1992]); recent studies demonstrated that ICD-10 coding has detection rates similar to the rates above (Pinhiero et al., 2004; Camidge et al., 2006). The appropriate procedure for pre-ICD-10 codes is not to use ICD codes alone but manually inspect death certificates, as was done by Sullivan (2007). There is also evidence that the detection rate of peritoneal mesothelioma is much lower than pleural mesothelioma (Selikoff and Seidman, 1992). This assessment has accounted for the impact of this underascertainment on the final IUR (Section 5.4.5.1.1).

Lung cancer mortality was based on the underlying cause of death identified by the ICD code on death certificates according to the ICD version in use at the time of death. Based on these different ICD codes, lung cancer mortality included malignant neoplasms of the trachea, bronchus, and lung, and was identified by the following codes: ICD-5 code '047', ICD-6 and ICD-7 codes '162' or '163', ICD-8 and ICD-9 code '162', and ICD-10 codes 'C33' or 'C34'. In all, there were 111 deaths with an underlying cause of death attributed to lung cancer. All deaths after 1960 were coded as bronchus or lung as the ICD versions in use as that time distinguished malignant neoplasms of the trachea as distinct from bronchus and lung. Other investigators of this cohort have used different definitions of lung cancer or used different follow-up periods, as described in Section 4.1.1.2 (Description of Study Cohorts).

5.4.2.3. *Description of Libby Amphibole Asbestos Exposures*

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

EPA adopted the job-exposure matrix (JEM) developed and used by Sullivan (2007) (Figure 5-6), which was, in turn, based on that used in the earlier NIOSH study for jobs through 1982 (Amandus and Wheeler, 1987). As discussed in more detail in Section 4.1, Amandus et al. (1987a) defined 25 location operations to which they assigned exposure intensity based on available information (Table 5-8). A job category may have involved more than one location operation, and the 8-hour time-weighted average exposure (8-hr TWA) for each job category in the JEM was calculated from the exposure intensity and time spent at each location operation (Amandus et al., 1987a).

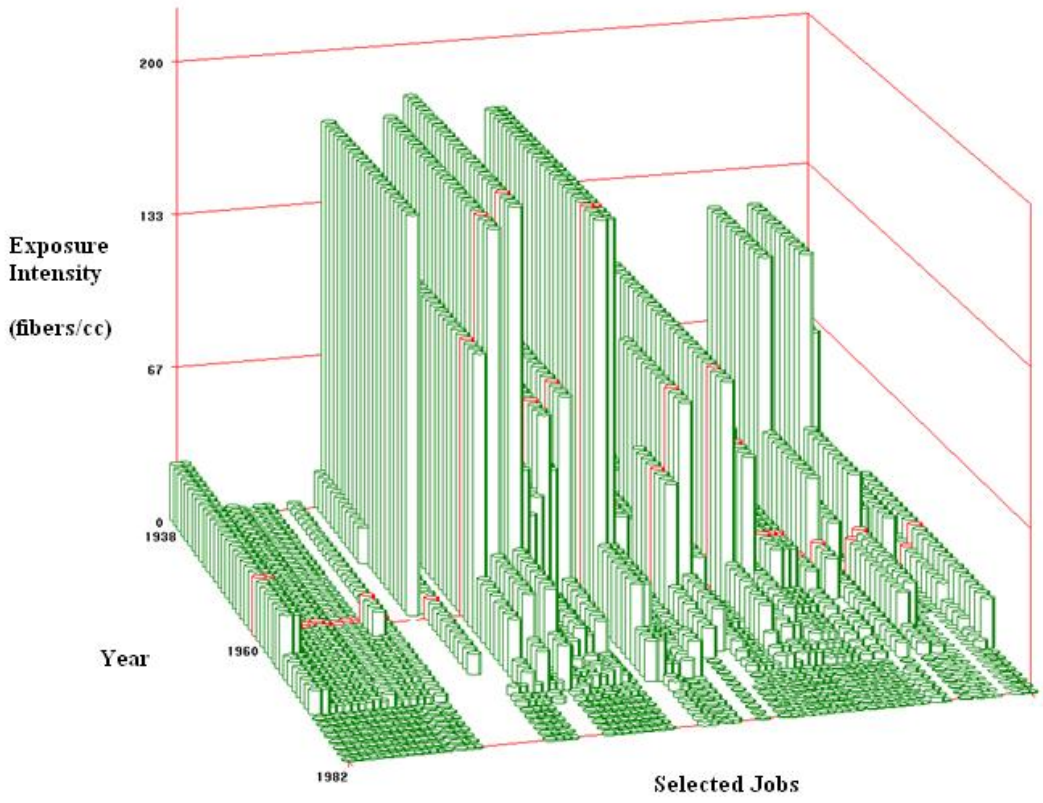

Figure 5-6. Plot of the NIOSH job exposure matrix for different job categories over time. The height of each bar represents the intensity of exposure as an 8-hr TWA (fibers/cc) for a job in a particular year. Each row for "Selected Jobs" represents a specific job category.

Table 5-8. Exposure intensity (fibers/cc) for each location operation from the beginning of operations through 1982 (Amandus et al., 1987a)

Location operation	Year									
	<50	**50-59**	**60-63**	**64-67**	**68-70**	**71**	**72-74**	**75-76**	**77-79**	**80-82**
Downtown office building	*0*	*0*	*0*	*0*	0	0	0	0	0	0
Bus ride	*1.2*	*1.2*	*1.2*	*1.2*	1.2	1.2	1.2	0	0	0
Mine office	*1.0*	*1.0*	*1.0*	*1.0*	1.0	1.0	1.0	0.5	0.5	0.5
Mine misc.	*1.6*	*1.6*	*1.6*	*1.6*	1.6	1.6	1.6	0.8	0.8	0.8
Mine—nondrilling	*2.6*	*2.6*	*2.6*	*2.6*	2.6	2.6	2.6	0.6	0.6	0.6
Transfer point	*2.2*	*2.2*	*2.2*	*2.2*	2.2	2.2	2.2	0.6	0.6	0.6
Quality control lab	*13.1*	*13.1*	*13.1*	*2.6*	2.6	2.6	2.6	0.6	0.6	0.6
Service area by mill	*1.9*	*1.9*	*1.9*	*3.8*	1.9	1.9	1.9	0.2	0.2	0.2
Dry mill	*168.4*	*168.4*	*168.4*	*33.2*	33.2	33.2	16.6	--	--	--
Dry mill sweeping	*182.1*	*182.1*	*182.1*	*35.9*	35.9	35.9	19	--	--	--
Old and New wet mill—millwright	--	*7.0*	*7.0*	*7.0*	7.0	7.0	7.0	0.6	0.6	0.6
Old wet mill—nonmillwright	--	*3.7*	*3.7*	*3.7*	3.7	3.7	3.7	--	--	--
New wet mill—nonmillwright	--	--	--	--	--	--	3.2	2.0	0.8	0.8
Skip area	*88.3*	*88.3*	*88.3*	*17.4*	17.4	17.4	4.8	0.6	0.6	0.6
Concentrate hauling	*5.5*	*5.5*	*5.5*	*5.5*	5.5	5.5	5.5	0.4	0.4	0.4
River station binside	*21.2*	*21.2*	*21.2*	*21.2*	21.2	21.2	21.2	0.7	0.7	0.7
River conveyor tunnel	*112.5*	*112.5*	*112.5*	*112.5*	112.5	112.5	112.5	0.3	0.3	0.3
River office binside	*10.6*	*10.6*	*10.6*	*10.6*	10.6	10.6	10.6	0.2	0.2	0.2
Verxite plant	*22.6*	*22.6*	*2.8*	*2.8*	2.8	--	--	--	--	--
Bagging plant	*12.9*	*12.9*	*12.9*	*12.9*	12.9	12.9	4.3	1.2	1.2	1.2
Tails belt	*7.3*	*7.3*	*7.3*	*7.3*	7.3	7.3	7.3	0.7	0.7	0.7

1

Table 5-8. Exposure intensity (fibers/cc) for each location operation from the beginning of operations through 1982 (continued)

Location operation		Year									
		<50	**50-59**	**60-63**	**64-67**	**68-70**	**71**	**72-74**	**75-76**	**77-79**	**80-82**
Screen plant		--	--	--	--	--	--	--	0.5	0.5	0.5
Drilling	High	*23*	*23*	*23*	*23*	9.2	9.2	9.2	0.6	0.6	0.6
	Low	*6.7*	*6.7*	*6.7*	*6.7*	6.7	9.2	9.2	0.6	0.6	0.6
Ore Loading	High	*82.5*	*27.7*	*10.7*	*10.7*	3.2	3.2	3.2	0.2	0.2	0.2
	Low	*24*	*15*	*9*	*9*	3.2	3.2	3.2	0.2	0.2	0.2
River dock	High	*116.9*	*42.5*	*17*	*17*	17	5.1	5.1	0.5	0.5	0.5
	Low	*38*	*19*	*6.4*	*6.4*	5.1	5.1	5.1	0.5	0.5	0.5
Bagging plant	High	*12.9*	*12.9*	*12.9*	*12.9*	12.9	12.9	4.3	1.2	1.2	1.2
	Low	*4.6*	*4.6*	*4.6*	*4.6*	4.6	4.6	4.3	1.2	1.2	1.2

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

However, the amount and quality of measurement data in the facility in earlier years was much more limited (Amandus et al. 1987a). A total of 40 dust samples were taken, exclusively in the dry mill, over the years 1950−1964. Using these measurements, much higher exposures were inferred to occur prior to 1964 than those measured in later years. Although air sampling for fibers by PCM was available beginning in 1967, average fiber concentrations (dry mill) differed rather widely between limited data sets from different investigators up through the early 1970s: 1967-68, NIOSH data, 65 f/cc (n = 14); 1970, company data, 11 f/cc (n = 15); 1971, MSHA data, 31 f/cc (n = 52); 1972, MSHA and company data, 15 f/cc (n = 45). Thus, estimated exposure levels continue to be uncertain during the period when fiber concentration measurements by PCM became available in 1967.

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

The exposure intensity (fibers/cc) for each of the location operations (Table 5-8) was used to calculate an estimate of daily occupational exposure for each job category in the JEM (Figure 5-6). For each job, the time spent at each location operation and the exposure intensity for each location operation were averaged to derive an estimate of the 8-hour TWA. The resulting JEM available for this assessment and previous epidemiologic studies of the Libby

worker cohort is based on the air concentration of fibers as enumerated by PCM which measures fibers longer than 5 μm with an aspect ratio >3:1 (i.e., the fiber size regulated under the OSHA standard [U.S. Department of Labor, 2006]). Additionally, only fibers that are wide enough to be viewed on PCM can be detected with this method. Amandus et al. (1987a) considered fibers >0.44 μm in diameter to be visible by PCM in the historical filter analysis. More recent techniques have refined the PCM method and fibers greater than 0.25 μm in diameter are now considered PCM fibers (WHO, 1980).

There was one important limitation of the NIOSH JEM. In the earlier study (Amandus and Wheeler, 1987), workers with "common laborer" job assignments and some workers with unknown job assignments hired between 1935 and 1959 were assigned the relatively low exposure levels estimated for the mill yard. In the more recent study by Sullivan (2007), these workers (686 from 991 hired before 1960) were assigned the same average estimated exposure intensity for all unskilled jobs during the relevant calendar time period. The lack of information on specific job assignments for these workers in the JEM resulted in the misclassification of the exposure and made exposure metrics, representative of duration of employment alone, describe this large part of the cohort. For this reason and because there was little measured fiber exposure data during the earlier period, difficulties were experienced identifying an adequate exposure-response model fit. These difficulties are described in detail in Section 5.4.3.3. As a result, the IUR analyses were based on the subset of workers hired after 1959 (i.e., on or after January 1, 1960) and consisted of 880 workers. Table 5-9 shows the demographic and exposure characteristics of this sub-cohort.

In addition, re-abstracting work histories for the more recent study (Sullivan, 2007) identified several job assignments not mentioned in the earlier publications. Sullivan (2007) re-abstracted work histories by extrapolating exposure estimates for the additional job and calendar time period-specific combinations based on professional experience and review of exposure records from earlier studies of the Libby worker cohort (Amandus and Wheeler, 1987; Amandus et al., 1987a, b; McDonald et al., 1986). While the Sullivan (2007) study was limited to the white male workers, EPA's analysis includes all workers regardless of race or gender. Figure 5-6 shows a three-dimensional representation of the job-exposure matrix used by Sullivan (2007) and in this assessment. Not all jobs were included; thus, the figure is not comprehensive but rather illustrative. The three axes show the intensity of fiber exposure as an 8-hour TWA (fibers/cc, vertical axis) for selected job categories over time (horizontal axes). For several jobs, the estimated 8 hr TWA was greater than 100 fibers/cc for the decades prior to 1963. Figure 5-6 shows the variability in exposures across jobs and over time. From 1967-1982, all exposure measurements that inform the JEM are based on location-specific air samples analyzed for fibers

by PCM. As stated above, pre-1968 exposures in the dry mill were based on measurement of dust levels from 1956-1967 that were converted to PCM by Amandus et al. (1987a) and extrapolated backwards in time. Pre-1968 exposures for all other locations within the JEM were extrapolated from post-1967 fiber levels based on reasoned assumptions (Amandus et al., 1987a).

Table 5-9. Demographic and exposure characteristics of the subset of the Libbyworker cohort hired after 1959

Characteristic	Sub-cohort hired after 1959
Number of workers	880
Number of deaths from all causes	230
Number of deaths from mesothelioma	7
Number of deaths from lung cancer	32
Mean year of birth	1942
Mean year of hire	1971
Mean age at hire (years)	28.6
Mean person-years of follow-up (no lag)	32.2
Total person-years of follow-up (no lag)	28,354
Mean employment duration (years)	3.3
Mean cumulative exposure (fibers/cc-years)	19.2
Median cumulative exposure (fibers/cc-years)	3.4

Amandus and coworkers (1987a) recognized the uncertainty in the pre-1968 exposures assigned to the cohort. Although there is some uncertainty in the dust–to-fiber conversion, this conversion (4.0 fibers/cc per mppcf) was based on contemporaneously collected dust and fiber data collected in the dry mill and only applied to the dry mill environment. Amandus and coworkers considered a range of possible conversion factors (1.2-11.5 fibers/cc per mppcf). Greater uncertainty may lie with the reasoned assumptions used to extrapolate exposures to the early decades for all location operations considered. For example, there were four location operations for which Amandus and coworkers estimated a range of possible exposure intensities: drilling location site, ore loading location site, river dock, and the bagging plant, where intensity of exposure may vary as much as 3-fold between the low and high estimates (Table 5-8). Finally, some workers were employed after 1982 through 1993 in plant close-out and clean-up operations, which have not been evaluated (Sullivan, 2007). However, none of the members of the post-1959 cohort (n = 880) remained employed by 1982 according to employment records.

5.4.2.4. *Description of Libby Worker Cohort Work Histories*

NIOSH staff and contractors abstracted demographic data and work history data from company personnel records, including W-2 federal tax forms. An individual's work history was

determined from job change slips, which recorded new job assignment, date of change, and change in hourly pay rate (which differed by the job assignment). Work history records span the time period from September 1935 to May 1982. Dates of termination were unknown for 58 of 640 workers (9%), who left employment before September 1953. EPA adopted the assumption used by NIOSH (Sullivan, 2007) that these people worked for 384 days, based on the mean duration of employment among all workers with known termination dates before September 1953. The majority of workers in this cohort as a whole and among those hired on or after January 1, 1960 worked at multiple jobs; many of the workers switched jobs repeatedly. Of the 880 hired in 1960 or afterwards, the mean number of job changes was 5, the median was 2, and the maximum number of job changes was 32 (Figure 5-7).

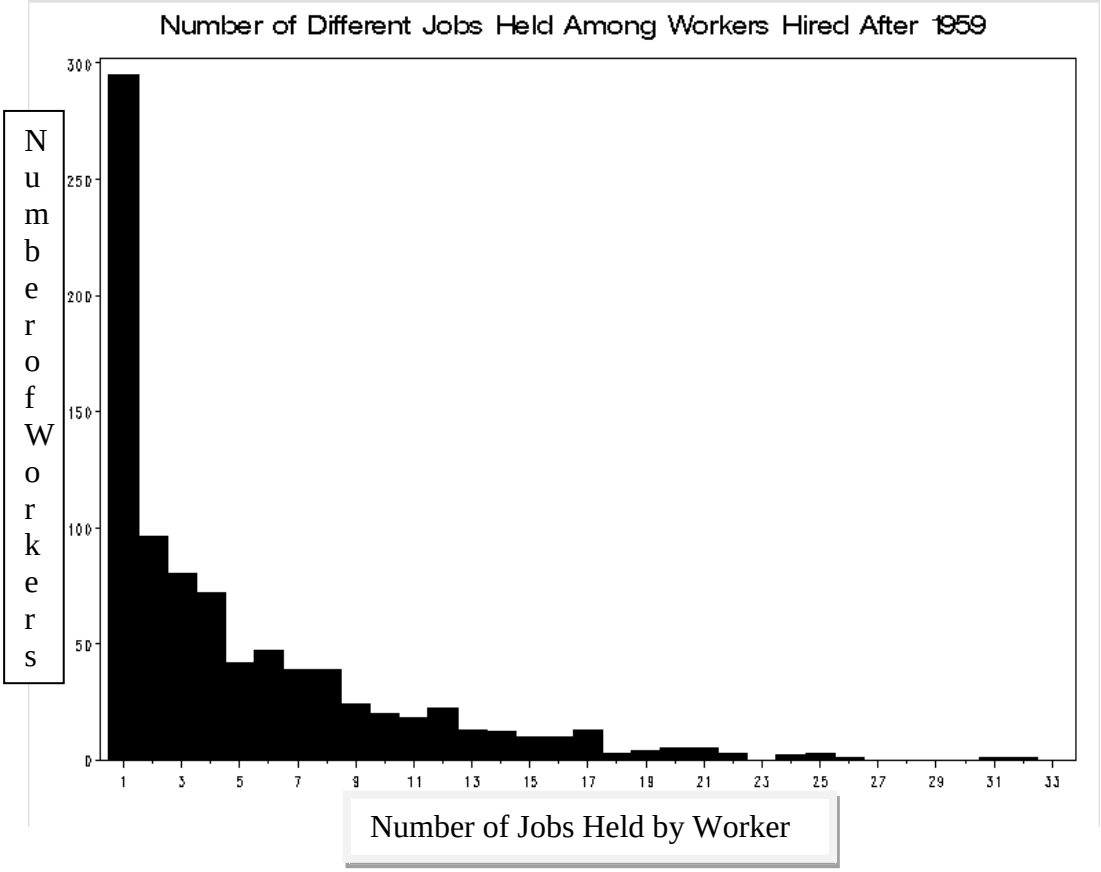

Figure 5-7. Histogram showing the number of workers who experienced each incremental number of different jobs among the 880 workers hired after 1959.

5.4.2.5. *Estimated Exposures Based on Job Exposure Matrix and Work Histories*

Exposure-response modeling of epidemiologic data is based on several considerations as summarized by Finkelstein (1985):

> After identification of an occupational hazard one of the goals of occupational epidemiology is to quantify the risks by determining the dose-response relations for the toxic agent. In many circumstances little is known about the dose received by target tissues; the data available usually pertain only to exposure to various concentrations of the toxic material in the workplace. The calculation of dose requires additional physiological and chemical information relating to absorption, distribution, biochemical reactions, retention, and clearance. In asbestos epidemiology the usual measure of exposure is the product of the concentration of asbestos dust in the air (fibres or particles per ml) and the duration of exposure to each concentration summed over the entire duration of exposure (years); this measure is the cumulative exposure.

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

Most studies of asbestos-related mortality have evaluated either cumulative exposure, exposure concentration, or the duration of employment as exposure metrics. Many studies have been limited in the availability of detailed exposure data—especially at the individual level. In the Libby worker cohort data developed by NIOSH and used in this assessment, detailed work

histories, together with job-specific exposure estimates, allowed for the reconstruction of each individual's occupational exposure experience over time to define multiple exposure metrics.

From this information-rich, individual-level dataset from NIOSH, EPA constructed a suite of the different metrics of occupational exposure which had been proposed in the asbestos literature or used in the IRIS asbestos assessment (U.S. EPA, 1988). This suite of models was defined a priori to encompass a reasonable set of proposed exposure metrics to allow sufficient flexibility in model fit to these data. These exposure metrics were evaluated in analytic-regression models to test which exposure metrics were the best empirical predictors of observed cancer mortality and the better fitting models were advanced for consideration as the basis of the exposure-response relationship for the IUR. The types of exposure metrics evaluated were intended to allow for variations of the classic metric of cumulative exposure, allowing for more or less weight to be placed on earlier or later exposures. These simulated exposure metrics were derived mathematically to approximate underlying processes that are not well understood (see Section 5.4.6). Thus the fit of exposure metrics is evaluated on the basis of maximizing the likelihood for the Libby worker cohort and the estimated parameters do not necessarily have biological interpretations.

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

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

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

where

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

t_k = the day on which the exposure is estimated.

A second exposure metric—residence time-weighted (RTW) exposure—gives additional weight to early exposures. By doing so, the RTW exposure metric allows the possibility that early exposures are more influential on cancer mortality predictions in the model. Unlike many chemicals that are rapidly metabolized in the body and excreted, asbestos fibers are durable and some may remain in the body for years. Fibers that remain in the lung may continue to damage lung cells and tissue until they are removed or cleared (Section 3.2). Similarly, fibers that translocate to the pleura may damage cells as long as they remain in this tissue. Therefore, a fiber exposure may not only damage tissue during the exposure, but fibers may remain in these tissues, with cellular and tissue damage accumulating over time.

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

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

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

where

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

t_k = the day on which the exposure is estimated.

The CE and RTW exposure metrics result in increasing or sustained metrics of exposure across time. However, it is known that some cellular and genetic damage may be repaired over time, which could decrease cancer risk from exposure over time. Additionally, asbestos fibers are cleared (removed) from the lung through natural processes and translocated to other tissues (Section 3.2.1.1). Therefore, when considering lung cancer, it is possible that removal of asbestos fibers from the lung would reduce lung cancer risk over time. Although less is known about removal of asbestos from the pleura, there may be clearance mechanisms operative in that tissue as well (Section 3.2.1.2). As noted earlier, Berry et al. (1979) proposed the use of exposure metrics based on occupational exposures which addressed the issue of clearance using a mathematical decay term to modify measured ambient exposures. For mesothelioma, modeling a decay term on exposure has been proposed by Berry (1999). Based on this proposal, several recent papers applied a decay term to modeling mesothelioma mortality (Reid et al., 2009; Berry et al., 2009; Barone-Adese et al., 2008; Gasparrini et al., 2008; Clemens et al., 2007; Hodgson et al., 2005; Berry, 2004). Similarly, recent publications indicate that the relative risk of lung cancer due to asbestos exposure declines 15-20 years after the cessation of exposure to asbestos (Magnani et al., 2008; Hauptmann et al., 2002).

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, where a decay rate was applied to the CE and RTW exposure metrics (Eqs. 5-3 and 5-4).

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 fiber kinetics of Libby Amphibole asbestos 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 metrics.

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

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

where

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

t_k = the day on which the exposure is estimated.

In addition to the exposure metrics used in the lung cancer mortality analysis, modeling of mesothelioma mortality (Section 5.4.3) included the exposure model used in the IRIS assessment for asbestos (U.S., 1988), originally proposed in Peto et al. (1982):

$$Im = C \cdot Q \cdot KM \quad \text{(Eq. 5-5)}$$

where

Im = the observed deaths from mesothelioma/person-years,

C = the average concentration of asbestos in the air,

KM = an estimated slope describing the relationship between Libby amphibole exposure and mesothelioma mortality, and

Q = the function of the time since first exposure (t) and the duration of employment (d):

For $t \leq 10$, $Q = 0$

For $10 < t \leq d + 10$, $Q = (t - 10)^3$

For $t > d + 10$, $Q = (t - 10)^3 - (t - 10 - d)^3$.

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

In addition to the use of these methods of describing exposure metrics representing estimated ambient exposure to Libby Amphibole asbestos dust for use in predicting the risk of mortality there is the important issue of potential modifying the exposure metrics to account for

cancer latency. Without knowledge of the specific timing of etiologically relevant exposure which may initiate and promote cancers ultimately resulting in mortality, any exposure metric may include exposures during some time period which do not have bearing on the risk of mortality. In the absence of such information on the specific cancer latency associated with a specific exposure, Rothman (1981) suggested that the most relevant exposure period could be identified by comparing the fit of exposure metrics across multiple lag periods to allow for the identification of the optimal latency period as an expression of a lag time between exposure and mortality. This has since become a standard practice in occupational and environmental epidemiology. Accordingly, exposure estimates for all exposure metrics were adjusted to account for the time period between the onset of cancer and mortality. The lag period defines an interval before death, or end of follow-up, during which, any exposure is excluded from the calculation of the exposure metric. Cohort members who died or were lost within the initial years of follow-up were assigned lagged exposure values of zero if they had not been followed for longer than the lag time. The various exposure metrics were lagged at 10, 15, and 20 years to account for different potential cancer latencies within the limitations of the available data. While mesothelioma is known to have an average latency as long as 55 years among selected occupations (e.g., Bianchi and Bianchi, 2009), several mesothelioma deaths in the cohort occurred within 30 years from the start of the exposure, suggesting a shorter latency period in this population. Metrics without a lag were fit for comparison purposes but were not considered to be biologically reasonable, given that the outcome under analysis is cancer mortality (specifically, mesothelioma and lung cancer), for which latency periods of 10 years or more have been established for asbestos (U.S. EPA, 1988). Consequently, metrics that were not adjusted by lagging exposure in the final years before mortality (or the end of follow-up) were not considered further in the development of an IUR for Libby Amphibole asbestos.

5.4.3. Exposure-Response Modeling

Sufficient biological information to select models for the epidemiology data on the basis of biological mechanism (Section 3) is not available. In this situation, EPA's practice is to investigate a range of model forms to determine how to best empirically model the exposure response relationship in the range of the observed data. For Libby Amphibole asbestos, possible exposure metrics were explored for model fit to the chosen models. The exposure metric options were selected to provide a range of shapes that was sufficiently flexible to allow for a variety of ways that time and duration might relate to cancer risk in the data being modeled. EPA then evaluated how well the models and exposure metric combinations fit the data being modeled. Metrics that did not fit the data well were rejected. For purposes of calculating a reasonable

upper-bound on the risk per exposure EPA accounted for uncertainty in the choice of exposure metrics by using the exposure metric (among those of reasonable fit) that estimated the highest risk. This is explained in more detail below and in Sections 5.4.4-5.4.5.

The risk estimates are based on epidemiological analysis of the primary NIOSH data (Libby worker cohort). The rationale for selection of the Libby worker cohort is presented in the previous section (Section 5.4.2). Analysis of this primary epidemiologic database allows the comparison of multiple metrics of exposure to quantify the exposure-response relationship. This approach is intended to support the empirical representation of the exposure-response relationship of estimated ambient occupational exposure to Libby Amphibole asbestos with observed cancer mortality risk. The exposure-response modeling may be influenced by uncertainties in the magnitude and time course of the exposure estimates and, therefore, may not necessarily reflect the biologic disposition of inhaled fibers, but simply, the empirical observation of estimated exposure to Libby Amphibole asbestos, and subsequent mortality as the mode of action, is not well understood (Section 5.4.6).

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

The background incidence of mesothelioma is extremely rare (Hillerdal, 1983). Since there is a very low background risk, the exposure-response model applied here examines the relationship of the absolute risk of mesothelioma mortality that is attributable to Libby Amphibole asbestos exposure because there is not a true background risk of mesothelioma mortality among people who were truly unexposed to Libby Amphibole asbestos (as opposed to the relative risk model, which is used for lung cancer mortality; see Section 5.4.3.2). Poisson regression models are employed here for estimating the absolute risk of mesothelioma, as the Poisson distribution is an appropriate model for use with data that are counts of a relatively rare outcome, such as observed mesothelioma deaths in the Libby worker cohort. Other analyses of mesothelioma mortality in the Libby worker cohort have also used the Poisson model (McDonald et al., 2004; Moolgavkar et al., 2010). In the Poisson model, probability of k events is specified as

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

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

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

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

Multiple metrics of exposure (Section 5.4.2.5) as well as exposure intensity, duration of employment, age at death or loss to follow-up, and time since first exposure were compared using the Deviance Information Criterion (DIC). DIC (Spiegelhalter et al., 2002) is used in Bayesian analysis and is an analogue of the Akaike Information Criterion (AIC), with smaller values indicating a better statistical fit to the data. Use of the DIC and AIC is standard practice in comparing the fit of non-nested models to the same dataset with the same dependent outcome variable, but different independent covariates. According to Burnham and Anderson (2002), 'These methods allow the data-based selection of a "best" fitting model and a ranking and weighting of the remaining models in a pre-defined set.' Because of the small number of deaths from mesotheliomas in absolute terms, only uni- and bi-variate models (with age or time since first exposure as the second covariate) were considered. Sex and race were not used as covariates since all mesotheliomas were observed in men assumed to be white (Sullivan, 2007).

[1] A credible interval is the Bayesian analogue of a confidence interval.

Each exposure metric was lagged by 0, 10, 15, or 20 years. The use of a lag period aims to account for the latency period between the onset of mesothelioma (which occurs some time before clinical diagnosis) and mesothelioma mortality.

Results of mesothelioma mortality analysis

For the full Libby worker cohort (n = 1,871), the duration of employment provided a considerably better univariate model fit than the other possible exposure metrics, indicating that this exposure metric was the best single predictor of mesothelioma mortality in the full Libby worker cohort. The bivariate model which included duration of employment and age at death or censoring provided the overall best fit (DIC = 196). The inclusion of information on the concentration of exposure beyond the duration of employment resulted in a degradation in model fit (Table 5-10). The metric used in the IUR for asbestos (U.S. EPA, 1988) (Eq. 5-5) had a higher DIC of 233.7 in the analysis here. It is likely that the poorer fit seen when using information on exposure concentration is the result of the fact that duration of employment is measured with comparatively little error, while derivation of specific exposure concentrations may be subject to a sizable measurement error. Moreover, as described in Section 5.4.2.3, for 686 of 991 (69%) workers hired from 1935 to 1959, only the duration of employment was known, but not the job category, and thus the same exposure concentration had been assigned to 653 of these workers (Sullivan, 2007). It is likely that because of the potential for particularly large exposure measurement error among more than two thirds of the workers hired prior to 1960 who were assigned the same exposure intensity, this resulted in the duration of employment being the best predictor of mesothelioma mortality. Additionally, estimates of exposure intensity prior to 1968 have greater uncertainty associated with them than more recent exposure measurements which are based on fiber counts in air samples analyzed by PCM. For the majority of job locations (23 of 25), no exposure measurements were available prior to 1968, and exposures were estimated based on employee interviews (in 1982) and what was known about major changes in operations between 1935 and 1967. For two exposure locations, the dust–to-fiber conversion ratio is based on measurements taken in the late 1960s, so extrapolations from the mid-1960s to the early 1960s is likely to be more certain than extrapolation further back in time. The fact that the metric using only duration of employment fit best and the additional incorporation of exposure intensity information worsened the fit indicates that it is unlikely that IUR estimates can be developed using the full cohort data because exposure values were not predictive of mesothelioma mortality.

Table 5-10. Comparison of univariate model fit of various exposure metrics for mesothelioma mortality in the full Libby worker cohort (n = 1,871)[a,b]

Variable	DIC
Duration of employment	202.9
Age at death or censoring	209.2
CE lagged 15 yr	209.5
CE lagged 10 yr	209.9
RTW lagged 10 yr with 5yr ½ life	210.4
CE lagged 10 yr with 20yr ½ life	210.6
RTW with 5 yr ½ life	210.7
RTW with 10 yr ½ life	211.0
CE	211.4
Time since first exposure	211.4

[a] Since one of the mesothelioma deaths occurred less than 20 years from start of the exposure, lag 20 metrics assigned no exposure to this case which resulted in the very poor fit of exposure metrics lagged 20 years.
[b] Lower DIC values represent better fits. Models with DIC within 10 units of the DIC of the model with the lowest DIC are shown.
DIC = Deviance Information Criterion.

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

5.4.3.2. *Modeling of Lung Cancer Exposure-Response in the Libby Worker Cohort*

To develop an exposure-response relationship for lung cancer, the lung cancer mortality data were modeled as a function of the historical exposure data for the Libby worker cohort. The mesothelioma mortality data were modeled to estimate the absolute risk because it is very rare in the general population (Hillerdal, 1983).. Lung cancer mortality does have a known background

risk and thus, modeling of lung cancer mortality is based on the relative risk rather than the absolute risk. As such, there are different analytic methods available which can use information on time-varying exposures. The NIOSH-developed individual-level exposure data for the Libby worker cohort are very detailed, with start and stop dates for each of the workers' jobs and estimated fiber exposures for 25 specific location-operations (Amandus et al., 1987). It is, therefore, important to find a model that makes efficient and effective use of these time-dependent data.

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

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

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

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

The Cox proportional hazards model was chosen to model the lung cancer mortality data for several reasons. Of primary importance is that it takes statistical advantage of the extensive exposure data collected for the cohort on time-varying exposures to Libby Amphibole asbestos. There are no other standard model formulations that allow for the analysis of time-varying exposures in the manner achieved by the Cox proportional hazards models. The exposure-response relationship (proportional hazards ratio) determined in this model intrinsically takes

into account the effects of other causes of mortality that are unrelated to exposure (i.e., independent censoring). Further, all comparisons are made within the cohort by comparing the mortality experience of people with different exposures within the same cohort population. The issue of competing risks that are dependent on exposure (e.g., asbestosis or non-malignant respiratory disease) is an acknowledged uncertainty for this type of analysis (see Section 5.4.6).

Other methods common to occupational epidemiology, such as the use of standardized mortality ratios (SMRs), typically rely upon comparisons of the mortality experience in an exposed population group compared to that in the general population. However, the comparison population may not always be appropriate due to differences in general health status (e.g., the healthy worker effect) and differences in exposure to other risk factors for a specific disease (e.g., smoking history). The lack of comparability between the study population and the comparison population can lead to confounding by other measured or unmeasured characteristics which may be statistically associated with both the exposure of interest and the endpoint. The Cox proportional hazards model controls for such potentially confounding characteristics by using a comparison group from within the study population (i.e., internal controls). Internal controls are a statistically appropriate comparison group because they are expected to be more similar in potentially confounding characteristics to the remainder of the cohort, thereby controlling for both measured and unmeasured confounding and helping ensure that comparisons are more statistically valid.

Results of lung cancer mortality analysis

As described in the previous section, quantitative exposure-response relationships for lung cancer mortality were evaluated using the Cox proportional hazards model. Cox models of this type require the specification of a time scale. Age is typically the time-related variable, with the strongest relationship to cancer mortality, and was used as the timescale in these analyses. Use of age as the time scale in a time-varying Cox proportional hazards model controls for age as a risk factor by design rather than by parametric modeling and effectively rules out age as a potential confounder. Individual covariates available to EPA in the complete analytic dataset compiled from the NIOSH data were evaluated for their ability to explain the lung cancer mortality. These included sex, race, birth year, age at hire, and various exposure-related variables including TWA workplace intensity of exposure in fibers/cc, job type, and the start and stop date of each different job. These data allowed for the computation of cumulative exposure, cumulative exposure with application of a half-life, and residence time-weighted cumulative exposure (with and without application of a half-life). Each exposure metric was also lagged by 0, 10, 15, or 20 years. The use of a lag period aims to account for the latency period between the

onset of lung cancer (which occurs some time before clinical diagnosis) and lung cancer mortality.

All lung cancer mortality analyses were conducted using SAS software version 9.1 (SAS, Cary, NC). There are two forms of the Cox model considered in this evaluation: the standard model, which allows only time-independent covariates, and the extended Cox model, which allows for time-dependent variables. Both forms of the Cox model rely on the assumption that the hazards are proportional.

Standard Cox proportional hazard models assess the risk of exposures at one particular point in time (e.g., death or loss to follow-up). While an individual's exposures may have changed over time, the only exposure value included in the analysis is the value of the exposure metric at the time of the event (i.e., death) or censoring at the end of the mortality follow-up period on December 31, 2006. Since Cox proportional hazard models rely on the assumption that the hazard rate among the exposed is proportional to the hazard rate among the unexposed, it is important to test the model against this assumption. Therefore, analyses of standard Cox models (based on a single summary exposure value for each person) tested this assumption using a Wald test on the model interaction term between the Libby Amphibole asbestos exposure metric and the time scale (i.e., age). As a general rule, a nonzero slope that is either increasing or decreasing indicates a violation of the proportional hazards assumption. Wald tests for the complete cohort showed that the interaction term was a statistically significant predictor of lung cancer mortality ($p < 0.05$) and was interpreted as evidence that the hazards did not remain proportional over time. The cause of the lack of proportionality is unknown, but several likely explanations are discussed in Section 5.4.3.3.

Having observed that the proportional hazards assumption was violated when using the time-independent exposure data, the EPA fit a variation of the extended Cox proportional hazards model (Kleinbaum, 1996; Tableman and Kim, 2004), which included both time-independent factors such as sex, race, and date of birth, as well as time-dependent measures of Libby Amphibole asbestos exposure over the entire time course of each individuals' lifetime from their date of hire until death or loss to follow-up. This method also allows for control of potential confounding by age by design rather than through multivariate covariate modeling.

EPA's analyses of time-dependent exposure data also checked the proportionality assumption for the Libby worker cohort and again found that it failed to remain proportional across the time scale based on age given the modeled covariates. While this methodology of using the extended Cox proportional hazards model does not have as strong a dependence on the assumption of truly proportional hazards (Kleinbaum, 1996; Tableman and Kim, 2004) it is still preferable to have the proportionality assumption hold.

5.4.3.3. *Summary of Analysis of Libby Worker Cohort*

Several possible explanations exist for the finding that duration of employment was the best fitting exposure metric for mesothelioma mortality, as well as the finding of the lack of proportionality of hazards in the lung cancer mortality modeling.

1) Duration of employment, but not job category, was known for 686 of 991 (69%) workers hired from 1935 to 1959. Without knowledge of the job category, the same exposure concentration had been assigned to 653 of these workers, likely resulting in a particularly large measurement error for exposure in approximately one third of the total cohort of 1,871 workers. This is a very likely explanation for the superior fit for duration of employment in modeling of mesothelioma mortality relative to the other exposure metrics based on measured exposures. Assigning the same exposure concentration to so many of the workers hired before 1960, regardless of job, likely resulted in significant exposure misclassification. Random error in exposure measurements generally attenuates the strength of epidemiologic associations between exposure and observed effect, weakening the predictive ability of any of the exposure-based metrics compared to duration of employment, which was more accurately determined for all workers in the cohort.

2) Even where the job category was identified, few exposure data exist prior to 1968. For the majority of job locations (23 of 25), no exposure measurements were available prior to 1967, and so exposures were estimated based on employee interviews (conducted in 1982) to determine what was known about major changes in operations between 1935 and 1967. For two job locations, dust–to--PCM extrapolations are based on measurements taken in the late 1960s, so extrapolating from the mid-1960s to the early 1960s is likely to be more certain than extrapolating further back in time. Random error in these exposure measurements would also generally attenuate the strength of association between exposure and observed effect during the earlier years of mine operation and, thus, a greater degree of measurement error in the earlier years could have resulted in the lack in proportionality of the hazard ratios for lung cancer over time. A greater degree of measurement error in the earlier years could also provide an explanation for the worse fit of the mesothelioma models that incorporated these exposure measures.

3) Another explanation for the lack of proportional hazards in modeling lung cancer mortality may be that this cohort has an anomalous age structure due to the hiring of much older individuals during the time of the Second World War. Among those workers in the cohort hired prior to 1960, 9% were older than 50 years, and 22% were older than 40 years. Among those workers hired in 1960 or afterwards, only 4% were older than 50 years, and 14% were older than 40 years. Older workers differ from younger workers in several potentially important ways that could alter their response to exposures. Older workers were born in a different era, with different nutritional and public health standards which may influence mortality patterns.

4) The lack of proportional hazards in modeling lung cancer mortality may also be a reflection of confounding or effect modification, which can change in magnitude over time. The most likely candidate for confounding or effect modification is smoking. NIOSH records show that of the 1,871 workers in the full Libby workers cohort, 1,121 workers (60%) were missing smoking status data, while 750 (40%) had data with values 'S' (Smoker), 'Q' (Former Smoker), or 'N' (Non-smoker). Given this high percentage of missing values, EPA did not consider these smoking data to be adequate for use in the evaluation of confounding or effect modification.

Smoking rates, over time, among the sub-cohort of workers hired after 1959 are likely to have been more similar since smoking rates change more slowly over shorter periods of time than over longer ones. This restriction in time period of hiring would also result in less variation by birth year cohort, which is strongly related to smoking patterns as people of different generations developed different smoking rates. Thus, this restriction in the time period of hiring may make the cohort members more similar to each other thereby reducing the potential impact of any smoking-related confounding. Further discussion of the relevance of smoking can be found in the section on uncertainties (Section 5.4.6).

When the assumption of proportionality is not met, the potential influence of confounding factors in the full-cohort analysis is of concern. Additionally, the lack of job category information for 69% of the workers hired prior to 1960 and greater measurement error in early exposures may result in significant random exposure measurement error, which may bias the observed exposure-response relationships towards the null.

Although duration of employment was the best exposure metric for modeling mesothelioma mortality in the full cohort, it made quantitatively estimating an exposure-response relationship difficult. In addition, violation of the underlying statistical assumptions adversely impacted modeling of lung cancer mortality in the full cohort. Therefore, EPA chose to undertake a sub-cohort analysis.

In particular, because uncertainty in retrospective assessment of workplace exposures is reduced in the later years, EPA decided to analyze a sub-cohort of all the workers with as late a starting employment date as possible, while still maintaining a sufficient number of lung cancer and, especially, mesothelioma mortalities. The last of the 686 workers with only duration of employment available as an exposure metric was hired in 1959, and so EPA developed a sub-cohort analysis by dividing the total cohort into those hired prior to 1960 (n = 991) and those hired after 1959 (n = 880). This cut point roughly divided the cohort in half. For the sub-cohort of those workers hired after 1959, there were sufficient numbers of both mesothelioma and lung cancer mortalities to apply the Poisson and Cox proportional hazards model, correspondingly. EPA initially examined the fit of these models using several exposure metrics to predict mortality from mesothelioma and found that in this sub-cohort, the exposure metrics that

included information on exposure concentration provided superior statistical fits to the exposure metrics based only on employment duration. In this same sub-cohort, the assumptions of the Cox proportional hazards model were also satisfied for the modeling of time-varying exposure.

While it is generally true that the use of more data is an advantage in statistical analyses because it allows for the computation of more statistically precise effect estimates, this advantage in precision may be offset by a negative impact on the accuracy of the effect estimate if an increase in sample size is accompanied by greater exposure misclassification or other biases. EPA's use of the sub-cohort analysis is based on the belief that it is important to accurately estimate the true underlying exposure-response relationships by relying on the most accurate exposure data (see also Section 5.4.6 on uncertainties).

5.4.3.4. *Analysis of Sub-cohort of Employees Hired After 1959*

5.4.3.4.1. Results of analysis of mesothelioma mortality in the sub-cohort

Of the 880 workers hired after 1959, 230 (26%) had died by December 31, 2006. The number of mesothelioma deaths in the sub-cohort is seven (2 deaths coded in ICD-10 and 5 deaths coded in ICD-9), and the mesothelioma death rate of 24.7 per 100,000 person-years for the sub-cohort is similar to the mesothelioma death rate of 26.8 per 100,000 person-years for the full cohort (18 mesothelioma deaths), with a difference of less than 10%.

Table 5-11 shows the relative fit of various exposure metrics for mesothelioma mortality in the sub-cohort hired after 1959, including only those exposure metrics whose information weight was greater than 0.01. Information weights are computed from the reported DICs (Burnham and Anderson, 2002). As discussed below, metrics with higher DICs and lower information weights are unlikely to provide a good fit and are thus not included in Table 5-11. Information weights are commonly used in Bayesian analyses. Information weights can be computed by first assessing the differences between the best DIC and each of the others (Δ DIC_i)

$$DIC\ w_i = \exp\left(-\frac{1}{2}\Delta\ DIC_i\right) \Big/ \sum_{r=1}^{R} \exp\left(-\frac{1}{2}\Delta\ DIC_i\right) \qquad \text{(Eq. 5-8)}$$

Table 5-11. Comparison of model fit of exposure metrics for mesothelioma mortality in the sub-cohort hired after 1959[a,b]. Only the model fits with information weights greater than 0.010 are shown

Exposure metric	Lag(yr)	DIC	Information Weight
CE with 5yr ½ life	15	70.6	0.428

CE with 5yr ½ life	10	72.8	0.143
CE with 10yr ½ life	10	73.9	0.082
CE with 10yr ½ life	15	74.0	0.078
CE with 10 yr ½ life	0	74.5	0.061
CE with 5 yr ½ life	0	75.0	0.047
CE with 15 yr ½ life	10	75.7	0.033
CE with 15 yr ½ life	0	76.0	0.029
CE with 15 yr ½ life	15	76.1	0.028
CE with 20 yr ½ life	10	76.7	0.020
CE with 20 yr ½ life	0	77.0	0.017
CE with 20 yr ½ life	15	77.2	0.016

[a] Lower DIC values represent better fits.
[b] Since one of mesothelioma deaths occurred in less than 20 years from start of the exposure, lag 20 metrics assigned no exposure to this case and the very poor fit of lag 20 metrics is a result.
DIC = Deviance Information Criterion.

The other exposure metrics that were fit included those metrics used in the full cohort analysis (duration of employment, time since first exposure, age at death or censoring, RTW metrics, CE with lag metrics and IRIS IUR (1988) metric), but all of them fit worse than any of the metrics in Table 5-11, irrespective of possible penalization for extra parameters as discussed in the analysis of the full cohort. The two metrics with cumulative exposure lagged 15 and 10 years, both with 5-year half-life, providing the two best fits as indicated by their lower DIC values and higher information weights (Table 5-11). Cumulative exposures lagged 10 or 15 years, both with 10-year half-life, provided the next two best fits according to DIC values, but models including each of these metrics exhibited noticeably lower information weights than the best metric. All metrics in Table 5-11 contain a decay term and have the same number of parameters in their corresponding model, allowing for a direct comparison of the DIC values (DICs are similar to AICs in what is considered an important difference) and information weights.

It is important to note that the suite of exposure metrics which were applied in this assessment to modeling mesothelioma mortality encompass the range of choices described in the asbestos literature including CE, RTW and decay metrics as well as the IRIS IUR(1988) metric.

In the sub-cohort hired after 1959, the DIC value for mesothelioma using the IRIS IUR (1988) metric (Eq. 5-5) is substantially higher (DIC=98.4) than for any of the metrics in Table 5-11. This indicates that the IRIS IUR (1988) metric does not provide as good a fit for the Libby Amphibole asbestos worker cohort, using the estimated historical exposure levels, as the other metrics in Table 5-11. Setting the exponents in the IRIS IUR (1988) metric to the values of 2 and 4, as suggested by Nicholson et al. (1980), did not improve the fit of the metric to the Libby Amphibole asbestos worker cohort data (results not shown). A substantial difference of this analysis from the IRIS IUR (1988) modeling is that this analysis is based on individual-level data, whereas IRIS IUR (1988) application was to aggregate data. Also, cohorts used in IRIS IUR (1988) did not include cohorts exposed to Libby amphibole asbestos and Libby Amphibole asbestos may be different from other types of asbestos. Alternately, the relative fit of this model may have been affected by uncertainties in the estimated exposure described in detail in Section 5.4.6.

Next, EPA considered which covariates should be added to the model with the exposure metric that provided the best fit. The addition of covariates 'age at death or censoring' and 'time since first exposure' did not improve the fit, as measured by DIC (results not shown).

As described in Section 5.4.1.5, only metrics with non-zero lag were retained for derivation of unit risks. Table 5-12 shows slopes and credible intervals for all retained metrics from Table 5-11. The units of the slopes are fibers/cc-year. These slopes and credible intervals represent calendar year continuous environmental exposure as described above and define the 'Exposed Hazard Rate' in the life-table procedure when multiplied by the exposure level (see Appendix G for details).

Based on the results from the exposure metric with the lowest DIC (cumulative exposure with a 5-year half-life for decay and a 15-year lag for cancer mortality latency), the slope was 2.06×10^{-4} per fiber/cc-year based on a 365-day calendar year and the 95% upper bound on the slope was 3.43×10^{-4} per fiber/cc-year. This point estimate and 95% upper bound represent the relative risk (including statistical uncertainty within the exposure metric) of mesothelioma mortality observed from exposure to Libby Amphibole asbestos fibers in the worker cohort for this exposure metric. Issues related to uncertainty in the choice of exposure metric are described further in the section on the derivation of the combined IUR of mesothelioma and lung cancer (Section 5.4.5.3).

Table 5-12. Mesothelioma mortality exposure metrics fits, slopes, and credible intervals

Exposure metric	Lag years	DIC	Slope $x10^{-5}$	90% CI for slope $x10^{-5}$
CE – 5 yr ½ life	15	70.6	20.6	(10.2, 34.3)
CE – 5 yr ½ life	10	72.8	31.1	(15.2, 50.8)
CE – 10 yr ½ life	10	73.9	9.93	(5.00, 16.3)
CE – 10 yr ½ life	15	74.0	7.78	(3.72, 12.9)
CE – 15 yr ½ life	10	75.7	6.17	(3.04, 10.1)
CE – 15 yr ½ life	15	76.1	5.30	(2.63, 8.69)
CE – 20 yr ½ life	10	76.7	4.71	(2.34, 7.71)
CE – 20 yr ½ life	15	77.2	4.27	(2.12, 6.98)

5.4.3.4.2. Results of the analysis of the lung cancer mortality in the sub-cohort

EPA based its final analyses for lung cancer mortality on the subset of workers hired after 1959. Thus, this analysis is based on 32 deaths from lung cancer[2] (ICD-8: two deaths with the code 162.1; ICD-9: one death with the code 162.2, 20 deaths with the code 162.9; ICD-10: nine deaths with the code C349) out of 230 deaths that occurred in sub-cohort of 880 workers.

All multivariate Cox proportional hazards models with time-varying exposures were initially fit, using one exposure metric at a time, to the sub-cohort hired after 1959 employing, with covariates for sex, race, and date of birth. Lung cancer mortality was modeled using cumulative exposure and residence-time-weighted exposure, where each metric was potentially modified by four different half-lives (5, 10, 15, or 20 years). Each of these exposure metrics was also evaluated with four different lag period to allow for cancer latencies of 0, 10, 15, or 20 years. The lag period is defined as immediately prior to observed cancer death, where exposure is not considered to be causally related to mortality. In all, 40 exposure-response multivariate models were evaluated for the adequacy of the exposure metric to fit the epidemiologic data. Each exposure metric and the comparative model fit statistics are presented in Table 5-13.

The assumptions of the Cox proportional hazards models were re-evaluated for the sub-cohort. Restricting the cohort addressed each of the previously listed potential explanations for

[2] Note that in the full cohort, it was unclear whether there were cases of tracheal cancer included in the definition of lung cancer as many of the recorded ICD codes on death certificates did not provided sufficient detail to distinguish tracheal cancer cases from lung cancer cases. However, among the sub-cohort of workers hired after 1959, all the deaths from the broader category of cancers of the lung, bronchus, and trachea did provide sufficient detail to show that there were no deaths from tracheal cancer.

Table 5-13. Model fit comparison for different exposure metrics and lung cancer mortality associated with Libby Amphibole asbestos, controlling for age, gender, race, and date of birth

Ordered by exposure metric			Ordered by model fit				
Exposure metric	Lag (yr)	AIC	Exposure metric	Lag (yr)	AIC	Multivariate model p-value	Exposure p-value
CE	0	361.610	CE 10yr ½ life	10	358.400	0.0071	0.0009
CE	10	361.073	CE 5yr ½ life	10	358.502	0.0075	0.0010
CE	15	363.124	CE 15yr ½ life	10	358.777	0.0084	0.0015
CE	20	364.964	CE 20yr ½ life	10	359.122	0.0098	0.0022
CE 20yr ½ life	0	361.123	CE 5yr ½ life	15	359.910	0.0138	0.0032
CE 20yr ½ life	10	359.122	CE 10yr ½ life	15	360.543	0.0181	0.0079
CE 20yr ½ life	15	361.533	CE	10	361.073	0.0227	0.0188
CE 20yr ½ life	20	364.703	CE 20yr ½ life	0	361.123	0.0232	0.0155
CE 15yr ½ life	0	361.382	CE 15yr ½ life	15	361.129	0.0232	0.0162
CE 15yr ½ life	10	358.777	CE 15yr ½ life	0	361.382	0.0258	0.0184
CE 15yr ½ life	15	361.129	CE 20yr ½ life	15	361.533	0.0276	0.0254
CE 15yr ½ life	20	364.588	RTW 5yr ½ life	0	361.593	0.0283	0.0309
CE 10yr ½ life	0	362.169	CE	0	361.610	0.0285	0.0307
CE 10yr ½ life	10	358.400	CE 10yr ½ life	0	362.169	0.0360	0.0358
CE 10yr ½ life	15	360.543	RTW 10yr ½ life	0	362.283	0.0378	0.0588
CE 10yr ½ life	20	364.342	RTW 15yr ½ life	0	362.714	0.0452	0.0863
CE 5yr ½ life	0	364.225	RTW 20yr ½ life	0	362.973	0.0503	0.1084
CE 5yr ½ life	10	358.502	CE	15	363.124	0.0535	0.1215
CE 5yr ½ life	15	359.910	RTW 5yr ½ life	10	363.224	0.0558	0.1343
CE 5yr ½ life	20	363.644	CE 5yr ½ life	20	363.644	0.0662	0.1751
RTW	0	363.869	RTW	0	363.869	0.0726	0.2397
RTW	10	364.835	RTW 10yr ½ life	10	364.041	0.0778	0.2810
RTW	15	364.990	CE 5yr ½ life	0	364.225	0.0838	0.2908
RTW	20	364.502	RTW 15yr ½ life	10	364.336	0.0876	0.3733
RTW 20yr ½ life	0	362.973	CE 10yr ½ life	20	364.342	0.0878	0.3661
RTW 20yr ½ life	10	364.477	RTW 20yr ½ life	10	364.477	0.0927	0.4314
RTW 20yr ½ life	15	365.011	RTW	20	364.502	0.0936	0.5307
RTW 20yr ½ life	20	364.628	CE 15yr ½ life	20	364.588	0.0969	0.4815
RTW 15yr ½ life	0	362.714	RTW 20yr ½ life	20	364.628	0.0985	0.5763

Table 5-13. Model fit comparison for different exposure metrics and lung cancer mortality associated with Libby Amphibole asbestos, controlling for age, gender, race, and date of birth (continued)

Ordered by exposure metric			Ordered by model fit				
Exposure metric	Lag (yr)	AIC	Exposure metric	Lag (yr)	AIC	Multivariate model p-value	Exposure p-value
RTW 15yr ½ life	10	364.336	RTW 15yr ½ life	20	364.662	0.0998	0.5909
RTW 15yr ½ life	15	365.001	CE 20yr ½ life	20	364.703	0.1014	0.5530
RTW 15yr ½ life	20	364.662	RTW 10yr ½ life	20	364.719	0.1021	0.6188
RTW 10yr ½ life	0	362.283	RTW 5yr ½ life	15	364.768	0.1041	0.6021
RTW 10yr ½ life	10	364.041	RTW 5yr ½ life	20	364.831	0.1067	0.6884
RTW 10yr ½ life	15	364.962	RTW	10	364.835	0.1069	0.6586
RTW 10yr ½ life	20	364.719	RTW 10yr ½ life	15	364.962	0.1124	0.8173
RTW 5yr ½ life	0	361.593	CE	20	364.964	0.1125	0.8204
RTW 5yr ½ life	10	363.224	RTW	15	364.990	0.1136	0.8809
RTW 5yr ½ life	15	364.768	RTW 15yr ½ life	15	365.001	0.1141	0.9100
RTW 5yr ½ life	20	364.831	RTW 20yr ½ 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. AIC: Akaike Information Criterion.

the lack of hazard proportionality (see Section 5.4.3.3). First, measurement error for exposures is likely to have been smaller after 1959 for several reasons. One reason is that the 686 workers for which job category information was missing during part or all of their employment were removed from the analysis. Also, beginning in 1968, fiber concentrations by PCM analysis of site-specific air samples were available for all location operations to inform the JEM. Prior to 1968, the exposure intensity for 23 of 25 location operations was estimated based on reasoned assumptions informed by employee interviews in the early 1980s. It is likely the uncertainty of these reasoned assumptions increased over time, making the earliest exposure estimates (1940s and 1950) less certain than those only a few years before fiber count data were available. Finally, between 1956 and 1967, dust-to-PCM extrapolation data were used to estimate exposures in the dry mill based on measurements taken in the late 1960s. Although there is some uncertainty in the conversion ratio selected by Amandus and coworkers (1987a), conversions from dust to fiber counts is likely to be less uncertain than extrapolations further backwards in time to the 1950s and 1940s, where only one air sample for dust was available in 1944. Thus,

the potential attenuation effect of non-differential measurement error is likely to be reduced by examining the post-1959 cohort alone compared to the entire cohort.

In addition, by focusing on the more homogeneous age distribution of workers hired after 1959, concerns about differential cancer mortality latency were diminished. Third, smoking rates among this more narrowly defined sub-cohort are likely to have been more homogeneous, and thus, restricting analysis to this sub-cohort would help to limit any potential confounding due to smoking. Finally, when the extended Cox proportional hazards model was applied to the sub-cohort hired post-1959, there was no evidence to reject the hypothesis of proportionality, and the exposure models demonstrated adequate fits to the data, with statistically significant effect estimates. In each of the Cox proportional hazards model analyses with time-varying exposures—across all the exposure metrics and across all the lag lengths—no violations of the assumption of proportionality of hazards were found.

As the exposure-response models cannot strictly be considered to be nested, a standard measure of fit called the Akaike Information Criterion (AIC [Burnham and Anderson, 2002]) was used for comparison of goodness of fit across models based on the same data set. In their text on model selection, Claeskens and Hjort (2008) state that 'for selecting a model among a list of candidates, Akaike's information criterion (AIC) is among the most popular and versatile strategies.' Smaller AIC values generally indicate a better fitting model relative to larger AIC values. While large differences in AIC values can reveal important differences in model fit, small differences are less conclusive. Nonetheless the model yielding the smallest AIC 'is judged the best one' (Claeskens and Hjort, 2008) and it is a common practice in environmental epidemiology to select the single model with the best statistical fit among the models that were evaluated. However, models differing in AIC by 2 units or less may not always be meaningfully differentiated from each other on the basis of AIC (Burnham and Anderson, 2002).

Table 5-13 shows the models and exposure metrics ordered by fit. Of interest is whether there are models with distinct exposure metrics that adequately fit these data (as measured by statistical significance of the model p-value) and then, a measure of relative weight among these adequately fitting models. Of the 40 exposure-response metrics, 14 demonstrated an adequate fit to the data as measured by the overall model fit, with the likelihood ratio test being statistically significant ($p < 0.05$), as well as having statistically significant exposure metrics ($p < 0.05$). However, note that only the nine models that demonstrated adequate model and exposure metric fit and incorporated a lag period to account for lung cancer mortality latency were advanced for potential use in developing a unit risk. While metrics that did not include an adjustment for lag on the exposure metric to account for cancer mortality latency were fit to these data for the sake of completeness, they were dropped from further consideration because they implicitly assume

no passage of time between the initiation of cancer, subsequent promotion of that cancer, and mortality.

Several general patterns were discernable with respect to which exposure metrics best predicted lung cancer mortality when comparing AICs for relative model fit. The data show that lagging exposure by 10 years best predicts lung cancer mortality compared to other lags. This trend is seen across both the cumulative exposure without decay and the various half-life cumulative exposure metrics where a 10-year lag of exposure best predicts lung cancer mortality for all cumulative exposure metrics compared to other lags; metrics with 15-year lags were generally the next best in terms of fit. Another clear conclusion is that the models that included residence time-weighted exposure metrics, regardless of half-life or lag, were less suitable than the models that employed cumulative exposure and its variants.

Among the 40 exposure metric models that were evaluated, the exposure model with the lowest AIC value was for cumulative exposure with a 10-year half-life for decay and a 10-year lag for cancer mortality latency and had a model p-value of 0.0071 (Table 5-13). This multivariate model controlled for age, gender, race, and date of birth. The extended Cox model with time-varying exposures estimated a slope (beta) of 1.26×10^{-2} per fiber/cc-year based on a 365-day calendar year[3] and the 95th percentile upper bound on this parameter was 1.88×10^{-2} per fiber/cc-year. The p-value for the Libby Amphibole asbestos regression coefficient (slope) was <0.001 indicating that this parameter was statistically significantly greater than zero.

According to the model results presented in Table 5-13, there were other exposure metrics that predicted lung cancer mortality and exhibited statistically significant effect estimates. Several other metrics were considered to fit nearly as well as the model with the smallest AIC since their AIC values were within two units of the exposure model with the lowest AIC, a proximity that can be considered to be a range that cannot clearly differentiate between models (Burnham and Anderson, 2002). As each of the other exposure metrics was based on a different reorganization of the same exposure data, the different slopes are not directly comparable, but all adequately fitting lagged models also produce statistically significant slopes for the exposure-response relationship ($p < 0.05$). Of particular note are the results of the cumulative exposure model, with a 10-year lag for latency, but without a decay function, since it showed the lowest AIC among non-decay models.

The AIC values for models that included lag and/or half-life adjustments to the exposure metrics were not penalized in the regression analyses for using these extra parameters because these factors were not represented as covariates but rather were embedded in the computation.

[3] The two-sided 90% confidence interval is (6.00×10^{-3}, 1.88×10^{-2}); the two-sided 95% confidence interval is (5.12×10^{-3}, 2.00×10^{-2}).

While these results were obtained using each instance of lag and/or half-life terms in separate model fit, it may be appropriate to mathematically penalize the AICs for inclusion of these additional parameters. AIC values, as typically computed by regression software, include the addition of a penalty for model complexity as measured by the number of parameters that are fit in the regression model (thereby increasing the AIC). In the AIC calculations presented in Table 5-13 the models are treated as having the same number of parameters since each model represents the same exposures in a different way but with a single exposure parameter in the regression models and are, therefore, equally penalized in software's AIC calculation. However, an argument can be made that exposure metrics, which do not include a decay function with their half-life term, are implicitly more parsimonious (simpler) because they do not include decay. Statistical adjustment for this type of model complexity is not straightforward, as an exposure metric without decay can also be thought of as an exposure metric with a sufficiently long decay (since human life is finite). In this sense, if the models without decay are indistinguishable from models with a sufficiently long half-life, then there is no difference in the inherent complexity. If the decay model fits were penalized for the inclusion of the decay function in the computation of the exposure metric then with such an adjustment, the relative fit of the CE models would improve as compared to the values in Table 5-13 (AICs are generally penalized 2 units for each additional parameter). However, the difference between the lowest AIC and the AIC of the CE model without decay exceeds any reasonable penalty, and thus the model results for cumulative exposure with a 10-year half-life for decay and a 10-year lag for cancer mortality latency would still have the lowest AIC regardless of whether a penalty was applied.

Table 5-14 displays the lagged exposure-response models and metrics with adequate model fit ($p < 0.05$) to the epidemiologic data that were further considered. Table 5-14 shows slopes and confidence intervals for all retained metrics from Table 5-13. The units of the slopes are fibers/cc-year. These slopes and confidence intervals represent calendar year continuous environmental exposure as described above and define the 'Exposed Hazard Rate' in the life-table procedure when multiplied by the exposure level (see Appendix G for details).

5.4.3.4.3. Summary of results of the analysis of the lung cancer mortality in the sub-cohort

As presented in Table 5-14 the CE model with 10 year half-life and lag provided an adequate fit to the data ($p < 0.05$) and had the lowest AIC value. The cumulative exposure model with a 10-year lag also yielded a statistically adequate fit to these data ($p < 0.05$), as did several decay models with a 15-year lag. These results demonstrate reasonable uncertainty in the metric of exposure such that no single exposure model can be definitively selected based on

goodness of fit alone. Uncertainty in the metric of exposure is addressed in Section 5.4.5.3 as IUR is based on the plausible upper bound of the effect estimate. Based on the results from the

Table 5-14. Lung cancer mortality exposure metrics fits, slopes, and confidence intervals

Exposure metric	Lag years	AIC	Slope (Beta)	SE	Exposure p-value	90% CI for the slope
CE 10yr ½ life	10	358.400	0.0126	0.0038	0.0009	(0.0063, 0.0189)
CE 5yr ½ life	10	358.502	0.0179	0.0055	0.0010	(0.0089, 0.0269)
CE 15yr ½ life	10	358.777	0.0106	0.0033	0.0015	(0.0052, 0.0160)
CE 20yr ½ life	10	359.122	0.0095	0.0031	0.0022	(0.0044, 0.0146)
CE 5yr ½ life	15	359.910	0.0155	0.0052	0.0032	(0.0069, 0.0241)
CE 10yr ½ life	15	360.543	0.0115	0.0043	0.0079	(0.0044, 0.0186)
CE	10	361.073	0.0058	0.0025	0.0188	(0.0017, 0.0099)
CE 15yr ½ life	15	361.129	0.0097	0.0040	0.0162	(0.0031, 0.0163)
CE 20yr ½ life	15	361.533	0.0087	0.0039	0.0254	(0.0023, 0.0151)

lowest AIC multivariate model (i.e., cumulative exposure with a 10-year half-life for decay and a 10-year lag for cancer mortality latency), the slope was 1.26×10^{-2} per fiber/cc-year based on a 365-day calendar year and the 95% upper bound on the slope was 1.88×10^{-2} per fiber/cc-year. This point estimate and 95% upper bound represent the relative risk (including statistical uncertainty within exposure metric) of lung cancer mortality observed from exposure to Libby Amphibole asbestos fibers in the worker cohort for this exposure metric. Issues related to uncertainty in the choice of exposure metric are described further in the section on the derivation of the combined IUR of mesothelioma and lung cancer (Section 5.4.5.3).

5.4.3.4.4. Sensitivity analysis of the influence of high exposures in early 1960s on the model fit

As discussed in Section 5.4.2.5, the comparison of model fit between various exposure metrics is an empirical process and does not reflect either a specific biological or other factor as an underlying cause for model fit. Although data do not exist to evaluate biological bases for model fit, other potential factors can be explored where data allow. For example, because of concerns that very high (>100 fibers/cc) early (1960-1963) 8-hour time-Libby Amphibole asbestos TWA exposures may have influenced the relative fit of the various exposure metrics, EPA conducted a sensitivity analysis of the impact of removing the 59 workers with such

exposures on the relative model fit. It is important to note that excluding these workers left only 5 mesothelioma deaths and 28 lung cancer deaths among 821 workers. The follow-up time for the 880 member sub-cohort was 28,354 person-years (mean 32.2), while excluding the 59 highly exposed workers resulted in 26,009 person-years (mean 31.7). The reduction in cancer-specific deaths and the abbreviation in the range of exposures leads to a diminished ability to differentiate the relative fit (i.e. smaller AIC/DIC differences) between the various exposure metrics due to reduced statistical power.

For modeling mesothelioma mortality, the absolute and relative differences in fit diminished with the exclusion of these highly exposed workers, but the observation that exposure metrics including decay fit better than exposure metrics without decay was unchanged. Moreover, the relative fit of the metrics remained almost unchanged (Table 5-15). Among this abbreviated data set, the relative fit of the best of cumulative exposure metrics including decay was at least three units lower DIC than the best of cumulative exposure metrics not involving decay (Table 5-15). Abbreviated dataset DIC for model used in IRIS IUR (1988) was 69.4.

Table 5-15. Relative fit of mesothelioma exposure metrics for full and abbreviated data sets. Only the best of non-decay metrics is shown. DIC cannot be compared across columns as they are based on different numbers of observations.

Exposure metric	Half-life	Lag	All workers higher after 1959 (n = 880); based on 7 mesothelioma deaths DIC (As shown in Table 5-11)	Excluding highly exposed workers (n = 821); based on 5 mesothelioma deaths DIC
CE	5	15	70.6	56.5
CE	5	10	72.8	57
CE	10	10	73.9	57
CE	10	15	74	57.3
CE	15	10	75.7	57.7
CE	15	15	76.1	58.3
CE	20	10	76.7	58.1
CE	20	15	77.2	58.2
CE		10	80.8	59.7

For modeling lung cancer mortality, among this abbreviated data set, based on AIC comparisons, there was no clear distinction between the fit of the same exposure models that fit the sub-cohort of workers hired after 1959 and included highly exposed workers during 1960-1963 (Table 5-16).

Table 5-16. Sensitivity analysis of model fit comparison for different exposure metrics and lung cancer mortality associated with Libby Amphibole Asbestos controlling for age, gender, race, and date of birth.
Excludes n = 59 workers who had job codes with exposure intensity greater than 100 f/cc during 1960-63. Lung cancer models presented include those with statistically significant multivariate model p-value and non-zero lag in exposure. AIC cannot be compared across columns as they are based on different numbers of observations

		All workers higher after 1959 (n = 880) Based on 32 deaths from lung cancer (As shown in Table 5-13)			Excluding highly exposed workers (n = 821) Based on 28 deaths from lung cancer		
Exposure Metric	**Lag (yr)**	**AIC**	**Multi-variate Model p-value**	**Exposure p-value**	**AIC**	**Multi-variate Model p-value**	**Exposure p-value**
CE 10yr ½ life	10	358.400	0.0071	0.0009	313.236	0.1697	0.4007
CE 5yr ½ life	10	358.502	0.0075	0.0010	313.684	0.2010	0.6996
CE 15yr ½ life	10	358.777	0.0084	0.0015	313.047	0.1578	0.3293
CE 20yr ½ life	10	359.122	0.0098	0.0022	312.975	0.1535	0.3045
CE 5yr ½ life	15	359.910	0.0138	0.0032	312.378	0.1217	0.1694
CE 10yr ½ life	15	360.543	0.0181	0.0079	311.660	0.1049	0.1141
CE	10	361.073	0.0227	0.0188	312.994	0.1546	0.2909
CE 15yr ½ life	15	361.129	0.0232	0.0162	312.044	0.1067	0.1113
CE 20yr ½ life	15	361.533	0.0276	0.0254	312.125	0.1102	0.1157

CE: Cumulative Exposure with or without exponential decay modeled with different ½ lives.
AIC: Akaike Information Criterion.

5.4.3.4.5. Additional analysis of the potential for confounding of lung cancer results by smoking in the sub-cohort of workers hired after 1959

In the full cohort analysis, the proportional hazard assumption was not found to hold and it was possible that one of the reasons for this failure was the presence of confounding by

smoking which altered the proportionality of the hazard rate in the exposed workers compared to the baseline hazard rate over time. By restricting the dates of hire in the sub-cohort, those workers in the sub-cohort may be made more similar to each other in ways that would reduce the potential for confounding by smoking and, in this sub-cohort, the proportional hazards assumption was found to hold thus reducing concern regarding confounding by smoking.

As an additional check on the potential for confounding, a new method was evaluated to test for confounding by smoking in occupational cohorts which do not have data on smoking. Confounding, which can bias observed results when there is an uncontrolled variable which is correlated with both explanatory variable and outcome variable, is a distinct concept from effect measure modification (i.e. synergy) which might reflect different observed effects of exposure to Libby amphibole asbestos among smokers as compared to non-smokers. The extent of effect measure modification cannot be assessed without adequate data on smoking; however, the issue is discussed in Section 5.4.6.

A method has been described by Richardson (2010) to determine if an identified exposure relationship with lung cancer is confounded by unmeasured smoking in an occupational cohort study. Richardson (2010) demonstrated that an exposure of interest (i.e., Libby Amphibole asbestos) can be used to predict an outcome other than lung cancer such as chronic obstructive pulmonary disease (COPD), which is known to be caused by smoking, but not thought to be related to the exposure of concern.[4] If a positive relationship is identified where no causal association is suspected, this would suggest that smoking and the exposure metric (Libby Amphibole asbestos) were positively correlated and that the identified exposure-response relationship was, in fact, confounded by smoking. EPA implemented this methodology to model the potential effects of Libby Amphibole asbestos on the risk of COPD mortality on the sub-cohort of workers hired after 1959. Using the exposure metric defined as cumulative exposure with a 10-year lag, the extended Cox model with time-varying exposures estimated a slope (beta) for COPD of -0.056 per fiber/cc-year based on a 365-day calendar year. The p-value for the coefficient (slope) was 0.102 indicating that this parameter was not statistically significantly different from zero. Using the exposure metric defined as cumulative exposure with a 10-year half-life for decay and a 10-year lag for cancer latency, the extended Cox model with time-varying exposures estimated a slope (beta) of -0.135 per fiber/cc-year based on a 365-day calendar year. The p-value for the coefficient (slope) was 0.116 indicating that this parameter was not statistically significantly different from zero.

[4] Richardson (2010) cited articles by Rushton (2007a, b) with possible associations between asbestos and COPD which, if true, would have explained a positive association among the Libby workers cohort but should not detract from the use of the Richardson method as applied to these Libby workers, where negative association is found.

Summarizing these findings, EPA used the method described by Richardson (2010) to evaluate whether exposures to Libby Amphibole asbestos predicted mortality from COPD as an indication of potential confounding by smoking and found a non-significant negative relationship, which was inconsistent with confounding by smoking in the sub-cohort of workers hired after 1959.

5.4.4. Exposure Adjustments and Extrapolation Methods

The estimated exposures based on job exposure matrix and work histories are discussed in Section 5.4.2.5. Note that all slopes presented with units of fibers/cc-years are for calendar year and not for occupational year.

5.4.5. Inhalation Unit Risk (IUR) of Cancer Mortality

The derivation of the unit risk estimates, defined as the lifetime risk of mortality from either mesothelioma or lung cancer from chronic inhalation of Libby Amphibole asbestos at a concentration of 1 fiber/cc of air, is presented in the following subsections. Note that all slopes are presented as per fiber/cc-year for a 365-day calendar year rather than for an occupational year. Also, note that while the slopes are not adjusted for differences in breathing rates and the number of hours of exposure in an occupational (eight-hour) day as compared to a whole (24-hour) day, the central risk and unit risk estimates do incorporate this adjustment.

5.4.5.1. *Unit Risk Estimates for Mesothelioma Mortality*

The increased risk of mesothelioma mortality attributable to continuous fiber exposure was estimated using a life-table procedure based on the general U.S. population. The life-table procedure involved the application of the estimated Libby Amphibole asbestos-specific toxicity to a structured representation of the general U.S. population in such a manner as to yield age-specific risk estimates for mesothelioma mortality in the absence of exposure to Libby Amphibole asbestos and in the presence of exposure to Libby Amphibole asbestos. Baseline all-cause mortality rates were included in the life-table in such a way as to enable computation of the specific absolute risk of mesothelioma mortality while accounting for other competing causes of mortality (Appendix G). For each age-interval in the life-table, the effect estimates of the Poisson model analysis (the absolute risk) was used to estimate mesothelioma mortality at a particular exposure level. These age-specific absolute risks can then be summed over a lifetime. Different exposure levels are evaluated to ascertain what magnitude of exposure would be expected to produce 1% absolute risk of mesothelioma mortality. By this method, the exposure-response relationship determined in the Libby worker cohort is used to estimate

mesothelioma mortality in the general U.S. population that would be expected from continuous lifetime environmental exposure to various concentrations of Libby Amphibole asbestos. Details of this life-table methodology are shown in Appendix G.

Assuming no background risk for mesothelioma, extra risk is the same as absolute risk. Absolute risk estimates were calculated using the effect estimates derived from the modeling of the mesothelioma mortality risk and a life-table analysis program that accounts for competing causes of death.[5] The unit risk of mesothelioma is computed using the 95% upper bound to estimate an upper bound for extra risk of mesothelioma due to Libby Amphibole asbestos exposure. The upper bound calculation is specific to the exposure metric parameters; the effect of metric uncertainty in these values is discussed below in Section 5.4.5.3. As this human health assessment derived a combined IUR for both mesothelioma and lung cancer mortality, an interim value based on the central effect estimate (rather than the upper bound) is also computed to avoid statistical concerns regarding the combination of upper bounds. Details are shown in Section 5.4.5.3. This assessment does not directly apply life-table calculations to estimate partial lifetime risk scenarios; the use of the IUR for partial lifetime extrapolations is discussed in Section 5.4.5.4.

U.S. age-specific all-cause mortality rates from the 2010 *National Vital Statistics Report* for deaths in 2007 among all race and gender groups combined (NCHS, 2010) were used to specify the all-cause background mortality rates (R_o) in the life-table analysis. The risk with exposure (R_x) was computed up to age 85 years,[6] assuming continuous environmental exposure to Libby Amphibole asbestos. Conversions between occupational Libby Amphibole asbestos exposures and continuous environmental asbestos exposures were made to account only for differences in the amount of air inhaled per day during a higher effort occupational shift (8 hours; 10 m^3) compared to a standard 24-hour (20 m^3) day (U.S. EPA, 1994), as results were already based on a 365-day calendar year. The computation of the unit risk involved three steps. As the estimated absolute risk of mesothelioma mortality was based on the exposure experiences of an occupational cohort and most directly applicable to adult exposures, the first step was to compute the unit risk for adults. This was achieved by initiating exposure at age 16 years and maintaining continuous exposure throughout the remainder of life while allowing for the

[5] This program is an adaptation of the approach previously used by the Committee on the Biological Effects of Ionizing Radiation (BEIR, 1988). Compared to life-table methods based on full life exposures from birth, the method used here yielded unit risk differences between full life exposure to scaled adult-only exposure between -3% to -2% for the mesothelioma mortality unit risks for the two mesothelioma models in Appendix G. A spreadsheet containing the extra risk calculation for the derivation of the LEC_{01} for mesothelioma mortality is presented in Appendix G.

[6] Note that 85 years is not employed here as an average lifespan but, rather, as a cut-off point for the life-table analysis, which uses actual age-specific mortality rates.

incremental mathematical decay of previously accumulated exposure.[7] An adjustment was also made in the life-table for the lag period, so that the age-specific risk calculations began at 16 + (the length of the lag period) years of age. The standard assumption used by EPA is that the average lifetime spans 70 years. Since the adult-only unit risk excluded the first 16 years, the adult-only unit risk based on 54 years was then rescaled for an entire life of continuous exposure by multiplying the interim value for adult-only exposures by 70/54 to cover the childhood years (<16 years) to compute the "adult-based" unit risk. After re-scaling, the resulting "adult-based" lifetime unit risk estimate (in contrast to the unscaled "adult-only-exposure" unit risk estimate obtained from the life-table calculations) may be prorated for less-than-lifetime exposure scenarios in the same manner as would be used for an "adult-based" unit risk estimate derived from a rodent bioassay (Section 5.4.5.4).

Consistent with the *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a), the same data and methodology were also used to estimate the exposure level (EC_x; "effective concentration") and the associated 95% lower confidence limit of that exposure level (LEC_x) corresponding to an absolute risk of 1% (x = 0.01). A 1%-risk level is commonly used for the determination of the point of departure (POD) for low-dose extrapolation from epidemiological data, and the LEC value corresponding to that risk level was used as the actual POD.

The modeling analysis presented above showed that metrics including lag and half-life parameters provided the best empirical fit to the Libby worker sub-cohort data. Although there is uncertainty in applying these models for occupational mortality to estimation of risks for different exposure levels and time patterns (Section 5.4.6), following the recommendations of the *Guidelines for Carcinogen Risk Assessment,* (U.S. EPA, 2005a), a linear low-dose extrapolation below the POD was used because the mode of action for Libby Amphibole asbestos for mesothelioma is largely unknown. Using the results of the cumulative exposure model with best-fitting lag and decay parameters, the LEC_{01} for the adult-only exposures was determined to be 0.245 fibers/cc, which yielded an adult-based unit risk of mesothelioma mortality of 0.041 (POD of 1% divided by the LEC_{01}), which when scaled by 70/54 to encompass the whole lifespan, yielded a lifetime unit risk of 0.053 per fiber/cc. The value of the risk corresponding to the measure of central tendency involves EC_{01} rather than LEC_{01}. The EC_{01} for the adult-only exposures was determined to be 0.406 per fiber/cc, which when divided into a POD of 1% yielded an adult-based central estimate for mesothelioma mortality of 0.025, which when scaled by 70/54 to encompass the whole lifespan, yielded a lifetime central estimate of 0.032 per fiber/cc.

[7] Exposures in the life tables were computed at the mid-point of each age interval and appropriately lagged.

The mesothelioma unit risks for model results presented in Table 5-12 and discussed in Section 5.4.3.4.1, are presented in Table 5-17. All of the metrics in Table 5-17 are cumulative exposure (CE) metrics lagged 10-15 years (the fit of 20-year lag models was much worse since one of seven mesothelioma deaths occurred before 20 years; lags longer than 15 years are possible, and this is an uncertainty described in Section 5.4.6). Issues related to uncertainty in the choice of exposure metric are described further in the section on the derivation of the combined IUR of mesothelioma and lung cancer (Section 5.4.5.3).

Table 5-217. Mesothelioma mortality exposure metrics unit risks

Exposure metric	Lag years	DIC	Information weight	Central risk Estimate	Unit risk
CE - 5yr ½ life	15	70.6	0.428	0.032	0.053
CE - 5yr ½ life	10	72.8	0.143	0.054	0.088
CE - 10yr ½ life	10	73.9	0.082	0.028	0.047
CE - 10yr ½ life	15	74.0	0.078	0.020	0.032
CE - 15yr ½ life	10	75.7	0.033	0.022	0.036
CE - 15yr ½ life	15	76.1	0.028	0.017	0.027
CE - 20yr ½ life	10	76.7	0.020	0.020	0.032
CE - 20yr ½ life	15	77.2	0.016	0.015	0.025

5.4.5.1.1 Adjustment for mesothelioma underascertainment

For mesothelioma, the undercounting of cases (underascertainment) is a particular concern given the limitations of the ICD classification systems used prior to 1999. In practical terms, this means that some true occurrences of mortality due to mesothelioma are missed on death certificates and in almost all administrative databases such as the National Death Index. Even after introduction of special ICD code for mesothelioma with introduction of ICD-10 in 1999, detection rates are still imperfect (Pinhiero et al., 2004; Camidge et al., 2006) and the reported numbers of cases typically reflect an undercount of the true number. Kopylev et al. (2011) reviewed the literature on this underascertainment and developed methods to account for the likely numbers of undocumented mesothelioma deaths.

Because the analysis of mesothelioma mortality was based on absolute risk, it was possible to compensate for mesothelioma underascertainment in Libby worker cohort. The mesothelioma mortality unit risk was adjusted, following the analysis of Kopylev et al. (2011).

With the adjustment factor of 1.39 (see Table 3 in Kopylev et al., 2011), the adjusted mesothelioma central risk (based on the EC_{01}), corresponding to the best-fit metric, was 0.044 per fiber/cc, and adjusted mesothelioma mortality unit risk was 0.074 per fiber/cc. This adjustment factor can be used because the number of peritoneal mesotheliomas is partly known and, therefore, the approach following Selikoff and Seidman (1992) provides the most appropriate estimate of the number of mesothelioma mortality cases.

Mesothelioma mortality-adjusted unit risks are listed in Table 5-18 along with their information weights.

Table 5-18. Adjusted for underascertainment unit risks for the sub-cohort hired after 1959 corresponding to the different metrics

Exposure metric	Lag years	Information weight	Adjusted central risk estimate	Adjusted unit risk
CE - 5yr ½ life	15	0.428	0.044	0.074
CE - 5yr ½ life	10	0.143	0.075	0.122
CE - 10yr ½ life	10	0.082	0.039	0.065
CE - 10yr ½ life	15	0.078	0.028	0.044
CE - 15yr ½ life	10	0.033	0.031	0.050
CE - 15yr ½ life	15	0.028	0.024	0.038
CE - 20yr ½ life	10	0.020	0.028	0.044
CE - 20yr ½ life	15	0.016	0.022	0.035

5.4.5.2. *Unit Risk Estimates for Lung Cancer Mortality*

As with mesothelioma mortality, the increased risk of lung cancer mortality attributable to continuous fiber exposure was estimated using a life-table procedure based on the general U.S. population. The life-table procedure involved the application of the estimated Libby Amphibole asbestos-specific toxicity to a structured representation of the general U.S. population in such a manner as to yield age-specific risk estimated for lung cancer mortality in the absence of exposure to Libby Amphibole asbestos and in the presence of exposure to Libby Amphibole asbestos. Baseline all-cause mortality and lung cancer-specific mortality rates were included in the life-table in such a way as to enable computation of the specific extra risk of lung cancer mortality while accounting for other competing causes of mortality (Appendix G). For each age-interval in the life-table, the effect estimates of the Cox proportional hazards model analysis

(the relative risk) were used to estimate extra lung cancer mortality at a particular exposure level, given the background risk. These age-specific extra risks can then be summed over a lifetime. Different exposure levels are evaluated to ascertain what magnitude of exposure would be expected to produce 1% extra risk of lung cancer mortality. By this method, the exposure-response relationship estimated in the worker cohort is used to estimate lung cancer mortality in the general U.S. population that would be expected from continuous lifetime environmental exposure to various concentrations of Libby Amphibole asbestos under the assumption of a 10-year latency for cancer mortality and a 10-year half-life decay of the exposure metric. Details of the life-table methodology are shown in Appendix G.

Extra risk is defined as equaling $(R_x-R_o)/(1-R_o)$, where, R_x is the lifetime lung cancer mortality risk in the exposed population and R_o is the lifetime lung cancer mortality risk in an unexposed population (i.e., the background risk). Extra risk estimates were calculated using the effect estimates derived from the multivariate modeling of the lung cancer mortality risk and a life-table analysis program that accounts for competing causes of death.[8] The unit risk of lung cancer mortality is computed using the 95% upper bound to estimate an upper bound for extra risk of lung cancer mortality due to Libby Amphibole asbestos exposure. As this human health assessment derived a combined IUR of mesothelioma and lung cancer mortality, an interim value based on the central effect estimate (rather than the upper bound) is also computed to avoid statistical concerns regarding the combination of upper bounds. Details are shown in Section 5.4.5.3.

U.S. age-specific all-cause mortality rates from the 2010 National Vital Statistics Report NVSR 58(19) 2010 for deaths in 2007 among all race and gender groups combined (NCHS, 2010) were used to specify the all-cause background mortality rates (R_o) in the life-table analysis. Cause-specific background mortality rates for cancers of the lung, trachea, and bronchus were obtained from a Surveillance, Epidemiology, and End Results (SEER) report on mortality during 2003-2007 (SEER Table 15.10, age-specific U.S. death rates).

The risk with exposure (R_x) was computed up to age 85 years[9] assuming continuous environmental exposure to Libby Amphibole asbestos using the life-table analysis (see Tables G-3 and G-4 in Appendix G for details). Conversions between occupational exposures

[8] This program is an adaptation of the approach previously used by the Committee on the Biological Effects of Ionizing Radiation (BEIR, 1988). Compared to life table methods based on full life exposures from birth, the method used here yielded unit risk differences between full life exposure to adult-only exposure between -18% to +6% for the lung cancer mortality unit risks for the two lung cancer models in Appendix G. A spreadsheet illustrating the extra risk calculation for the derivation of the LEC01 for lung cancer mortality is presented in Appendix G.

[9] Rates above age 85 years are not included because cause-specific disease rates are less stable for those ages. Note that 85 years is not employed here as an average lifespan but, rather, as a cut-off point for the life-table analysis, which uses actual age-specific all cause and cause-specific mortality rates.

and continuous environmental exposures to Libby Amphibole asbestos were made to account only for differences in the amount of air inhaled per day during a higher effort occupational shift (8 hours; 10 m^3) compared to a standard 24-hour (20-m^3) day (U.S. EPA, 1994), as results were already based on a 365-day calendar year. The computation of the unit risk involved three steps. As the estimated RR of lung cancer mortality was based on the exposure experiences of an occupational cohort and most directly applicable to adult exposures, the first step was to compute the unit risk for adults. This was achieved by initiating exposure at age 16 years and maintaining continuous exposure throughout the remainder of life while allowing for the incremental mathematical decay of previously accumulated exposure depending on the particular exposure metric.[10] An adjustment was also made in the life-table for the lag period, so that the age-specific risk calculations began at (16 + lag) years of age. The standard assumption used by EPA is that the average lifetime spans 70 years. Since the "adult-only-exposure" unit risk excluded the first 16 years, the "adult-only-exposure" unit risk based on 54 years was then rescaled for an entire life of continuous exposure by multiplying the interim value for adult-only exposures by 70/54 to cover the childhood years (<16 years) to compute the "adult-based" unit risk. After re-scaling, the resulting "adult-based" lifetime unit risk estimate (in contrast to the unscaled "adult-only-exposure" unit risk estimate obtained from the life-table calculations) may be prorated for less-than-lifetime exposure scenarios in the same manner as would be used for an "adult-based" unit risk estimate derived from a rodent bioassay.

Although there is uncertainty in applying these models for occupational mortality to the estimation of risks for different exposure levels and time patterns (Section 5.4.6), following the recommendations of the *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a), a linear low-dose extrapolation below the POD was used because the mode of action for Libby Amphibole asbestos for lung cancer is undetermined. The nine exposure-response models retained from Table 5-13 all had reasonably similar goodness of fits. No single model stands out as clearly statistically superior; however, there is a range of quality of fit within the set that could be considered adequate. The lung cancer mortality unit risks are shown in Table 5-19.

Using the results of the exposure model with the lowest AIC value (i.e., cumulative exposure with a 10-year half-life for decay and a 10-year lag for cancer latency) alone, the LEC_{01}

Table 5-39. 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})

[10] Exposures in the life tables were computed at the mid-point of each age interval and appropriately lagged.

CE 10yr ½ life	10	358.400	0.0009	0.0260	0.0389
CE 5yr ½ life	10	358.502	0.0010	0.0195	0.0293
CE 15yr ½ life	10	358.777	0.0015	0.0300	0.0455
CE 20yr ½ life	10	359.122	0.0022	0.0326	0.0501
CE 5yr ½ life	15	359.910	0.0032	0.0167	0.0260
CE 10yr ½ life	15	360.543	0.0079	0.0231	0.0375
CE	10	361.073	0.0188	0.0399	0.0679
CE 15yr ½ life	15	361.129	0.0162	0.0258	0.0434
CE 20yr ½ life	15	361.533	0.0254	0.0280	0.0486

for the adult-only exposures was determined to be 0.333 fibers/cc which yielded an adult-based unit risk of lung cancer mortality of 0.0300 (POD of 1% divided by the LEC_{01}) which when scaled by 70/54 to encompass the whole lifespan yielded a lifetime unit risk of 0.0389 per fiber/cc. The value of the risk that would correspond to the measure of central tendency involves EC_{01} rather than LEC_{01}. The EC_{01} for the adult only exposures was determined to be 0.499 per fiber/cc which when divided into a POD of 1% yielded an adult-based central estimate for lung cancer mortality of 0.0200 which when scaled by 70/54 to encompass the whole lifespan yielded a lifetime central estimate of 0.0260 per fiber/cc.

Using the results of the exposure model based on cumulative exposure with a 10-year lag for cancer latency, the LEC_{01} for the adult-only exposures was determined to be 0.191 fibers/cc which yielded an adult-based unit risk of lung cancer mortality of 0.0524 (POD of 1% divided by the LEC_{01}) which when scaled by 70/54 to encompass the whole lifespan yielded a lifetime unit risk of 0.0679 per fiber/cc. The EC_{01} for the adult only exposures was determined to be 0.325 per fiber/cc which when divided into a POD of 1% yielded an adult-based central estimate for lung cancer mortality of 0.0308 which when scaled by 70/54 to encompass the whole lifespan yielded a lifetime central estimate of 0.0399 per fiber/cc.

The resulting unit risks in Table 5-19 ranged from 0.0260 to 0.0679 fibers/cc. This shows that the unit risk (i.e., 0.0389 per fiber/cc) based on the exposure metric with the lowest AIC value (i.e., cumulative exposure with a 10-year half-life for decay and a 10-year lag for cancer latency) is in the center of this range and is thus statistically robust. However, because this estimate is in the middle of the range it does not capture the uncertainty across metrics with similar goodness of fit. As noted (Section 5.4.2.2), an argument can be made that the CE metric with a 10 year lag and no half-life is implicitly more parsimonious (simpler) because it was not explicitly adjusted to include decay, although this metric is mathematically equivalent to CE

metric with 10 year lag and an infinitely long decay half-life. Conceptually, the AIC values are penalized for increased model complexity (thereby increasing the AIC). The AIC for the CE models may reasonably be thought to be somewhat lower than through the standard calculation of AIC. However, such a hypothesized adjustment would not alter the identification of the exposure model with the lowest AIC value which remains the CE model with a 10 year lag and a 10 year half-life. Nonetheless, the CE metric with a 10 year lag does fit these data, is a simpler and more straightforward metric and has an extensive tradition of use in the epidemiologic literature and in the practice of risk assessment.

Issues related to uncertainty in the choice of exposure metric are described in the section on the derivation of the combined IUR of mesothelioma and lung cancer below.

5.4.5.3. *IUR Derivation for Combined Mesothelioma and Lung Cancer Mortality*

Before risks can be combined, it is important to understand several concepts that are pertinent to the evaluation and comparison of the cancer-specific mortality unit risks that will be combined. First, there is statistical uncertainty in the potency estimate within the exposure response model defined by each exposure metric. This within metric uncertainty is accounted for by the 95^{th} CI around the potency estimates (see Tables 5-6 and 5-8). Next, there is uncertainty in the choice of metrics for developing IUR (called cross-metric uncertainty, described below). Finally, when unit risks corresponding to metrics are chosen accounting for uncertainty, these are statistically combined into IUR. Details are provided below.

For this assessment, EPA obtained the best available demographic, exposure, and vital status data from NIOSH. Subsequently, the best-fitting statistical models were identified, which were then applied to derive central estimates of the lifetime mesothelioma and lung cancer mortality risk in the general population exposed to a continuous concentration of 1 fiber/cc of Libby Amphibole asbestos. Then, the individual exposure metric-specific risks were calculated as the statistical (95%) upper confidence bounds on these central estimates. Use of the upper confidence bound accounts for uncertainty in the effect estimate for each metric—otherwise referred to as the within-metric uncertainty.

Another source of uncertainty is the choice of the appropriate exposure metric among a set of results that appear to fit the data similarly well. This uncertainty is referred to as the between-metric or cross-metric uncertainty. For the Libby worker cohort data, the best-fit (lowest information criterion values) metrics lead to estimates of risks that are more like mid-range estimates among the other metrics (Tables 5-11 and 5-13) with sufficiently close information criterion values, rather than upper bound estimates. While the lung cancer unit risk computed from the model with the lowest AIC appears to be robust, Table 5-19 shows that there

is a range of possible unit risk values from the set of models with adequate fit (as measured by a statistically significant p-value for the exposure metric term) and similar goodness of fit. Likewise, for mesothelioma mortality, among the models with adequate fit shown in Table 5-17, there is a range of possible unit risk values.

The IUR should be a reasonable upper bound on the extra risk. As is clear from Tables 5-11 and 5-13 in the preceding sections, the unit risks based on the metrics with the lowest information criterion values provide a lower estimate of cancer mortality risk than some other similarly fitting metrics. While the models with the lowest information criterion values have the greatest statistical support, other models that yield higher unit risks are also statistically plausible. This assessment selected the upper bound unit risk among the plausible exposure metrics (regardless of the small residual differences in quality of fit) to account for cross-metric uncertainty. Because there were few metrics with unit risks higher than the best fitting metric's unit risk for each cancer mortality endpoint, this method effectively selects the highest unit risk among those considered for each cancer mortality endpoint.

Once the cancer-specific mortality unit risks are selected, the two are then combined. 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 overstate 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 cancers. 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 the estimated risk for both mesothelioma and lung cancer mortality were derived using Poisson and Cox proportional hazards models, correspondingly, 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.

The upper bound among the mesothelioma mortality unit risks was 0.122 per fiber/cc. The upper bound among the computed lung cancer mortality unit risks was 0.0680 per fiber/cc. The central estimate of risk was 0.075 for mesothelioma mortality per fiber/cc and 0.0399 per fiber/cc for lung cancer mortality (Tables 5-7 and 5-9).

In order to combine the unit risks, one first obtains an estimate of standard deviation of the sum of the individual unit risks as

Sqrt { [[(0.122 - 0.075) / 1.645]^2 +(0.068 - 0.0399) / 1.645]^2 } = 0.033 per fiber/cc (Eq. 5-9)

Then, the combined central estimate of risk of mortality from either mesothelioma or lung cancer is 0.0399 + 0.075 = 0.115 per fiber/cc, and the combined IUR is 0.115 + 0.033*1.645 = 0.169 per fiber/cc.

Selecting the upper bound unit risk estimates for use in combining unit risks accounts for many potential uncertainties. It accounts for uncertainty in the effect estimate (i.e., the within-metric uncertainty) and the uncertainty attributable to the choice of exposure metric (i.e., the cross-metric uncertainty). The combined IUR from the best fitting mesothelioma and lung cancer mortality models (using two different model selection criteria) can be computed for comparison with Tables 5-7 and 5-9, respectively, by the same steps as above, and the results are shown in Table 5-20.

Compared to the combined IUR from the best fitting exposure models, the EPA's selected combined IUR of mesothelioma and lung cancer mortality accounts for both the demonstrated cross-metric uncertainty as well as several additional potential uncertainties, which could have resulted in underestimates of the mesothelioma and lung cancer mortality risks from the epidemiologic data. These additional uncertainties are discussed in Section 5.4.6. The IUR value of 0.169 per fiber/cc accounts for important quantitative uncertainties in the selection of the specific exposure metric that may have remained in an IUR that might have been based on the best fitting exposure models alone.

5.4.5.3.1. Comparison with other published studies of Libby Workers Cohort

For lung cancer, two alternative analytic approaches to the use of EPA's extended Cox proportional hazards models could have been used for the calculation of a unit risk of lung cancer mortality. All of the choices are based on different analyses of the Libby worker cohort; however, inclusion criteria differ among the analyses as does the length of mortality follow-up. Each of the two approaches has two options to estimate the slope of the exposure-response relationship in place of the regression slope estimated from the Cox proportional hazards model and follow through with the same life-table procedure to calculate the unit risk of lung cancer mortality.

Table 5-20. Reasonable upper bound and lowest information criteria estimates of central risks and unit risks, per fiber/cc, for mesothelioma mortality, lung cancer mortality, and the IUR for the combined mortality risk from mesothelioma and lung cancer

Model	Mesothelioma		Lung cancer		Combined mesothelioma and lung cancer	
	Central estimate	Unit risk	Central estimate	Unit risk	Central estimate	IUR
Reasonable upper bound[a]	0.075	0.122	0.040	0.068	0.115	0.169
Lowest information criteria[b]	0.044	0.074	0.026	0.040	0.070	0.103

[a] For mesothelioma, the selected model parameterized exposure as cumulative exposure with exponential decay half-life of 5 years and a 15-year lag. For lung cancer, the selected model parameterized exposure as cumulative exposure without decay and a 10-year lag.

[b] For mesothelioma, the selected model parameterized exposure as cumulative exposure with exponential decay half-life of 5 years and a 10 -year lag. For lung cancer, the selected model parameterized exposure as cumulative exposure with exponential decay half-life of 10 years and a 10-year lag.

The first approach would be to use the published categorical results based on Sullivan (2007). The first option in this approach was for EPA to estimate a slope to those categorical data. The second option was to use the slope estimated in a published re-analysis of categorical data of Sullivan (2007) cohort by Berman and Crump (2008). The second approach would be to use the published regression results of other researchers who modeled the underlying continuous data. The first option in this approach was to use the slope estimated by Larson et al. (2010a). The second option was to use the slope estimated by Moolgavkar et al. (2010).

For comparison purposes, the lung cancer unit risk from these alternatives are computed, however, as all analyses are based upon different subsets of the Libby workers cohort and used different analytic methods, the results are not necessarily interchangeable. Table 5-21 summarizes lung cancer risks derived from these studies.

The first alternative analytic approach to estimating the extra risk from a linear regression of individual mortality data was to use a standard technique used in EPA cancer risk assessments (U.S. EPA, 2005a) when individual-level data are not available. This approach used a weighted linear regression of standardized rate ratio (SRR) estimators for lung cancer mortality in white males, as calculated in the NIOSH cohort analysis (Sullivan, 2007), with categorical cumulative exposure and a 15-year lag. The Sullivan (2007) analysis was based only on those who have not died or been lost to follow-up before January 1, 1960 (in contrast to employment beginning after January 1, 1960) because the NIOSH software program (LTAS) used for this analysis only has statistics on external comparison rates for asbestosis (one of the primary outcomes of interest in

the Sullivan [2007] analysis) beginning in 1960. The SRR analysis involves internal comparisons of lung cancer mortality rates in the lowest exposure category to the lung cancer mortality rates in the higher exposure categories. The weights used for the SRRs were the inverses of the variances. Midpoints of the exposure intervals were used, and for the unbounded interval, the midpoint was assumed to be twice the starting point of that interval.

Table 5-24. 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	Lung cancer cases/N	Slope per fibers/cc-years x10^{-3} (calendar year)	Risk based on UCL on the slope (per fiber/cc)
This assessment	Hired post-1959	32/880	5.8	0.068
Sullivan, 2007	Full cohort; still employed post-1959 White males	99/1672	4.2	0.037
Moolgavkar et al., 2010[a]	Full cohort, White males	95/1662	1.69	0.011
Berman and Crump, 2008[a]	Full cohort, White males	93/1672	3.96	0.079
Larson et al., 2010	Full cohort	98/1862	1.61	0.010

[a] Re-analysis of Sullivan (2007)

Using this approach, a regression coefficient of 4.2 x 10^{-3} per fiber/cc-year (standard error [SE] = 7.7 x 10^{-4} per fiber/cc-year, p = 0.03) was obtained from the weighted linear regression of the categorical SRR results. Because the data from Sullivan (2007) were already adjusted for the length of an occupational year (240 days) to the length of a calendar year (365 days), only the standard adjustment for inhaled air volume was performed. The concentration estimate obtained using this regression modeling and the life-table analysis procedure was LEC_{01} = 0.272 fibers/cc resulting in the lung cancer unit risk of 0.0368 per fiber/cc.

Berman and Crump (2008) re-analyzed Sullivan (2007) data except they used lag of 10 years. They fit IRIS IUR (1988) lung cancer model to aggregate data using extra multiplicative parameter α. In this model, the relative risk at zero exposure is α rather than 1. With α = 1, their model does not fit and with α estimated, the fit was satisfactory. Berman and Crump (2008)

chose central estimate of slope from the fit with α estimated, but constructed "informal" 90% confidence interval by the union of two confidence intervals (this upper bound is shown in Table 5-21). This was done to address uncertainty in estimated parameter α, similar to what is done in this assessment with estimated lag and decay. Note also, that Berman and Crump (2008) also provide an uncertainty factor to adjust for several sources of uncertainty in exposures, resulting in upper bound risk of 0.3162.

The second alternative analytic approach to estimating the extra risk of lung cancer from a Cox regression with time-dependent covariates of individual mortality data was to use the results published by Larson et al. (2010a), with cumulative exposure and a 20-year lag. This analysis of lung cancer mortality was based on the full cohort of 1,862 workers updated until 2006 and using the same model form as the current EPA analysis (the extended Cox proportional hazards model). Larson et al. (2010a) reported a regression coefficient of 1.06×10^{-3} per fiber/cc-year (SE = 3.1×10^{-4} per fiber/cc-year, p = 0.0006).[11] EPA assumed that the cumulative exposures reported by Larson et al. (2010) were based on years of occupational exposure (240 days per year) during a 365-day calendar year. In order to account for exposure on every day of the year for a calculation of unit risk, adjustment for exposures during the length of an occupational year (240 days) to the length of an calendar year (365 days) and the adjustment for the volume of inhaled air were performed to match EPA's analyses. The concentration estimate obtained using the Larson et al. (2010) regression modeling and the life-table analysis procedure was LEC_{01} = 1.26 fibers/cc resulting in a lung cancer unit risk of 0.0103 per fiber/cc.

Moolgavkar et al. (2010) also used the Cox model with time-dependent covariates for analysis of the Sullivan (2007) cohort with a 15-year lag. The parameter in this study estimates (1.11×10^{-3} per fiber/cc-year (SE = 2.5×10^{-4} per fiber/cc-year) are very close to Larson et al. (2010a), and, therefore, the lung cancer unit risk based on their analysis would be very close to Larson et al. (2010a). Comparison with McDonald et al. (2004) is difficult, since their definition of lung cancer (ICD-9 160-165) is much more expansive than other researchers' definitions; however, the parameter estimate resulting from the Poisson analysis by McDonald et al. (2004) was 3.6×10^{-3}.

EPA based their analyses on the exposures that occurred after 1959, while the Sullivan (2007), Larson et al. (2010a), and Moolgavkar et al. (2010) analyses were based on the cohort including those hired before 1960, and McDonald et al. (2004) included only workers hired before 1964. As explained in detail in the discussion (Section 5.4.6) on uncertainty in the exposure assessment, there were only several measurements from the 1950s and one from 1942,

[11] Note that EPA results based on the sub-cohort hired after 1959 were from the same model form but based on the cumulative exposure with a 10-year lag and had a slope of 5.81×10^{-3} per fiber/cc-year (SE = 2.48×10^{-3} per fiber-cc/year, p = 0.018).

and most of the exposure estimation for the early years of the cohort's experience were based on estimates of the ratio of dust to fibers estimated in the late 1960s and extrapolated backwards in time for several decades. Moreover, 686 workers hired before 1960 (not necessarily short-term) did not have exposure measurement assigned to them at all, leading to much larger measurement error. These limitations in the underlying exposure assessment for the years prior to 1968 likely resulted in exposure measurement error that could have attenuated the analytic regression results, thereby yielding a smaller effect estimate for the whole cohort compared to the sub-cohort hired after 1959. It appears the differences in results are mostly attributable to the time periods of analysis and corresponding to the time period measurement errors rather than the analytic approach. The small discrepancy between observed lung cancer deaths between this assessment and Larson et al. (2010a), described in Section 4.1.1.1, is unlikely to play a role in the difference between risk estimates. Moreover, for the sub-cohort hired after 1959, all deaths are included in the Larson et al. (2010a) lung cancer-counting rules.

Neither of the approaches used by McDonald et al. (2004), Sullivan (2007), nor Larson et al. (2010a) could have been appropriately used for the unit risk of mesothelioma as they are not based on absolute risk metrics of association, and the current assessment considered the relevant metric of association to be the absolute risk. Berman and Crump (2008) did not evaluate risk of mesothelioma. Moolgavkar et al. (2010) used an absolute risk model for mesothelioma. These results are summarized in Table 5-22. The upper bound results for the full cohort presented by Moolgavkar et al. (2010) are about 80% of the IRIS IUR (1988) estimate of mesothelioma slope factor in a similar RTW-type metric, leading to approximately 80% estimate of the mesothelioma unit risk, as dependence is linear in the mesothelioma slope factor (Eq. 5-5). This is very close to this assessment's estimate based on sub-cohort, which is also about 80% of the IRIS IUR (1988) estimate of mesothelioma risk. Duration of employment is the best metric for the full cohort, and it does not support dose-response estimation.

Table 5-225 Mesothelioma 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.

Mesothelioma analysis	Cohort definition	Mesothelioma cases/N	Mesothelioma risk (absolute risk model) (per fiber/cc)
This assessment	Hired post-1959	7 /880	Upper Bound = 0.12 Central = 0.08
Sullivan. 2007	Full cohort; still employed post-1959; White males	15/1672	No estimates of absolute risk
Moolgavkar et al.. 2010[a]	Full cohort; White males	15/1662	Upper Bound ≈ 0.13 Central ≈ 0.08
Larson et al., 2010	Full Cohort	19/1862	No estimates of absolute risk
Berman and Crump, 2008[a]	No estimates provided		

[a] Re-analysis of Sullivan (2007)

5.4.5.4. *Applications of the Combined Mesothelioma and Lung Cancer Mortality IUR to Partial Lifetime Environmental Exposure Scenarios*

In the application of the IUR, scenarios other than lifetime environmental exposure are often of interest to risk assessors. The life-table analysis in the (general) IRIS IUR for asbestos (U.S. EPA, 1988) predicts risk increases as the age of the first exposure decreases. The authors of that analysis recommended the life-tables in that analysis be consulted when assessing partial lifetime exposures (U.S. EPA, 1986). In 2009, EPA (OSWER) provided guidance for calculating risk estimates for less-than-lifetime exposures based on the source life-table analysis (U.S. EPA, 2009). The age-at-onset of exposure and duration-dependent unit risks reflect the influence of the time cubed function in the mesothelioma model (eq. 5-5) (U.S. EPA, 1986, 2009) used in the 1986 assessment. Because the time-cubed model, or parameterization of exposure metrics, did not fit the data for mesothelioma mortality from exposure to the Libby Amphibole asbestos, the approach to estimating risk of partial life exposure recommended by EPA when applying the general IRIS IUR for asbestos (U.S. EPA, 1988) is not appropriate when applying the Libby amphibole asbestos-specific IUR.

Thus this assessment recommends that estimates of the risks of less-than-lifetime exposures be computed by simple calculations of average lifetime exposure concentration multiplied by IUR. This recommendation is consistent with standard Superfund guidance (U.S.

EPA, 1986b), where exposures are estimated, averaged across a lifetime exposure, and the IUR simply applied to calculate excess cancer risk (U.S. EPA, 2005).

5.4.6. Uncertainties in the Cancer Risk Values

It is important to consider the discussion of uncertainties in the derivation of the mesothelioma and lung cancer mortality risks in this assessment in the context of uncertainties in animal-based health assessments. This assessment does not involve extrapolation from high dose in animals to low dose in humans. The current assessment is based on a well-documented and well-studied cohort of workers with adequate years of follow-up to evaluate mesothelioma and lung cancer mortality risks with PODs within the range of the data. The discussions below explore uncertainty in the derivation of the IUR in order 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 the 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 unit risks,*
10) *Uncertainty in combining of mortality risks to derive a composite cancer mortality IUR,*
11) *Uncertainty due to extrapolation of findings in adults to children.*

1) *Uncertainty in low-dose extrapolation*

A major 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 employing occupational epidemiology data is considered to be somewhat reduced 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 exposures in this occupational database may be representative of non-occupational 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 workers cohort experienced exposures that were near or below the PODs derived from the life-table analysis. The POD for the selected lung cancer mortality exposure metric was 0.191 fibers/cc. The POD for the selected mesothelioma mortality exposure metric was 0.106 fibers/cc. Among the workers hired after 1959 who had at least 1 year of occupational exposure (n = 470), there were 19 (4%) with exposures to average occupational concentrations of less than 0.3 fibers/cc, including one out of 20 lung cancer deaths (5%) in these workers.

Although data might have been modeled all the way down to a very low level, the *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a) recommends defining a POD for low-exposure extrapolation in order 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 since the linear extrapolations from the dose associated with the POD from the life-table analyses of each cancer endpoint was encompassed within the observed data range. Nonetheless, some uncertainty remains in the extrapolation from occupational exposures to lower environmental exposures when using a POD.

2) *Uncertainty in exposure assessment*

Accurate exposure assessment is generally considered to be a major challenge for occupational epidemiologic studies and is a challenge that is well recognized by the NIOSH investigators (Amandus et al., 1987a). As stated previously in Section 5.4.3.3, while it is generally true that the use of more data is an advantage in statistical analyses because it allows for the computation of more statistically precise effect estimates, this advantage in precision may be offset by a negative impact on the accuracy of the effect estimate if an increase in sample size is accompanied by greater exposure misclassification or other biases. Therefore, EPA decided to base this Libby Amphibole asbestos-specific human health risk assessment upon the mortality experience of workers hired on or after January 1, 1960. EPA's use of the sub-cohort analysis is based on the belief that it is important to accurately estimate the true underlying

exposure-response relationships by relying on the most accurate exposure data. The use of this sub-cohort greatly reduces the uncertainty in exposure error compared to evaluations based on the entire cohort. More specifically,

a) Job assignment was unknown for 686 of the 991 workers employed from 1935 to 1959 (69% of the cohort for this time period). Almost all of these workers were assigned the same exposure concentration for all years without job category information. Examination of the post-1959 cohort removes this significant source of exposure misclassification.

b) Using the more recently hired cohort minimizes the uncertainty in estimated worker exposures based on the job exposure matrix, which was informed by air sampling data available in 1956 and later years. Although there are still uncertainties in the task-specific exposure estimates from 1960-1967, uncertainty in the assessment of earlier exposure levels is considerably greater.

c) Exposure measurements were collected from the area samples and represented exposures for all the workers with the same job code. Statistically, this causes Berkson-type measurement error effect which is described later in this section.

As the EPA exposure-response modeling for mesothelioma and lung cancer mortality is based on the post-1959 sub-cohort, the remaining discussion of uncertainty in exposure measurement will address these data.

Sources of uncertainty in job history information

Worker exposures for the EPA exposure-response modeling were calculated based on job histories and the JEM from 1960 through 1982 (Figure 5-6). Overall, there is little uncertainty in the job history information. Regarding exposure estimation for the occupational cohort, the NIOSH investigators (Amandus et al., 1987a) conducted a detailed retrospective exposure assessment to estimate the individual worker exposures. NIOSH used extensive occupational exposure data to construct the time-specific job exposure matrix, spanning decades (Amandus, 1987a). These data were re-abstracted from the workers' employment records for quality assurance (Sullivan, 2007). NIOSH records on work histories and job-specific exposure extended from the 1930s through May 1982. But, the vermiculite mining and milling operation continued on for several years, and some workers were retained through 1993 for plant close-out activities. However, none of the members of the post-1959 cohort (n = 880) were employed as of the 1982 employment records. Of the employees still working in 1982 (n = 167), all were hired prior to 1960.

Sources of uncertainty in exposure intensity for the identified location operations

The available exposure data that inform the JEM include over 4,000 air samples, the majority of which were collected after 1967 (Table 4-1). All of the job location exposure estimates (Table 5-8) from 1968-1982 were directly informed from air samples collected on membrane filters and analyzed for fibers by PCM. The availability of site- and task-specific air samples for these years provides a good basis for the exposure estimates. However, there are some uncertainties in estimating asbestos exposures using air samples analyzed by PCM.

1) **PCM analysis does not determine the mineral or chemical make-up of the fiber:** The PCM method defines and counts fibers based on the size (aspect ratio and length) of the particle without regard for the material that makes up the fiber being viewed. The PCM method was developed for use in occupational environments where asbestos was present, and the nature of the fibers should be further evaluated to confirm the fibers viewed under PCM are asbestos. McGill University researchers evaluated the fibers collected on membrane filters in the early 1980s and confirmed the presence of asbestos fibers in the tremolite-actinolite solution series consistent with the Libby Amphibole asbestos (McDonald et al., 1986). NIOSH researchers confirmed the presence of tremolite asbestos in bulk dust samples but not in air samples from the facility (Amandus et al. (1987a). Although less specific to fibers, 60-80% of the airborne dust in the mills in 1968 was tremolite, further supporting the presence of asbestos in the air (based on State of Montana air sampling, and x-ray diffraction analysis by the Public Health Service) [PHS correspondence, October 17, 1968]. However, although the presence of mineral fibers in the actinolite-tremolite series was confirmed in the work environment, it is possible that there were also fibers counted by PCM from other materials (such as textiles from clothes and packaging materials). Therefore, it is unknown from these data what proportion of the counted PCM fibers were mineralogically asbestos, or other materials present in the workplace.

2) **PCM defines fibers as particles with an aspect ratio greater than 3:1:** There is an ongoing debate in the literature on asbestos toxicity regarding the influence of aspect ratio on relative toxicity. Specifically, in mining environments, it has been speculated that a larger proportion of low aspect ratio fibers from mineral dusts may significantly impact the apparent cancer potency of the measured PCM fibers in those environments (IRIS IUR, 1988, Berman, 2010). There are few data 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. 1986a). For these air samples, over 96% of the fibers viewed by PCM had an aspect ratio greater than 10:1 (Table 4-2, Amandus et al., 1987a). 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., 1987a). It is possible that prior to industrial hygiene (IH) modifications in 1974, the dry

and old wet mills generated proportionally more mineral dusts than screening 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.

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 (Skinke, 1980; Amandus et al., 1987a). McDonald et al. (1986) compared fibers viewed by PCM and TEM and estimated that approximately 1/3 of the total fibers could be viewed by the optical microscope. 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.

Prior to 1968, no air sampling data were available for 23 of the 25 job location operations (Table 4-2), and the exposure estimates were extrapolated from later air sampling data. Amandus et al. (1987) recognized there is significant uncertainty in the extrapolation of available air sampling data to previous time periods. The researchers took into account major changes in operations and interviewed employees in the early 1980s regarding previous years of operation. The assumptions used to make these extrapolations are clearly stated for each of the plant operations. For four operations, high and low estimates of pre-1968 exposures were provided based on different sets of exposure assumptions (Table 5-8). For ore loading, there were negligible differences in the exposure estimates for the period from 1960-1967 (10.7 versus 9 fibers/cc). For drilling, the river dock, and the bagging plant, there were 3.4-, 2.6-, and 2.8-fold differences, respectively, between the high and low estimates of exposure between 1960 and 1968.

Dry mill exposures between 1960 and 1968 were informed by air sampling for total dust collected in the dry mill facility from 1956-1969 (where total dust was collected by midget impingers). Amandus et al. (1987a) derived a conversion factor of 4.0 fibers/cc per mppcf to apply to the two location operations in the dry mill during these years. There was a range of conversion factors considered for the dry mill depending on how the dust and fiber air samples (PCM) were grouped and averaged (1.2 to 11.5 fibers/cc per mppcf). A subset of dust and fiber samples available over the same time period (1967-1968) resulted in a ratio 8.0 fibers/cc per mppcf. In contrast, a ratio of 1.9 fibers/cc resulted when total dust samples from 1969 were

compared with fiber samples from 1970. However, both of these subsets had limited numbers of samples available. Therefore, the conversion factor of 4.0 fibers/cc per mppcf was selected based on using the maximum samples available over a time period when the dry mill exposures were considered similar: dust samples (1965-1969) and fiber samples (1967-1971). This conversion factor is within a factor of two of the similar datasets considered.

Sources of uncertainty in the calculation of the job exposure matrix (JEM)

The exposures in the job exposure matrix (Figure 5-6) were calculated from the exposure intensities of the various task-specific exposure intensities shown by job location operation (Table 5-8). The uncertainties in the exposure intensity for the job location operations will impact the JEM. Additionally, for each of the job categories in the JEM, NIOSH researchers defined which tasks (job location operations) were conducted and for what proportion of the work day. A TWA exposure for each job category across time was calculated based upon these assumptions and the task-specific exposure estimates. There is a measure of uncertainty in these assumptions for each job category. Additionally, there is inter-individual variation within the job categories. These uncertainties are common to exposure reconstruction for epidemiological cohorts.

Uncertainty in the exposure metric

The PCM measurement is the available exposure metric for analysis of Libby worker cohort at this time. Currently, there is no optimal choice of the best dose metric for asbestos in general and in particular for Libby amphibole asbestos, even if TEM-based dose-response JEM were available. Uncertainties related to PCM analytical method are discussed in Section 2.3. Briefly, PCM cannot distinguish between asbestos and non-asbestos material, or differentiate between specific types of asbestos. Further, due to limitations of this methodology, PCM does not take into account fibers smaller than 5 μm in length.

Evaluation of the effects of uncertainties in exposure measurement

An understanding of the effects of exposure measurement error on the risks estimated from epidemiologic analyses is important to place these possible exposure measurement errors in context. The effect of exposure measurement error on estimates of the risk of mesothelioma or lung cancer mortality attributable to exposure depends upon the degree to which that error may be related to the likelihood of mesothelioma or lung cancer mortality. Exposure measurement error that is similar in pattern among workers who died of lung cancer to exposure measurement error in people who did not die of lung cancer is a non-differential exposure measurement error.

Differential exposure measurement error that is associated with the outcome can cause bias in an effect estimate towards or away from the null, while non-differential exposure error typically results in bias towards the null (Rothman, 1998). From the above evaluation of uncertainties, there is no indication that the uncertainties in job history information, exposure estimates for specific tasks, or calculation of the JEM would be differential based on the cancer health outcome data. Therefore, these uncertainties are considered non-differential, and the general result is likely to be an attenuation in risk estimates towards the null (that is, the addition of random noise to a clear signal tends to reduce the clarity of the observed signal and the avoidance of random noise – here from poor quality exposure measurements, results are a stronger observed signal).

Generally speaking, if the exposure concentrations estimated by NIOSH were systematically too high, then the associated risks of exposure estimated in the regression analysis would be low since the same actual risk would be spread across a larger magnitude of exposure. Similarly, if the exposure concentrations estimated by NIOSH were systematically too low, then the associated risks of exposure estimated in the regression analysis would be too high. From the above evaluation, the majority of the sources of uncertainty are not systematic. There are a few areas of uncertainty that may be classified as biased:

1) High- and low-exposure estimates for four job location operations were provided between 1960 and 1967. Amandus et al. (1987a) choose the high estimates of exposure for these job location operations when calculating the JEM. Therefore, there will be a bias towards the high end for the job categories informed by these data. There was a 1.1- to 3.4-fold difference between the high and low estimates. This difference will be less pronounced where these exposure concentrations are averaged with other job location operations in the JEM and across multiple jobs for the majority of the workers (Figure 5-7).

2) Current PCM analysis would count more fibers relative to early PCM methods based on minimum fiber width resolution. For example, Amandus et al. (1987a) used a minimum width cutoff of 0.44 in their review of PCM fibers in the 1980s, which may have resulted in as much as a 2-fold underestimate compared to current PCM methods with a width resolution of 0.25 µm. Additionally, as PCM methodology has developed over time, it is unknown when PCM results from company records would be considered relatively standard to a minimum width resolution between 0.2 and 0.25 µm. Also, prior to standardization of PCM to 0.25-µm minimum width, there was inter-laboratory 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 over-count of fibers in the dusty environment due to interference from mineral fragments. This likely impacts 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.

Non-differential 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 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 that is being measured and attenuates true linear effects of exposure, resulting in effect estimates in epidemiologic studies that are biased towards the null (Zeger et al., 2000; Armstrong, 1998; Heid et al., 2004). Such errors occur 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 error). Examples of random variability in personal behavior that may produce Berkson-type error in personal exposure estimates include the volume of air breathed per day among the workers and the effectiveness of individuals' nasal filtration at removing contaminants. In general, Berkson error is not thought to bias effect estimates but rather increases the standard errors of effect estimates (Zeger et al., 2000). However, some epidemiologic studies have suggested that Berkson error can produce a quantitatively small bias towards the null in some analyses (Burr, 1988; Reeves et al., 1998; Kim et al., 2006; Bateson and Wright, 2010).

Exposure to other kinds of asbestos and residential exposure

Another source of uncertainty in the estimation of exposures in the Libby workers cohort is the potential contribution of non-occupational or residential exposures as well as exposures to other kinds of asbestos in employment before or after working in Libby.

Many of the workers resided in Libby, MT, before and/or after their employment at the mining and milling facilities ended. The vermiculite from the mine had been used at numerous sites around the town, including baseball fields around the expansion plant and as filler in gardens (U.S. EPA, 2001, 2010). Exposure to asbestos could have occurred among individuals outside of the workplace, particularly through activities with the potential of stirring up dirt or other materials that had been mixed with the vermiculite (Weis, 2001). The results of community sampling indicated that even 10 years after mill operations ceased during some activities, asbestos fiber concentrations in the air could exceed OSHA standards established for the protection of workers (Weis, 2001).

Therefore, the workers' actual personal exposures as the sum of occupational and non-occupational exposures are likely to have been underestimated by the use of estimated Libby-related occupational exposure alone. The difficulty stems from the lack of data on residential exposures and lack of information on pre- and post-employment residence of the Libby workers. Non-occupational exposures were likely to have been smaller in magnitude than the occupational exposures, but workers may have lived in and around Libby, MT, for many more years than they were exposed occupationally. The impact of residential exposure could be more prominent for workers with lower occupational exposure who resided in Libby for a long time. Whitehouse et al. (2008) has reported several cases of mesothelioma among residents of the Libby, MT region who were not occupationally exposed. However, since the report by Whitehouse et al. (2008) details only the cases and does not define or enumerate the population from which those cases were derived, computed relative risks from non-occupational exposures were not available. ATSDR (2000) reported higher relative risks of mesothelioma among the population of Libby, MT, including former workers residing in Libby, but did not provide relative risk for non-occupational exposure. Instead, the ATSDR report on mortality (2000) grouped cases among the former workers with non-occupationally exposed cases. Therefore, it is not clear what the magnitude of the contribution of workers' non-occupational exposures were to their overall risk.

Some of the occupational workers with lower exposures, such as short-term workers, may have either been high school or college students working during the summer or may have been transient workers who may not have stayed for a long time in Libby. Sullivan (2007) analyzed differences between short and long term workers and reported little difference between the

groups except for age at hire. As the shorter term workers were younger on average, this supported the suggestions that some of the short term workers may have been college students working during the summer. It is not clear that this population of short-term workers is well defined; however, it is possible that transient workers could potentially have been exposed to other kinds of asbestos or other lung carcinogens in their non-Libby occupational career, which might have affected their pre- and post-Libby risk profile for asbestos exposure. While their occupational histories are unknown, it is very unlikely that they include exposures of the magnitude that were encountered in the Libby mine and mill. This type of underestimation of exposure related to unknown occupational histories outside of Libby could potentially lead to overestimation of regression slopes for occupational exposures in Libby and, hence, somewhat overestimated risks, although the magnitude of this overestimation is unquantifiable. Counterbalancing any upward bias on the estimated effects of occupational exposures due to non-occupational exposures is the downward bias from random exposure measurement error with lower occupational exposure affected disproportionately.

Conclusion regarding uncertainty in exposure assessment

Overall, there were likely to be multiple sources of uncertainty attributable to exposure measurement error. It is possible that systematic error may have been introduced into the exposure intensities assigned to several of the job location operations discussed above. In each case, these errors in estimating exposures were overestimates. The magnitude of the potential overestimates of drilling and dry and old wet mill exposures is uncertain. The dust-to-fiber conversion ratio applied to the dry mill during 1960-1967 could be an over or underestimate by as much as 2-fold. Random error in the measurement of dust or fibers would likely have produced an underestimation of risk. There is no known bias in the assumptions to extrapolate exposure to pre-1968 location operations outside of the dry mill, and random bias would also likely have produced an underestimation of risk.

3) *Uncertainty in model form*

For mesothelioma mortality, the Poisson model is commonly used for rare outcomes and has been applied by McDonald et al. (2004) and Moolgavkar et al. (2010) to model mesothelioma risk in the Libby worker cohort. For lung cancer mortality, the Cox proportional hazards model is a well-established method that is commonly used in cohort studies, including by Larson et al. (2010a) and Moolgavkar et al. (2010) for the Libby worker cohort, because this type of survival analysis takes into account differences in follow-up time among the cohort. Larson et al. (2010a) conducted Poisson regression analyses and reported that their lung cancer

results using this different model form were similar to those from their extended Cox proportional models, but those results were not shown.

Both of these model forms allow for the evaluation and control of important potential confounding factors such as age, sex, and race, and allow for the modeling of exposure as a continuous variable. Both model forms yielded exposure-response results with good fit to the occupational exposure data. The default assumption of the extended Cox proportional hazards model as well as the Poisson model is that all censoring (due to death or loss to follow-up) is assumed to be independent of exposure to the Libby Amphibole asbestos (e.g., death in an automobile accident or moved to Canada). However, exposure to Libby Amphibole asbestos may be causing deaths from other causes such as asbestosis or non-malignant respiratory disease (Larson et al., 2010a), which is referred to as dependent censoring. The concern is that the observation of lung cancer mortality may be precluded by mortality from other causes.

In the cohort of 880 workers hired after 1959, 32 died of lung cancer, while 10 died of asbestosis and 21 died of non-malignant respiratory disease. The mean length of follow-up from the date of hire until death for the workers who died of lung cancer was 24.9 years. However, the mean length of follow-up for the workers who died of asbestosis or non-malignant respiratory disease was 30.4 years, so it does not appear that early deaths from other causes associated with exposure to the Libby Amphibole asbestos (Larson et al., 2010a) would have precluded many cases of lung cancer. This implies that any potential bias in the lung cancer risk estimates due to dependent competing risks is small.

With respect to mesothelioma mortality, it should be noted that the exposure-response modeling is limited by the number of deaths. However, dependent censoring, as described above, is not accounted for in the Poisson model and likely causes a downward bias in the estimation of risk. The mean length of follow-up for the workers who died of mesothelioma was 30.1 years, and there is some evidence that early deaths from other exposure-related causes precluded an individual's risk of death from mesothelioma; only lung cancer exhibited a shorter average follow-up time compared to mesothelioma, and in 419 cases of mesothelioma, mesothelioma and lung cancer were never co-identified (Roggli and Vollmer, 2008).

4) *Uncertainty in selection of exposure metric*

There is uncertainty about what metric should be used for modeling exposure to Libby Amphibole asbestos. The previous IRIS IUR assessment for asbestos (1988) found that cumulative exposure with a 10-year lag was the best metric for lung cancer mortality, and a more complicated model (Eq. 5-5) based on average cohort exposure intensity, average cohort time since first exposure, and average duration of employment was the best metric for mesothelioma

mortality. This assessment evaluated these models, but also models that include unlagged and lagged cumulative exposure with and without a half-life of various lengths, and residence-time weighted exposure with and without a half-life. In the analysis of comparative model fit, lagged cumulative exposure with a half-life provided the best fits for both mesothelioma and lung cancer mortality associated with Libby Amphibole asbestos. However, evaluation of 20-year lag and longer lag times for mesothelioma was not possible, as the earliest mesothelioma death happened less than 20 years from the start of the exposure, and, hence, exposure was zeroed out, and the fit of any model with 20-year lag was very poor. Latency time for mesothelioma may be as long as 60-70 years (e.g., Bianchi and Bianchi, 2009), so the precise lag time is uncertain.

In evaluating the data on lung fiber burden, Berry et al. (2009) estimated the range of the half-life for crocidolite to be between 5 and 10 years. That range is consistent with the finding of a 5-10 year half-life with 10-15 years lag that provided the best fit to the Libby workers cohort mesothelioma mortality data. Similarly, recent publications indicate that the relative risk of lung cancer due to asbestos exposure declines 15-20 years after the cessation of exposure to asbestos (Hauptmann et al., 2002; Magnani et al., 2008). The marginally best fit for the Libby workers cohort lung cancer mortality data was for CE models with a 5-20-year half-life and 10-year lag. However, the precise lag and half-life times are somewhat uncertain. Sensitivity analysis that excluded people with high exposure during 1960-1963 (Section 5.4.5.3) provides further evidence that distinguishing between various lag and decays may be difficult with these data. A limitation of this sensitivity analysis is the decrease in the number of cases, especially for mesothelioma. Resolving this uncertainty will require longer follow-up time that would allow for a sub-cohort analysis of workers hired in 1967 or afterwards (when exposure estimates began to be based on PCM measurements) until a sufficient number of cases would be available for additional analysis.

These simulated decay models were derived mathematically to approximate underlying biological processes that are not well understood, and their better fit is based on maximizing the likelihood for the workers cohort and may not necessarily apply to the environmental exposure patterns. Nonetheless, while the mode of action for carcinogenicity is unknown, the models incorporating a half-life in the exposure metric were clearly preferable for mesothelioma mortality, and the goal of the regression modeling effort was to identify the best fitting exposure model for the Libby worker cohort.

The selection of the exposure metric is a source of cross-metric variability discussed in Section 5.4.5.3, and the IUR incorporates this variability. The difference between this value and the value derived from the best fitting exposure model describes the quantitative uncertainty, which is less than 2-fold.

5) ***Uncertainty in assessing of mortality corresponding to the cancer-specific endpoints***

As well established in the literature, mortality rates calculated from death certificates are lower than the true rate of death due to both lung cancer, and to a larger degree, mesothelioma (lung cancer sensitivity: ranging from 86% in an asbestos cohort [Selikoff and Seidman, 1992] to 95% in general [Percy et al., 1981]; mesothelioma sensitivity: ranging from 40% for ICD-9 [Selikoff and Seidman, 1992] to about 80% for ICD-10 [Camidge et al., 2006; Pinhiero et al., 2004]). This underestimation of the true rate will result in a lower estimated risk compared with that which would be estimated based on the true rate. The underestimation of risk is much more pronounced for the absolute risk model (mesothelioma) than for the relative risk model (lung cancer). Misdiagnosis rates would need to be quite disparate in the cohort and the comparison population to impact relative risks, and this is unlikely for internal controls that were used in the lung cancer analysis using the Cox model. Therefore, EPA considered use of a procedure to adjust risks for mesothelioma, but not for lung cancer—underascertainment (Section 5.4.5.1.1). This procedure makes certain assumptions, in particular, that an adjustment factor derived for the full cohort applies to the sub-cohort hired after 1959, and that the rate of misdiagnosis of peritoneal mesotheliomas has not improved recently and that the proportion of peritoneal mesotheliomas in the cohort is estimated from the available information on the type of mesothelioma in one-third of mesothelioma cases. However, overall uncertainty in this adjustment is low, and the application of the adjustment reduces the bias associated with the diagnostic underascertainment.

The endpoint for both mesothelioma and lung cancer was mortality, not incidence. The latter is generally desirable, but median survival with lung cancer and, especially, mesothelioma is not very long, so uncertainty related to the endpoint being death and not incidence is low.

There is evidence that other cancer endpoints may also be associated with exposure to the commercial forms of asbestos. IARC concluded that there was sufficient evidence in humans that commercial asbestos (chrysotile, crocidolite, amosite, tremolite, actinolite, and anthophyllite) was causally associated with lung cancer and mesothelioma, as well as cancer of the larynx and the ovary (Straif et al., 2009). Among the entire Libby workers cohort, only 2 deaths were found to be due to laryngeal cancer, and there were no deaths from ovarian cancer among the 24 deaths of 84 female workers. The lack of sufficient number of workers to estimate risk of ovarian cancer is an uncertainty in an overall cancer health assessment.

The remaining uncertainties attributed to assessing mortality corresponding to the cancer endpoints are considered to be low.

6) *Uncertainty in control of potential confounding in modeling lung cancer*

It is well known that smoking is a strong independent risk factor for lung cancer and may have a synergistic effect with asbestos exposure (Wraith and Mengersen, 2007). In contrast, smoking is not considered a risk factor for mesothelioma (Mossman et al., 1990; Selikoff and Lee, 1978).

As an important potential confounder of the lung cancer mortality analysis, the possible effect of smoking on the estimated risk of lung cancer mortality associated with exposure to Libby Amphibole asbestos needs to be evaluated to the fullest extent possible. This consideration was discussed in Amandus and Wheeler (1987) and in Section 4.1.1.3 .

Additionally, WR Grace instituted a smoking ban on the property in 1979 (Peacock, 2003). However, it is unclear how the ban on smoking at work relates to smoking patterns outside of the work environment. Moreover, since only about 30% of the sub-cohort was still employed in 1979 and all of the post-1959 cohort had been terminated by May of 1982, the impact of a workplace smoking ban on cohort smoking history is unlikely to be a significant factor but may explain the higher proportion of former smokers in the Amandus and Wheeler (1987) data.

Without high-quality individual-level data on smoking that could be used to control for potential confounding, it is still possible to comment upon the likelihood and potential magnitude of confounding and the impact any confounding would be expected to have on the lung cancer mortality risk estimates. Confounding can be controlled for in a number of ways including by modeling and by restriction. Restriction of the study population can reduce any potential confounding by making the resulting population more similar. For instance, there can be no confounding by gender when a study population is restricted to only men. This assessment restricted the study population to those workers hired after 1959. Smoking habits have changed over time, and it can reasonably be assumed that the range of smoking habits among those hired after 1959 is less variable than that among the whole cohort, particularly because of the narrower range of birth cohorts represented in this sub-cohort. This should have the effect of reducing some of the potential for confounding.

Additionally, the extended Cox proportional hazards models controlled for date of birth, which effectively controls for any secular trends in confounders over time (Tableman and Kim, 2004). Amandus and Wheeler (1987) cite data from the U.S. Public Health Service (1979) showing a steady decrease in the prevalence of current smoking from 52.9% in 1964 when the U.S. Surgeon General's report on smoking was released to 42.3% in 1970 and 37.5% in 1978 (U.S. Surgeon General, 1990). If current smoking were a meaningful confounder, such a reduction in smoking rates over time should have produced a noticeable distortion in the

proportionality of the hazards as the magnitude of confounding by smoking changes with smoking prevalence. No violation of the proportional hazards assumption was observed in the context of the Cox model; hence, there is no evidence of confounding by smoking in the analyses of workers hired after 1959.

Lastly, a method has been described by Richardson (2010) to determine if an identified exposure relationship with lung cancer is confounded by unmeasured smoking in an occupational cohort study. EPA implemented this methodology to model the potential effects of Libby Amphibole asbestos on the risk of COPD mortality on the sub-cohort of workers hired after 1959 (see Section 5.4.3.4.4). Summarizing these findings, EPA used the method described by Richardson (2010) to evaluate whether exposures to Libby Amphibole asbestos predicted mortality from COPD as an indication of potential confounding by smoking and found a non-significant negative relationship, which was inconsistent with confounding by smoking.

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 Libby Amphibole asbestos among known non-smokers were not available.

It is theoretically possible that the risk of lung cancer mortality estimated in this assessment is a reflection of a positive synergy between smoking and asbestos, and that the adverse effect of Libby Amphibole asbestos among the potentially non-smoking 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.

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 (2001) reviewed 1517 mesothelioma cases from 1975 through 2000 and was able to estimate the latency for 800. Suzuki (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.

The effect of insufficient length of follow-up for mesothelioma mortality would be to underestimate the risk of exposure since there would be workers who may eventually die of mesothelioma that are not counted in this assessment. As the risk of mesothelioma mortality is evaluated as an absolute risk, the unit risk of mesothelioma mortality may reasonably be expected to rise with time moderated by the increase in person-years of follow-up. According to the results of Suzuki (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, depending on the relationship between the number of additional deaths and increase in person-years.

9) *Uncertainty in use of life-tables to calculate cancer mortality 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 2003-2007 SEER 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.

10) *Uncertainty in combining of risk for composite cancer IUR*

For the purpose of combining risks, it is assumed that the unit risks of mesothelioma and lung cancer mortality are normally distributed. Since risks were derived from a large epidemiological cohort, this is a reasonable assumption supported by the statistical theory, and uncertainty related to it is low.

11) *Uncertainty in extrapolation of findings in adults to children*

The analysis of lung cancer mortality specifically tested and confirmed the assumption that the relative risk of exposure is independent of age within the age range of the occupational sub-cohort hired after 1959. However, no comparable data are available to estimate the lifetime risk from early life exposures. The life-table procedure is conducted so as to initiate exposure at age 16 to represent adult exposures. Then, the adult-only-exposure IUR estimates derived from the life-table analysis need to be re-scaled to a 70-year lifespan in order to yield the standard lifetime IUR, allowing risk estimate calculations involving less-than-lifetime exposure scenarios, in the standard manner. After re-scaling, the resulting "adult-based" IUR estimate (in contrast to the unscaled "adult-only-exposure" IUR estimate obtained from the life-table calculations) can be used seamlessly by the end-user in the same manner as for an adult-based IUR estimate derived from a rodent bioassay. Lack of published information on risks associated with Libby Amphibole asbestos-specific exposure during childhood is the uncertainty associated with the proposed extrapolation. If such information is subsequently published, the extrapolation procedure can be updated. As per the EPA Cancer Guidelines (U.S. EPA, 2005b), when the information regarding early-life susceptibility to cancer is not available, the linear low-dose extrapolation approach will be used.

5.4.6.2. *Summary*

In the discussion of the overall uncertainty in the IUR, it is important to distinguish between uncertainty that encompasses both the direction and the magnitude from uncertainty with known directional effects on the IUR but of unknown magnitude. In this summary, only the latter uncertainties, which may result in underestimated or overestimated risk, are listed below. Uncertainties that are not thought to alter the estimated magnitude of the risk in a systematic direction are not included in this summary.

The sources of uncertainty that could lead to a likely underestimation of the cancer risk value include the following:

- *Use of historical PCM exposure measurements*. As asbestos was a contaminant of vermiculite that was the primary object of production, mine and dry and old wet mill ambient air may have contained material other than asbestos that could have contributed to fibers counted by PCM. Therefore, it is possible that exposure estimates for some, or possibly a large portion of the cohort, are overestimated, and, therefore, the resulting IUR may be underestimated**.**

- *Measurement error in exposure assessment and assignment*. This assessment showed that unit risk results from analysis of the lung cancer mortality in the full cohort

(Sullivan, 2007; Larson et al., 2010a) compared to the sub-cohort hired after 1959 may have been attenuated as much as 2-6 times (see earlier section on statistical uncertainty). By excluding those cohort members hired before 1960 on whom there was insufficient work history information to estimate their exposures, the unit risk for lung cancer was less attenuated due to exposure measurement error. However, exposure measurements from the 1960s are also imperfect and include a lesser degree of exposure measurement error, which could have led to underestimated risk even in the sub-cohort hired after 1959.

- *Limited length of follow-up.* Absolute risk is used for mesothelioma; therefore, the unit risk of mesothelioma mortality could be larger than was estimated from existing data, depending on the relationship between the number of additional deaths and an increase in person-years.

- *Use of life-tables to calculate the IUR based on cancer mortality.* The lung cancer mortality unit risk based on the LEC_{01} would be somewhat larger, about 5-10%, and the mesothelioma unit risk would be slightly less (about 3%) than that if the life-tables were extended from 85 to 90 years to account for longer life spans.

- *Small number of women and ovarian cancer.* While asbestos is causally associated with increased risks of ovarian cancer (Straif et al., 2009), there were only 84 women in the whole cohort, and there were no deaths from ovarian cancer among 24 total deaths. To the extent that there was an increased risk of ovarian cancer in the Libby workers cohort due to inhalation exposures that was unobserved, then the IUR would be somewhat underestimated. However, it was not possible to estimate the magnitude of this underestimation on the total cancer risk.

- *Dependent competing risks*. Competing risk of mortality from other diseases related to exposure may have resulted in underestimates of the risk of mortality from either mesothelioma or lung cancer. The mean length of follow-up for the Libby workers who died of mesothelioma was to 30.1 years, and evidence exists (Suzuki, 2001; Bianchi and Bianchi, 2009) that early deaths from other exposure-related causes could have precluded an individual's risks of death from mesothelioma. However, it was not possible to estimate the magnitude of this effect on the total cancer risk.

The sources of uncertainty that could lead to a likely overestimation of the cancer risk value include the following:

- *Potential residual confounding and effect modification.* The unit risk of lung cancer mortality estimated herein, and the combined mesothelioma and lung cancer mortality IUR, would over-estimate the risk in any population that had a lower prevalence of smoking than that of the Libby worker cohort. Since the Libby worker cohort had a large prevalence of smokers and no known non-smokers developed lung cancer, it is also possible that estimated risk for lung cancer is actually risk for an interaction of lung

cancer and smoking and effects of smoking and asbestos are known to be between additive and multiplicative (Section 4).

- *The resolution of visible PCM fibers in 1960s and 1970s and use of TEM-based PCMe*. It is likely that early PCM counts were underestimated relative to the later PCM measurements. Since PCMe counts fibers that correspond to modern PCM, using PCMe for risk derived partially in old PCM fibers could lead to overestimation of mortality risk.

6. MAJOR CONCLUSIONS IN THE CHARACTERIZATION OF HAZARD AND EXPOSURE RESPONSE

Libby Amphibole asbestos, a contaminant of vermiculite mined near Libby, MT, is a complex mixture of amphibole fibers—both mineralogically and morphologically (Section 2.2). The mixture primarily includes tremolite, winchite, and richterite fibers. These fibers exhibit a range of morphologies from asbestiform to cleavage fragments (Meeker et al., 2003). Given the exposure potential to Libby Amphibole asbestos—and its unique mineral composition—a hazard characterization and cancer dose-response assessment is presented.

As discussed in Section 1, there is currently no RfC for asbestos and the U.S. EPA IRIS inhalation unit risk (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, 1986). There is uncertainty in applying the resulting IUR to environments and minerals that are not included in the studies considered for the asbestos IUR derivation (U.S. EPA, 1988). Published mortality studies on the Libby, MT worker cohort have become available since the derivation of the IRIS asbestos IUR (i.e., McDonald et al., 1986a, 2004; Amandus and Wheeler, 1987; Sullivan, 2007; Larson et al., 2010a; Moolgavkar et al., 2010). This assessment documents non-cancer and cancer health effects from inhalation exposure to Libby Amphibole asbestos. Data are not available to support derivation of either an RfD or a cancer slope factor following oral exposures to Libby Amphibole asbestos.

6.1. HUMAN HAZARD POTENTIAL

6.1.1. Exposure

Libby Amphibole asbestos was not mined for industrial or commercial use, but it was a contaminant of vermiculite mined near Libby, MT (Section 2). Vermiculite from the Libby, MT mine was used commercially from the 1920s to 1990, and it comprised approximately 80% of the total vermiculite sold in this country until that point. Vermiculite was most notably used as attic insulation, as a soil amender for gardening, and in the manufacturing of gypsum wallboard. The exposure potential to Libby Amphibole asbestos includes historical exposures (both occupational and community); as well as the potential for ongoing exposures to waste materials, contaminated soils and vegetation, and consumer products (e.g., vermiculite attic insulation).

There are many ways in which workers and residents in Libby, MT, and the surrounding communities may have been exposed while the mining and milling operations were active. Historical routes of exposure include (1) occupational exposure; (2) take-home exposure for household contacts of the workers (including children); (3) dust/fiber emissions to the community from the milling and exfoliating facilities; (4) distribution of waste material into the

community as fill (including yards and recreational areas); (5) use of vermiculite attic insulation in homes; (6) use of vermiculite in gardening/horticulture; and (7) children playing in the waste rock piles (stoner rock) (ATSDR, 2001). Other than documentation of dust and fiber exposure levels for mine and mill workers, there are few data to inform the levels of exposure to household contacts and community members during mine and mill operations. Although no historical exposure measurements are available from the homes of the workers, the EPA has conducted some sampling to determine exposure levels from vermiculite and waste materials that remain in the community (U.S. EPA, 2001; Appendix B). These data provide information useful to understand what historical exposures might have been for similar activities.

Outside of Libby, MT, milled vermiculite ore was shipped to 271 domestic sites that served as processing facilities (GAO-08-71). These sites included exfoliation plants (e.g. for the production of vermiculite insulation) as well as non-exfoliation facilities (e.g., production of gypsum wallboard). The vermiculite ore was exfoliated by heat-induced expansion resulting in vermiculite produced for commercial purposes. Both the commercial vermiculite and the waste rock (i.e. residual waste rock from exfoliation) were contaminated with Libby Amphibole asbestos fibers. Potential exposure routes in these communities located around the country parallel the exposures in Libby, MT, including occupational exposures, take-home exposures from workers, and children playing in the piles of waste rock near the facility (ATSDR, 2008). Waste materials (expanded vermiculite and waste rock) from some of these facilities were also used for fill in local communities, potentially creating additional exposure pathways based on an ATSDR review of 28 facilities, and a survey of the Western Minerals Plant, MN (ATSDR, 2001, 2008). Few historical samples that could be used to quantify the exposure potential for workers or for the surrounding communities are available from these facilities. Air modeling conducted for one exfoliating facility in Minnesota does provide support for the potential of dust/fiber emissions from exfoliating plants to impact ambient air quality in the vicinity of the plant (ATSDR, 2005).

While the mine was active, there was exposure potential to commercial products containing vermiculite from Libby, MT, especially in gardening soils and vermiculite attic insulation. No studies have evaluated the potential for consumer exposure when vermiculite from Libby, MT, was employed as a soil amender, but air sampling at one facility where this was produced (O.M. Scott facility in Marysville, OH) demonstrated that workers handling this material during manufacture were exposed to asbestos fibers (Lockey et al., 1984). There is potential for exposure for homes that contain vermiculite attic insulation from Libby, MT, as residents and workers enter attics for various uses, repairs, and renovations and for using firewood from Libby, MT area (Section 2.3.3).

6.1.2. Fiber Toxicokinetics

There is no specific information available at the time of this assessment on the fiber toxicokinetics of Libby Amphibole asbestos. However, as a mineral fiber, the characteristics that define the deposition, clearance, and translocation of other amphibole fibers might apply to Libby Amphibole asbestos. As discussed in Section 3, the specific fiber dimensions and density of Libby Amphibole asbestos will determine the probable pattern of deposition in the respiratory tract and other tissues (e.g., pleura, peritoneum). Based on the fiber-size profile of airborne Libby Amphibole asbestos fibers, deposition is expected throughout the respiratory tract including the alveolar regions. Less is known about mineral fiber translocation to other target tissues in general, and, to date, no studies have specifically examined translocation following exposure to Libby Amphibole asbestos.

As with other mineral fibers, clearance is likely to occur via the mucociliary apparatus in the upper respiratory tract and the mucociliary escalator for those fibers deposited in the trachea and bronchioles. This clearance is enhanced by macrophage action, which may transport some of the fibers from the alveolar sac to the mucociliary system. Fibers may also be dissolved in lung fluids or through the more aggressive action of alveolar macrophages. In general, amphibole asbestos is considered more persistent and less likely to dissolve than other natural fibers. However, no data are available for Libby Amphibole asbestos specifically, and it is unknown if Libby Amphibole asbestos fibers would split or break in the pulmonary compartment as has been shown with some amphibole fibers (e.g., ferroactinolite) (Coffin et al., 1983).

Any fibers deposited in the respiratory tract and not cleared via the mucociliary system, or which are not dissolved, can remain in the lung or can be transported to other tissues. Although data specific to Libby Amphibole asbestos are not yet available, other asbestos fiber types may translocate from the lung via macrophage action and transport through the lymph system, or direct migration may occur through tissues from the mechanical action of the lung. Pleural and peritoneal effects documented in Libby Amphibole asbestos-exposed individuals support the potential for translocation of Libby Amphibole asbestos into the pleura.

6.1.3. Noncancer Health Effects in Humans and Laboratory Animals

Noncancer health effects identified in humans include effects on the respiratory system (e.g., lung function, pleural and parenchymal effects) following inhalation exposure to Libby Amphibole asbestos, as well as increased mortality from non-cancer causes. Five cohort mortality studies of Libby miners identified increased risk of mortality from non-cancer causes, including nonmalignant respiratory disease (McDonald et al., 1986a; Amandus and Wheeler 1987; McDonald et al., 2004; Sullivan, 2007; Larson et al., 2010a) and cardiovascular disease (Larson et. al., 2010a). Studies of respiratory system effects comprise six studies in community

members living in Libby, MT (Weill et al., 2010; Peipins et al., 2003; Peipins et al., 2004; Whitehouse 2004; Muravov et al., 2005; Vinikoor et al., 2010), two studies among Libby miners (McDonald et al., 1986b; Amandus et al., 1987b), and two studies among Marysville workers (Lockey et al., 1984; Rohs et al., 2008). Among the studies in community members, all but one (Vinikoor et al., 2010) included former vermiculite facility workers, and none of the six provided quantitative exposure information. The four studies conducted in two occupational cohorts (McDonald et al., 1986b; Amandus et al., 1987b; Lockey et al., 1984; Rohs et al., 2008) did provide quantitative exposure estimates, and were considered suitable for exposure-response analysis to support RfC derivation. Each of the four studies demonstrated an increased risk of pleural anomalies in workers.

Although laboratory animal data and experimental data on toxicity mechanisms are limited for Libby Amphibole asbestos, the existing data are consistent with the health effects observed in both Libby workers and community members. Animal studies have demonstrated increased collagen deposition consistent with fibrosis following intratracheal instillation of Libby Amphibole asbestos fibers in C57Bl6 mice (sex unspecified, Putnam et al., 2008; male and female, Smartt et al., 2009) and increased markers of pulmonary inflammation in a rat model for human cardiovascular disease (Shannahan et al., 2011). Pulmonary fibrosis, inflammation, and granulomas were observed after tremolite inhalation exposure in SPF male Wistar rats (Bernstein et al., 2003, 2005) and intratracheal instillation in male albino Swiss mice (Sahu et al., 1975). Davis et al. (1985) also reported pulmonary effects after inhalation exposure to tremolite in SPF male Wistar rats including increases in peribronchiolar fibrosis, alveolar wall thickening, and interstitial fibrosis.

6.1.4. Carcinogenicity in Humans and Laboratory Animals

Libby Amphibole asbestos fibers are associated with lung cancer and mesothelioma in workers from the Libby vermiculite mining and milling operations (Larson et al., 2010a; Moolgavkar et al., 2010; Sullivan, 2007; McDonald et al., 1986a; 2004; Amandus et al., 1988; Amandus and Wheeler, 1987; NIOSH, 1986). No other occupational cohort with exposures to Libby Amphibole asbestos has been studied with respect to mortality risks. Whitehouse et al. (2008) documented 11 mesothelioma cases in non-workers exposed to Libby Amphibole in Libby, MT. Increased lung cancer and mesothelioma deaths are also reported for worker cohorts exposed to other forms of amphibole fibers (amosite and crocidolite) (de Klerk, 1989; Seidman et al., 1986; Henderson and Enterline, 1979). These findings are consistent with the increased cancers reported for communities exposed to various rocks and soils containing tremolite fibers, which are a component of Libby Amphibole asbestos (Baris, 1987; Yaziciglu, 1976; Yaziciglu et al., 1973; Langer et al., 1987; Baris et al., 1979; Sichletides et al., 1992;

Hasanoglu et al., 2006). Although potency, fiber dimension, and mineralogy differ between amphiboles, these studies are supportive of the hazard identification of Libby Amphibole asbestos fibers described in this document.

Although there is a limited laboratory animal database, the studies that are available support the carcinogenicity of Libby Amphibole asbestos fibers. Smith (1978) demonstrated mesotheliomas in hamsters given a single intrapleural injection of Libby Amphibole asbestos material (Table 4-16). Tremolite, which comprises approximately 6% of the fiber mixture in Libby Amphibole asbestos, is also carcinogenic in studies in rats, hamsters, and mice, resulting in pleural mesothelioma, peritoneal mesothelioma, and lung cancer depending on the route of exposure (Table 4-17) (Davis et al., 1985; Davis et al., 1991; Stanton, 1981; Roller et al., 1996; Bernstein et al., 2003, 2005). Although comparing the potency of the tremolite used in these studies is difficult given the lack of information on fiber characteristics and other study limitations, these results show an increased risk for lung cancer and mesothelioma following exposure to tremolite asbestos.

6.1.5. Susceptible Populations

Certain populations could be more susceptible than the general population to adverse health effects from exposure to Libby Amphibole asbestos. In general, factors that may contribute to increased susceptibility from environmental exposures include lifestage, gender, race/ethnicity, genetic polymorphisms, health status, and lifestyle. However, little data exist to address the potential of increased susceptibility to cancer from exposure to the Libby Amphibole asbestos.

Most occupational studies of workers exposed to Libby Amphibole asbestos have examined the effects only in men because this group represents the vast majority of workers in these settings (Amandus and Wheeler, 1987; Amandus et al., 1987c, 1988; McDonald et al., 1986a, 1986b, 2004; Sullivan, 2007; Moolgavkar et al., 2010). The analysis presented here includes all workers, but there were few women and, consequently, no determination can be made regarding increased susceptibility to lung cancer or mesothelioma. Gender-related differences in exposure patterns, physiology, and dose-response are some of the factors that may contribute to gender-related differences in risk from asbestos exposure (Smith, 2002). The limited data available from community-based studies (ATSDR, 2000) do not provide a basis for drawing conclusions regarding gender-related differences in carcinogenic effects from Libby Amphibole asbestos. Racial diversity among workers exposed to Libby Amphibole asbestos is also limited, and data on ethnic groups absent, precluding the ability to examine racial and ethnicity-related differences in the mortality risks within the Libby worker cohort. Finally, the potential modifying effects of genetic polymorphisms, pre-existing health conditions, nutritional

status, and other lifestyle factors have not been studied sufficiently to determine their possible contribution to variation in risk in the population.

6.1.6. Mode-of-Action Information

Limited information is available on the biological effects that may contribute to a specific mode of action. Laboratory animal studies of mice (Putnam et al., 2008; Smartt et al., 2009), hamsters (Smith, 1978) or rats (Shannahan et al., 2011) exposed to Libby Amphibole asbestos suggest an inflammatory response similar to that observed with other mineral fibers; however, no inhalation studies have been performed. In vivo studies in rats, hamsters, or mice exposed to tremolite (McConnell et al., 1983a; Davis et al., 1991; Smith et al., 1979; Wagner et al., 1982; Stanton et al., 1981; Roller et al., 1996, 1997) show results similar to other amphibole asbestos fibers including lung cancer and mesothelioma, although again with limited inhalation studies (Davis et al., 1985; Bernstein et al., 2003; 2005). In vitro studies demonstrate that the uptake of Libby Amphibole asbestos fibers by macrophage, mesothelial, and lung epithelial cell lines may lead to an increase in oxidative stress as measured by reactive oxygen species production, gene expression changes (Blake et al., 2007; Hillegass et al., 2010), or genotoxicity (Pietruska et al., 2010). Thus the available data indicate that Libby Amphibole asbestos induces biological responses similar to other forms of asbestos such as oxidative stress, chronic inflammation, genotoxicity, and increased cell proliferation. These mechanisms are potentially related to the adverse health effects of asbestos fibers and one or more of these activities may be relevant to the carcinogenicity of Libby Amphibole asbestos fibers. However, data are not sufficient to establish a mode of action for Libby Amphibole asbestos.

6.1.7. Weight-of-Evidence Descriptor for Cancer Hazard

Libby Amphibole asbestos is carcinogenic to humans through inhalation exposure based on the framework provided in the *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005). Epidemiologic evidence provides an association between exposure to Libby Amphibole asbestos fibers in the workplace and the mortality from lung cancer and mesothelioma (Larson et al., 2010a; Sullivan, 2007; McDonald et al., 1986a, 2002, 2004; Amandus et al., 1988; Amandus and Wheeler, 1987; NIOSH, 1986). Although limited, the available chronic laboratory animal study involving exposure to Libby Amphibole asbestos supports these findings (Smith, 1978).

As specified in the *Guidelines for Carcinogen Risk Assessment*, the descriptor "carcinogenic to humans" is appropriate when there is convincing epidemiologic evidence of a causal association between human exposure and cancer (U.S. EPA, 2005). As described in Section 4.1, the evidence of both lung cancer and mesothelioma in the Libby worker cohort is consistent over time. Additionally, this association and a convincing exposure-response

relationship are observed when examining both workers with a minimum tenure (McDonald et al., 2004; Amandus and Wheeler, 1987), as well as when including workers regardless of duration of employment (Sullivan, 2007).

6.2. EXPOSURE-RESPONSE

This assessment contains a derivation of a RfC for noncancer effects and an IUR for cancer based on epidemiologic data. It does not contain an RfD or oral cancer slope factor.

6.2.1. Noncancer/Inhalation

Libby Amphibole asbestos has been shown to cause localized pleural thickening, diffuse pleural thickening, and parenchymal changes in exposed populations. The study of Marysville workers (Lockey et al., 1984 and the follow-up by Rohs et al., 2008) was selected as the principal study due to the availability of quantitative exposure information and information on important covariates, increased risk of pleural and parenchymal effects, at lower cumulative exposure levels (compared to the Libby worker cohort—McDonald et al., 1986b; Amandus et al., 1987), the length of follow-up, use of more recent 2000 ILO diagnostic criteria, and the availability of detailed exposure and health outcome information for each worker. The outcomes examined in this cohort included localized and diffuse pleural thickening, as well as parenchymal changes. Localized pleural thickening was selected as the critical effect due to its higher prevalence relative to the other outcomes, minimal adversity (compared with other effects), and specificity for durable mineral fiber exposure. For RfC derivation, analyses focused on the subcohort of Marysville workers described by Rohs et al. (2008) who started employment after 1972, due to the greater certainty in exposure assessment in this group.

Benchmark dose modeling, with a BMR of 10% extra risk, was used to derive the POD. A log-logistic regression model was used to estimate the exposure-response relationship for Libby Amphibole asbestos and localized pleural thickening. Cumulative exposure with a lag of 10 years was selected as the exposure metric, based on evidence for biological latency and model fit considerations. A background rate of localized pleural thickening of 1% was assumed. The resulting BMD under these modeling assumptions was 0.2543 fibers-yr/cc; the corresponding BMDL of 0.076 fibers-yr/cc is the POD for RfC derivation. The RfC is obtained by first dividing the POD by a total uncertainty factor of 100 (10 for interspecies variability and 10 for database deficiencies): 0.076 fibers-yr/cc x 1/100 = 0.00076 fibers-yr/cc. The RfC is for continuous exposure (24 hours/day, 365 days/year, with exposure beginning at birth and continuing for 70 years), adjusting for the 10-year lagged exposure, is 0.00076 fibers-yr/cc x 1/(70-10) years = 1.27×10^{-5} or rounded to one significant digit, 1×10^{-5} fibers/cc. Table 5-6 shows estimated RfCs for less than lifetime exposure scenarios. Modeling was also conducted in

the full cohort of workers described in Lockey at al. (1984) and Rohs et al. (2008). These analyses used a different modeling approach, due to the wider range of exposures and time since first exposure (T). A modified Michaelis-Menten model provided the best fit to the full cohort data, which incorporated T via the plateau term for the model. For a T of 30 years, the BMD and BMDL corresponding to a 10% extra risk of localized pleural thickening were 0.1384 and 0.0541 fibers-yr/cc, respectively. These are quite similar to the values obtained in the analysis for the RfC, and provide important support for the selected modeling approach.

Confidence in the principal study is considered medium- to-high. The data used are human, epidemiological data rather than animal bioassays, and the principal study is conducted in a population of occupationally exposed workers with long-term, relatively low intensity exposures. Confidence in the database is low-to-medium. The database contains long-term mortality and morbidity studies in humans exposed via inhalation to Libby Amphibole asbestos, but there is a lack of data on effects other than in the respiratory system and uncertainties in time from first exposure. Therefore, confidence in the RfC is medium reflecting medium-to-high confidence in the principal study and low-to-medium confidence in the database.

It is important to consider the sources of uncertainties in the derivation of the RfC for Libby Amphibole asbestos. These include:

Measurement error in exposure assessment and assignment. The estimated exposure for each individual relied on self-reported employment history, which may be subject to recall error. Only data from post-1972 were used for RfC derivation, based on lack of measured exposure prior to this date; however, for certain occupations/tasks, no measurements were available until 1974 (Lockey, 1980). There is also uncertainty in the post-1972 data regarding asbestos content in other ore sources (Virginia, South Carolina and South Africa). Although Libby Amphibole asbestos was not used in the facility after 1980, industrial hygiene measurements collected after 1980 showed low levels of fibers in the facility. However, because the concentration of fibers in the workplace was near background after 1980, this exposure makes only a small contribution to an individual's cumulative exposure estimate. Similarly, any exposure to Libby Amphibole asbestos outside of the workplace is not likely to contribute significantly to cumulative exposure—only ~10% of workers reported bringing raw vermiculite home, and the majority showered and changed clothes before leaving the work place.

Radiographic assessment of localized pleural thickening. Conventional radiographs, rather than the more sensitive high-resolution computed tomography, were used to determine the health outcome. Discrete pleural thickening may be difficult to detect, leading to the potential for outcome misclassification. However, uncertainty in the prevalence of localized pleural thickening in each individual is considered minimal due to the use of a team of highly qualified chest radiologists evaluating the radiographic films and the use of consensus diagnosis.

Length of follow-up. Time from first exposure to x-ray was 23.2-32.7 years in the recommended sub-cohort. However, it is likely that the prevalence of localized pleural thickening may continue to show some increase with increased follow-up. In this case, the modeling approach may not accurately reflect the exposure-response relationship that would be seen with a longer follow-up time. Note that the likelihood that prevalence of localized pleural thickening may further beyond 30 years after first exposure is a principal rationale cited for the selection of a database UF of 10 for RfC derivation.

Background rate of localized pleural thickening. In the derivation of the RfC, a background rate of 1% for localized pleural thickening was used. Previous studies have reported a range of prevalence estimates (0.02% to 3.9%) in populations not known to be occupationally exposed to asbestos. However, in statistical modeling of the Marysville sub-cohort, uncertainty in the background rate of localized pleural thickening is very low. Both the fixed and estimated values are in the range of estimates above and the difference in the POD when the background rate is fixed at 1% versus when it is estimated (estimated background rate of 3.76%) is less than 3%.

Model Form. A number of model forms were explored in the initial stages of analysis (Appendix E), before selecting the log-logistic model. The log-logistic model is appropriate and widely used for epidemiologic data, and is easily interpreted. Further, BMCs and BMCLs estimated from other candidate models for the sub-cohort, as well as those obtained in modeling from the full cohort, were in a similar range to the selected model. A second model-based uncertainty is the choice of lag for cumulative exposure. The RfC derivation is based on the exposure lagged by 10 years, since this lag yielded the lowest AIC. However, if other lags (with similar AICs) are used, the difference in POD may fluctuate to be approximately 8% higher or approximately 40% lower. However, as the RfC is rounded to one significant digit, the choice of lag does not affect the estimated RfC.

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 Libby Amphibole asbestos exposure in humans is the cohort of workers employed at the vermiculite mining and milling operation near Libby, MT (see Section 4.1). No data were available pertaining to cancer incidence or mortality in the Marysville, OH cohort, and mortality and exposure data for other populations exposed to Libby Amphibole asbestos are very limited. Whitehouse et. al. (2008) provided detailed information on 11 mesothelioma cases among non-workers, but this information could not be used in exposure-response analyses for this risk

assessment, as there is no quantitative exposure information for these cases and no information on the population from which these cases arose.

The Libby worker cohort has been the focus of two epidemiologic investigations by NIOSH scientists. A database created by NIOSH in the 1980s contains demographic data, work history, and vital status at the end of 1981 for 1,881 workers at the vermiculite mine, mill, and processing plant in Libby, MT (see Section 4.1.1.1). Vital status follow-up was completed by NIOSH through 2006 using the National Death Index (NDI-Plus; Bilgrad, 1995). Nearly 54% of workers in the cohort (n = 1,009) had died by December 31, 2006.

EPA does not have sufficient biological information to select models for the epidemiology data on the basis of biological mechanism (Section 5). In this situation, EPA's practice is to investigate a range of model forms to determine how to best empirically model the exposure response relationship in the range of the observed data. In this case, possible exposure metrics were explored for model fit to the chosen models. The exposure metric options were selected to provide a range of shapes that was sufficiently flexible to allow for a variety of ways that time and duration might relate to cancer risk in the data being modeled. EPA then evaluated how well the models and exposure metric combinations fit the data being modeled. Metrics that did not fit the data well were rejected. For purposes of calculating a reasonable upper-bound on the risk per exposure EPA accounted for uncertainty in the choice of exposure metrics by using the exposure metric (among those of reasonable fit) that estimated the highest risk. This is explained in more detail below and in Sections 5.4.3-5.4.5. However, there are other uncertainties in the modeling of the epidemiological data that may impact the IUR and these are described in detail in Section 5.4.6.

Finkelstein (1985) provides an excellent summary of exposure-response modeling of epidemiologic data: "After identification of an occupational hazard one of the goals of occupational epidemiology is to quantify the risks by determining the dose-response relations for the toxic agent. In many circumstances little is known about the dose received by target tissues; the data available usually pertain only to exposure to various concentrations of the toxic material in the workplace. The calculation of dose requires additional physiological and chemical information relating to absorption, distribution, biochemical reactions, retention, and clearance. In asbestos epidemiology, the usual measure of exposure is the product of the concentration of asbestos dust in the air (fibers or particles per mL) and the duration of exposure to each concentration summed over the entire duration of exposure (years); this measure is the cumulative exposure."

Cumulative exposure has been the traditional method of measuring exposure in epidemiologic analyses of many different occupational and environmental exposures and was the exposure metric applied for to the risk of lung cancer mortality in the general asbestos evaluation

in the 1988 U.S. EPA. Two alternative approaches to developing exposure metrics to describe the effects of air concentrations of asbestos dust in the air on the risks of mortality have also been proposed. The first alternative was proposed by Jahr (1974) who studied silica-induced pneumoconiosis. He also suggested that exposures to occupational dusts could be weighted by the time since exposure yielding an exposure metric which gives greater weight to earlier exposures. Berry et al. (1979) subsequently suggested the application of exposure metrics that allowed for the clearance of dust or fibers by using a decay term on exposures. For the evaluation of mortality risk from mesothelioma, U.S. EPA (1988) used a different exposure metric than was used for lung cancer mortality which factored in the time since first exposure. It is important to note that different characterizations of ambient exposures may be reasonably expected to be associated with different endpoints (i.e. lung cancer or mesothelioma).

Most studies of asbestos-related mortality have evaluated either cumulative exposure, exposure concentration, or the duration of employment as exposure metrics. Many studies have been limited in the availability of detailed exposure data—especially at the individual level. In the Libby worker cohort data developed by NIOSH and used by the EPA in this assessment, detailed work histories, together with job-specific exposure estimates, allowed for the reconstruction of each individual's occupational exposure experience over time to define multiple exposure metrics. From this information-rich individual-level dataset from NIOSH, the EPA constructed a suite of the different metrics of occupational exposure which had been proposed in the asbestos literature or used in the U.S. EPA health assessment on general asbestos exposures (U.S. EPA, 1988). This suite of models was defined a priori to encompass a reasonable set of proposed exposure metrics to allow sufficient flexibility in model fit to these data. These exposure metrics were evaluated in analytic-regression models to test which exposure metrics were the best empirical predictors of observed cancer mortality and the better fitting models were advanced for consideration as the basis of the exposure-response relationship for the IUR. The types of exposure metrics evaluated were intended to allow for variations of the classic metric of cumulative exposure, allowing for more or less weight to be placed on earlier or later exposures. These simulated exposure metrics were derived mathematically to approximate underlying processes that are not well understood, and their fit is evaluated on the basis of maximizing the likelihood for the workers cohort and estimated parameters does not necessarily have biological interpretation (see Section 5.4.2.5 for details).

Exposure estimates for all exposure metrics were adjusted to account for the time period between the onset of cancer and mortality. The lag period defines an interval before death, or end of follow-up, during which, any exposure is excluded from the calculation of the exposure metric. Modeling of mesothelioma mortality included two additional exposure metrics: duration of exposure and the exposure metric including a cubic function of time (see Eq. 5-5), originally

proposed in Peto et al. (1982) and employed in derivation of the IUR for asbestos (U.S. EPA, 1988).

Analyses of mesothelioma mortality were conducted using a Poisson model with a Markov chain Monte Carlo (MCMC) Bayesian approach, whereas analyses of lung cancer mortality were conducted using the Cox proportional hazards model with time-varying exposures. There was one important limitation of the NIOSH JEM. 686 workers with "common laborer" job assignments and some workers with unknown job assignments hired between 1935 and 1959 were assigned the same average estimated exposure intensity for all unskilled jobs during the relevant calendar time period. That aspect of the JEM resulted in the misclassification of the exposure and made cumulative exposure metrics represent duration for the large part of the cohort. 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 (Section 5.4.3.3). As a result, EPA developed a sub-cohort analysis by dividing the whole cohort into two groups: those hired prior to 1960 and those hired after 1959. This removed all 686 cohort members with missing job category information and lessened the effect of estimates of early exposures where no air sampling data were available. For the sub-cohort of those hired after 1959, those two biggest problems were resolved: the assumptions of Cox models 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 sub-cohort is relatively small (n = 7, 2 deaths coded in ICD-10 and 5 deaths coded in ICD-9), but it was very similar rate of 24.7 per 100,000 person-years vs. 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 Libby Amphibole asbestos, as the Poisson distribution is an appropriate model for use with data that are counts of a relatively rare outcome, such as observed mesothelioma deaths in the Libby 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 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, Deviance Information Criterion (DIC) was used. DIC is used in

Bayesian analysis and is an analogue of AIC (Akaike Information Criterion [Burnham and Anderson, 2002]). Use of the DIC and AIC is standard practice in comparing the fit of non-nested models to the same dataset with the same dependent outcome variable but different independent covariates.

Two cumulative exposure metrics with decay provided two best model fits. Both metrics had a common 5-year half life, with lag times of either 10 or 15 years. In the sub-cohort hired after 1959, the DIC value for mesothelioma using the IRIS IUR (U.S. EPA, 1988) metric (Eq. 5-5) is substantially higher (DIC = 98.4) than for any of the metrics in Table 5-11, where the lowest DIC is 70.6. This difference of over 20 DIC units, is an indication that the model used for mesothelioma in the EPA (1988) IUR derivation (eq. 5-5), does not fit these data from the Libby work cohort, compared to other exposure metrics presented (Table 5-11). It should be noted that the data modeled here are very different from the data on which the IRIS assessment for asbestos (U.S EPA, 1988) is based—and one does not necessarily expect the same model to fit different datasets—this is why EPA goes through a process to determine the best fitting model in each case. One difference with IRIS IUR (U.S. EPA, 1988) modeling is that this analysis is based on individual-level data, whereas IRIS IUR (U.S. EPA, 1988) application was to aggregate data. Also, cohorts used in IRIS IUR (U.S. EPA, 1988) did not include cohorts exposed to Libby amphibole asbestos and Libby amphibole asbestos may be different from other types of asbestos. Alternately, the relative fit of this model may have been affected by uncertainties in the estimated exposure described in detail in Section 5.4.6.

As it is less likely that exposure during the last few years before death were contributory to the development of the cancer, the zero lag metrics were dropped from further consideration. All eight models retained for derivation of IUR include a decay half-life in the exposure metric. For the sub-cohort hired after 1959, the best fitting exposure metric was cumulative exposure with a 5 year half-life and a 15 year lag time with central estimate for the β of 2.07E-4 with 95% UCL 3.42E-4.

6.2.4. Unit Risk Estimates for Mesothelioma Mortality

The increased risk of mesothelioma mortality attributable to continuous fiber exposure was estimated using a life-table procedure based on the general U.S. population. The life-table procedure involved the application of the estimated Libby Amphibole asbestos toxicity to a structured representation of the general U.S. population in such a manner as to yield age-specific risk estimates for cancer mortality in the presence or absence of exposure to Libby Amphibole asbestos (Section 5.4.5; Appendix G).

A default linear low-dose extrapolation below the point of departure (POD) was used because the mode of action by which Libby Amphibole asbestos causes mesothelioma is largely

unknown. The lower limit on the effective concentration (LEC_{01}) was determined to be 0.245 fibers/cc, which yielded a unit risk for mesothelioma mortality of 0.053 per fiber/cc (POD of 1% divided by the LEC_{01}).

The value of the effective concentration that would correspond to the measure of central tendency is the EC_{01}. This value is used in the derivation of a combined risk of mesothelioma and of lung cancer. The EC_{01} was determined to be 0.406 per fiber/cc, which when divided into a POD of 1% and scaled (by 70/54) to encompass the whole lifespan, gives a lifetime central estimate value of 0.032 per fiber/cc.

For mesothelioma, the undercounting of cases (underascertainment) is a particular concern given the limitations of the ICD classification systems used prior to 1999. In practical terms, this means that some true occurrences of mortality due to mesothelioma are missed on death certificates and in almost all administrative databases such as the National Death Index. Even after introduction of special ICD code for mesothelioma with introduction of ICD-10 in 1999, detection rates are still imperfect (Pinhiero et al., 2004; Camidge et al., 2006) and the reported numbers of cases typically reflect an undercount of the true number. Kopylev et al. (2011) reviewed the literature on this underascertainment and developed methods to account for the likely numbers of undocumented mesothelioma deaths.

To compensate for mesothelioma underascertainment attributable to ICD coding, the mesothelioma mortality unit risk was further adjusted following the analysis of Kopylev et al. (2011). The adjusted mesothelioma central (MLE) risk, corresponding to the best-fit metric, was 0.044 per fiber/cc, and the adjusted mesothelioma mortality unit risk was 0.074 per fiber/cc. The adjusted mesothelioma mortality unit risks from all eight exposure parameterization models with adequate fit produced a range of unit risk values (Table 5-14) from 0.044 to 0.122. The second best fit metric, cumulative exposure with 10 year lag and 5-year decay, corresponded to the highest unit risk (details are in Section 5.4.5.1.1).

6.2.5. Modeling of Lung Cancer Exposure-Response

All multivariate extended Cox models were fit to the sub-cohort hired after 1959 with covariates for sex, race, and date of birth, and exposure. Exposure for each of the 40 exposure parameterizations was calculated independently and fit of these exposure metrics was evaluated one at a time. As the exposure-response models cannot strictly be considered to be nested, a standard measure of fit, the AIC (Burnham and Anderson, 2002), was used for comparison of model fit with smaller values of AIC, indicating better goodness of fit. Of the 40 exposure-response metrics, 14 demonstrated an adequate fit to the data as measured by the overall model fit with the likelihood ratio test ($p < 0.05$) as well as having statistically significant exposure metrics ($p < 0.05$). However, only the nine models that demonstrated adequate model and

exposure metric fit and incorporated a lag period to account for cancer latency were considered further in the development of the IUR (Table 5-19).

Lagging exposure by 10 years was a better predictor of lung cancer mortality compared to other lags. As it is less likely that exposure during the last few years before death were contributory to the development of the cancer, the zero lag metrics were dropped from further consideration. The residence time-weighted cumulative exposure, both with and without decay of the exposure metric, did not fit these lung cancer mortality data well compared to the other models (Table 5-13); this form of exposure metric does not demonstrate evidence of an empirical fit to these epidemiologic data.

The model with the smallest AIC was for cumulative exposure with a 10-year half-life for decay and a 10-year lag for cancer latency. This multivariate model controlled for age, gender, race, and date of birth within the occupational cohort. The extended Cox model with time-varying exposures estimated a slope (beta) of 1.26×10^{-2} per fiber/cc-year based on a 365-day year, and the 95th percentile upper bound was 1.88×10^{-2} per fiber/cc-year. The p-value for the Libby Amphibole asbestos regression coefficient (slope) was <0.001. The slopes and confidence interval for the other exposure metrics, which had similar fits to these data are reported in Table 5-14. Uncertainty in the choice of the exposure metric (cross-metric uncertainty) is considered in the derivation of the final unit risk (see details in Section 5.4.5.3), representing the range of unit risks that are derived from these similarly fitting metrics. The model results which were ultimately selected to reflect the upper-bound among the range of results were based on the cumulative exposure with a 10-year lag exposure metric (CE10). The extended Cox model with time-varying exposures estimated a slope (beta) of 5.28×10^{-3} per fiber/cc-year based on a 365-day year, and the 95th percentile upper bound was 1.00×10^{-2} per fiber/cc-year.

6.2.6. Unit Risk Estimates for Lung Cancer Mortality

The increased risk of lung cancer mortality attributable to continuous fiber exposure was estimated using a life-table procedure based on the general U.S. population. The life-table procedure involved the application of the estimated Libby Amphibole asbestos-specific toxicity to a structured representation of the general U.S. population in such a manner as to yield age-specific risk estimated for cancer mortality in the presence or absence of exposure to Libby Amphibole asbestos (Section 5.4.5; Appendix G).

The nine exposure-response models retained in Table 5-18 all had reasonably similar goodness of fits. No single model stands out as clearly statistically superior; however, there is a range of quality of fit within the set that could be considered to have adequate fit. The lung cancer mortality unit risks are shown in Table 5-19.

Using the results of the exposure model with the lowest AIC value (i.e., cumulative exposure with a 10-year half-life for decay and a 10-year lag for cancer latency) alone, the LEC_{01} for the adult-only exposures was determined to be 0.333 fibers/cc. This yields an adult-based unit risk of lung cancer mortality of 0.0300 (POD of 1% divided by the LEC_{01}). This estimate was then scaled by 70/54 to encompass the whole lifespan; it yielded a lifetime unit risk of 0.0389 per fiber/cc. The value of the concentration that would correspond to the measure of central tendency was based on the EC_{01} rather than LEC_{01}. The EC_{01} for the adult-only exposures was determined to be 0.499 per fiber/cc, which, when divided into a POD of 1%, yielded an adult-based central estimate for lung cancer mortality of 0.0200. This estimate was then scaled by 70/54 to encompass the whole lifespan to, yielded a lifetime central estimate of 0.0260 per fiber/cc.

Using the results of the exposure model based on cumulative exposure with a 10-year lag for cancer latency, the LEC_{01} for the adult-only exposures was determined to be 0.191 fibers/cc, yielding an adult-based unit risk of lung cancer mortality of 0.0524 (POD of 1% divided by the LEC_{01}). When scaled by 70/54 to encompass the whole lifespan, it yielded a lifetime unit risk of 0.0679 per fiber/cc. The value of the risk that would correspond to the measure of central tendency involves the EC_{01} rather than the LEC_{01}. The EC_{01} for the adult-only exposures was determined to be 0.325 per fiber/cc, which, when divided into a POD of 1%, yielded an adult-based central estimate for lung cancer mortality of 0.0308. This estimate was then scaled by 70/54 to encompass the whole lifespan to, yielded a lifetime central estimate of 0.0399 per fiber/cc.

The resulting unit risks in Table 5-19 ranged from 0.0260 to 0.0679 fibers/cc. This shows that the unit risk (i.e., 0.0389 per fiber/cc) based on the exposure metric with the lowest AIC value (i.e., cumulative exposure with a 10-year half-life for decay and a 10-year lag for cancer latency) is in the center of this range and is thus statistically robust. However, because this estimate is in the middle of the range it does not capture the uncertainty across metrics with similar goodness of fit. The model results which were ultimately selected to reflect the upper-bound among the range of results were based on the CE10 exposure metric. The CE metric with a 10 year lag does fit these data, is a simpler and more straightforward metric and has an extensive tradition of use in the epidemiologic literature and in the practice of risk assessment.

6.2.7. IUR Derivation Based on Combined Mesothelioma and Lung Cancer Mortality from Exposure to Libby Amphibole Asbestos

When risks are combined, it is important to understand several concepts that are pertinent to the evaluation and comparison of the cancer-specific mortality unit risks that will be combined. First, there is statistical uncertainty in the potency estimate within the exposure

response model defined by each exposure metric. This within metric uncertainty is accounted for in the confidence interval on slope. Next, there is an uncertainty in the choice of metrics for developing IUR (cross-metric uncertainty). Finally, when unit risks corresponding to metrics are chosen accounting for uncertainty, these are statistically combined into IUR. Details are provided in Section 5.4.5.3.

Table 6-1 shows cancer-specific unit risks as well as combined risk of mesothelioma and lunch cancer. The IUR value of 0.169 per fiber/cc accounts for important quantitative uncertainties in the selection of the specific exposure metric that may have remained in an IUR that might have been based on the best fitting exposure models alone. Additional uncertainties are discussed in detail in Section 5.4.6.

Table 6-1. Reasonable upper bound and lowest information criteria estimates of central risks and unit risks, per fibers/cc, for mesothelioma mortality, lung cancer mortality, and the IUR for the combined mortality risk from mesothelioma and lung cancer

Model	Mesothelioma		Lung cancer		Combined mesothelioma and lung cancer	
	Central estimate	Unit risk	Central estimate	Unit risk	Central estimate	IUR
Reasonable upper bound[a]	0.075	0.122	0.040	0.068	0.115	0.169
Lowest information criteria[b]	0.044	0.074	0.026	0.040	0.070	0.103

[a] For mesothelioma, the selected model parameterized exposure as cumulative exposure with exponential decay half-life of 5 years and a 15-year lag. For lung cancer, the selected model parameterized exposure as cumulative exposure without decay and a 10 year lag.

[b] For mesothelioma, the selected model parameterized exposure as cumulative exposure with exponential decay half-life of 5 years and a 10-year lag. For lung cancer, the selected model parameterized exposure as cumulative exposure with exponential decay half-life of 10 years and a 10-year lag.

6.2.7.1. *Comparison with Other Published Studies of Libby Workers Cohort*

For lung cancer, two alternative analytic approaches to the use of EPA's extended Cox proportional hazards models could have been used for the calculation of a unit risk of lung cancer mortality. All of the choices are based on different analyses of the Libby worker cohort; however, inclusion criteria differ among the analyses as does the length of mortality follow-up. Each of the two approaches has two options to estimate the slope of the exposure-response relationship in place of the regression slope estimated from the Cox proportional hazards model and follow through with the same life-table procedure to calculate the unit risk of lung cancer mortality.

The first approach would be to use the published categorical results based on Sullivan (2007). The first option in this approach was for EPA to estimate a slope to those categorical data. The second option was to use the slope estimated in a published re-analysis of categorical data of Sullivan (2007) cohort by Berman and Crump (2008). The second approach would be to use the published regression results of other researchers who modeled the underlying continuous data. The first option in this approach was to use the slope estimated by Larson et al. (2010a). The second option was to use the slope estimated by Moolgavkar et al. (2010).

For comparison purposes, the lung cancer unit risk from these alternatives are computed, however, as all analyses are based upon different subsets of the Libby workers cohort and used different analytic methods, the results are not necessarily interchangeable. Table 6-2 summarizes lung cancer risks derived from these studies.

Table 6-2. 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	Lung cancer cases/N	Slope per fibers/cc-years $\times 10^{-3}$ (calendar year)	Risk based on UCL on the slope (per fiber/cc)
This assessment	Hired post-1959	32/880	5.8	0.068
Sullivan, 2007	Full cohort; still employed post-1959 White males	99/1672	4.2	0.037
Moolgavkar et al., 2010[a]	Full cohort, White males	95/1662	1.69	0.011
Berman and Crump, 2008[a]	Full cohort, White males	93/1672	3.96	0.079[b]
Larson et al., 2010	Full cohort	98/1862	1.61	0.010

[a] Reanalysis of Sullivan (2007)
[b] Obtained from confidence interval that also addresses model uncertainty (details in Section 5.4.5.3.1).

For mesothelioma, neither of the approaches used by McDonald et al. (2004), Sullivan (2007), nor Larson et al. (2010a) could have been appropriately used for the unit risk of mesothelioma as they are not based on absolute risk metrics of association, and the current assessment considered the relevant metric of association to be the absolute risk. Berman and Crump (2008) did not evaluate risk of mesothelioma. Moolgavkar et al. (2010) did use an absolute risk model for mesothelioma. These results are summarized in Table 6-3. The upper

bound results for the full cohort presented by Moolgavkar et al. (2010) are about 80% of the EPA IRIS (1988) estimate of mesothelioma slope factor in a similar RTW-type metric, leading to approximately 80% estimate of the mesothelioma unit risk, as dependence is linear in the mesothelioma slope factor (Eq. 5-5). This is very close to this assessment's estimate based on the analyzed sub-cohort, which is also about 80% of the EPA IRIS (1988) estimate of mesothelioma risk. Duration of employment is the best metric for the full cohort, and it does not support dose-response estimation.

Table 6-3. Mesothelioma 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

Mesothelioma analysis	Cohort definition	Mesothelioma cases/N	Mesothelioma risk (absolute risk model) (per fiber/cc)
This assessment	Hired post-1959	7/880	Upper Bound = 0.12 Central = 0.08
Sullivan, 2007	Full cohort; still employed post-1959; White males	15/1672	No estimates of absolute risk
Moolgavkar et al., 2010[a]	Full cohort; White males	15/1662	Upper Bound ≈ 0.13 Central ≈ 0.08
Larson et al., 2010	Full Cohort	19/1862	No estimates of absolute risk
Berman and Crump, 2008[a]	No estimates provided		

[a] Reanalysis of Sullivan (2007).

6.2.8. Uncertainty in the Cancer Risk Values

It is important to consider the uncertainties in the derivation of the mesothelioma and lung cancer mortality risks in this assessment in the context of uncertainties in animal-based health assessments. This assessment does not involve extrapolation from high dose in animals to low dose in humans. The current assessment is based on a well-documented and well-studied cohort of workers with adequate years of follow-up to evaluate mesothelioma and lung cancer mortality risks with PODs within the range of the data. The discussions in Section 5.4.6 explore uncertainty in the derivation of the IUR in order to provide a comprehensive and transparent context for the resulting cancer mortality risk estimates.

The summary below includes likely one–sided uncertainties (biases) associated with the derivation of the IUR in order to provide a context for the resulting cancer risk estimates.

The sources of uncertainty that could lead to a likely underestimation of the cancer risk value include the following:

- *Use of historical PCM exposure measurements*. As asbestos was a contaminant of vermiculite that was the primary object of production, mine and dry and old wet mill ambient air may have contained material other than asbestos that could have contributed to fibers counted by PCM. Therefore, it is possible that exposure estimates for some or possibly a large portion of the cohort are overestimated, and, therefore, the resulting IUR may be underestimated**.**

- *Measurement error in exposure assessment and assignment*. Results from the analyses of the lung cancer mortality in the full cohort compared to the sub-cohort hired after the 1959 sub-cohort were attenuated as much as 2-6 times. Job assignments were unknown for 686 of the 991 workers employed from 1935 to 1959 (69% of the cohort for this time period). The majority of these workers were assigned the same exposure concentration for all years without job category information. Examination of the post-1959 cohort removes this significant source of exposure misclassification.

- *Limited length of follow-up.* The IUR for mesothelioma mortality could be larger than was estimated from existing data, since latency of mesothelioma can be as long as 60 years. The maximum length of follow-up was 46 years in this cohort. The magnitude of underestimation would depend on the relationship between the number of additional deaths and the increase in person-years.

- *Use of life-tables to calculate the IUR based on cancer mortality*. The life-table procedure computes the extra risk of death from birth up to 85 years of age. This cut-off at age 85 ignores a small additional risk of lung cancer mortality among a small percentage of people who have a higher background risk because of the increase in lung cancer risk that is seen with increasing age. The lung-cancer mortality unit risk based on the LEC_{01} would be somewhat larger, on the order of 5-10%. On the other hand, the additional mesothelioma mortality risk, if the life-tables were extended to account for longer life spans, would be about 3%

- *Small number of women and ovarian cancer*. While asbestos is causally associated with increased risks of ovarian cancer (Straif et al., 2009), there were only 84 women in the whole cohort, and there were no deaths from ovarian cancer among 24 total deaths. The lack of observed ovarian cancer in this cohort may be a function of the limited number of female deaths in the cohort allowing for the possibility that exposure to LAA could result in increased risk of ovarian cancer. However, it was not possible to estimate the magnitude of this underestimation on the total cancer risk.

- *Dependent competing risks.* Competing risk of mortality from other diseases related to exposure may have resulted in underestimates of the risk of mortality from either

mesothelioma or lung cancer. The mean length of follow-up for the Libby workers who died of mesothelioma was to 30.1 years, and evidence exists (Suzuki, 2001; Bianchi and Bianchi, 2009) that early deaths from other exposure-related causes could have precluded an individual's risks of death from mesothelioma. However, it was not possible to estimate the magnitude of this effect on the total cancer risk.

The source of uncertainty that could lead to a likely overestimation of the cancer risk value:

- *Effect modification.* It is theoretically possible that the risk of lung cancer mortality estimated in this assessment is a reflection of a positive synergy between smoking and asbestos, and that the adverse effect of Libby Amphibole asbestos among the potentially nonsmoker workers has been overestimated. The IUR for lung cancer mortality estimated herein, and the combined lung cancer and mesothelioma IUR would then be health protective for any population that had a lower prevalence of smoking than that of the Libby worker cohort.

6.3. APPLICATION OF THE LIBBY AMPHIBOLE ASBESTOS RFC AND IUR

6.3.1. Sites and Materials

This Libby Amphibole asbestos specific assessment is based on the evaluation of worker cohorts, exposed to asbestos from a single mine in Libby, MT**,** and is intended to allow for estimates of the risk due to exposure to the asbestos fibers from that mine, or exposures to asbestos fibers that arise from the management or use of the vermiculite ore and exfoliated vermiculite from this mine. Therefore, it is appropriate to apply the Libby Amphibole asbestos-specific RfC and/or IUR to sites which are believed to have been contaminated by these materials when assessing risk from the amphibole fibers present from this contamination. This may include sites where the ore was shipped or handled, where the vermiculite was exfoliated and further processed, facilities which in other ways shipped or handled the exfoliated vermiculite, where products containing the raw or exfoliated vermiculite were present, the consumer products themselves (e.g., VAI) and any waste streams from the above processes which contain vermiculite and the related LAA-fibers. The assessment was derived from PCM measurements taken at the Libby occupational sites and the mixture of minerals found in those measurements. It does not estimate the risk attributable to specific subsets of those fibers whether based on size, shape, or mineral composition other than the limitations on size and shape reflected in the PCM methodology and counting rules. As detailed in Section 2, the amphibole asbestos present in the mine, ore and expanded vermiculite, do not fit cleanly into a single category of nomenclature for amphibole minerals. Most Libby Amphibole fibers are classified

as winchite (84%), with lesser amounts of richterite (11%) and tremolite (6%), based on the nomenclature proposed by Leake et al. (1997) (Meeker et al., 2003). There are also trace amounts of magnesioriebeckite, edenite, and magnesio-arfvedsonite present in Libby Amphibole asbestos (Meeker et al., 2003). Within the 30 samples taken from the mine the proportion of these minerals differed between samples (Meeker et al., 2003) and the relative proportions of these species may have varied over time (as ore from different locations were processed). This assessment estimates the risk of exposure to the varying range of mineral fiber mixtures that result from material originating from the geological deposit, recognizing there is variation and uncertainty as to variations in the exposure to the underlying cohort and complex variation in settings to which these estimates will be applied.

6.3.2. Exposure Units for Libby Amphibole Asbestos

As with the IRIS assessment for asbestos (U.S. EPA, 1988), the RfC and IUR specific to Libby Amphibole asbestos are presented here as fibers-yr/cc exposure, where exposure measurements are based on analysis of air filters by Phase Contrast Microscopy (PCM). For example, analysis of mortality data presented in Section 5 for both mesothelioma and lung cancer used the available measurements of worker exposure for the facilities in Libby, MT. From 1968 forward, exposure measurements were available for all work environments as fiber counts by PCM analysis. Between 1960 and 1968, fiber counts were estimated, and a dust-to-fiber conversion ratio was applied to exposures in the dry mill to generate estimated fiber exposures in PCM units. Therefore, the IUR is given in units based on PCM fiber analysis and is intended to estimate the risk per exposure to PCM-countable Libby amphibole asbestos fibers.

Early PCM analytical techniques did not have the same resolution as current analytical methods, and it is understood that PCM data for the majority of the exposures characterized for the Libby workers would likely have a width resolution of 0.4-0.44 μm (Skinke, 1980; Amandus et al., 1987a; WHO, 1980). Therefore, as with the IRIS assessment for asbestos (U.S. EPA, 1988), the dimensions of the PCM fibers for the Libby Amphibole asbestos unit risk are defined as fibers ≥5 μm in length with an aspect ratio of 3:1 or greater and a width >0.4 μm.

Environmental air sampling for asbestos is now often analyzed by transmission electron microscopes (TEM) to confirm that the fibers viewed are asbestos, and often it is used to identify the mineralogy of the fiber. Although some historical data do exist providing TEM analysis of airborne fibers from the Libby, MT mill operation (McDonald et al., 1986a; Langer et al., 1974), these data are not sufficient to provide an alternative set of exposure measurements in TEM units for the Libby worker cohort, or provide a PCM to TEM conversion across the various work environments.

Different sampling environments and varied site conditions may pose the potential for airborne fibers from various materials. Because of that, it is expected that for many environmental risk assessments conducted now and in the near future, measures of exposure may be done with methods such as TEM and then adjusted through fiber-counting rules to estimate the number of PCM-countable asbestos fibers. Site-specific environmental conditions should be considered in determining how to best identify PCM-countable asbestos fibers in relevant air samples for exposure assessments used in conjunction with this health assessment to yield estimates of risk.

6.3.3. Applications to Early Lifetime and Partial Lifetime Environmental Exposure Scenarios for IUR

The life-table analysis in the IRIS assessment for asbestos (U.S. EPA, 1988) predicts risk increases as the age of first exposure decreases. It was recommended that this life-table analysis be consulted when assessing partial lifetime exposures (U.S. EPA, 1988). In 2009, EPA provided guidance for calculating risk estimates for less-than-lifetime exposures based on the 1988 life-table analysis (U.S. EPA, 2009). The age-at-onset of exposure and duration-dependent unit risks reflect the influence of the time cubed function in the mesothelioma model (eq. 5-5) (U.S. EPA, 1986; 1988; 2009) used in the 1988 assessment. Because the time-cubed model, or parameterization of exposure metrics, did not fit the data for mesothelioma mortality from exposure to Libby Amphibole asbestos, the approach to estimating risk of partial life exposure recommended by EPA when applying the IRIS IUR for asbestos (U.S. EPA, 1988) is not appropriate when applying the Libby Amphibole asbestos-specific IUR.

The Libby Amphibole asbestos-specific unit risk derived in this assessment is a combined risk of lung cancer and mesothelioma, each with its own adjustment for uncertainty in metrics. The life table analyses for Libby Amphibole asbestos do not predict greater risk from early-life exposures. Thus this assessment recommends that estimates of the risks of less-than-lifetime exposures be computed by simple calculations of average lifetime exposure concentration multiplied by IUR. This recommendation is consistent with standard Superfund guidance (U.S. EPA, 1986b), where exposures are estimated, averaged across a lifetime exposure, and the IUR simply applied to calculate excess cancer risk (U.S. EPA, 2005). The weight of evidence does not support a mutagenic mode of action for Libby Amphibole asbestos carcinogenicity. Therefore, according to EPA's *Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens* (U.S. EPA, 2005b), the application of the Age-Dependent Adjustment Factors (ADAFs) is not recommended.

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APPENDIX A. SUMMARY OF EXTERNAL PEER REVIEW AND PUBLIC COMMENTS AND DISPOSITION

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

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

July 14, 2010

Prepared by:
U.S. Environmental Protection Agency
Region 8
Denver, CO

With Technical Assistance from:

SRC, Inc.
Denver, CO

APPROVAL PAGE

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

_____ _____

Bonita Lavelle
U.S. EPA, Region 8

Date

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

1.0 INTRODUCTION

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

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

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

2.0 METHODS

2.1 Data Overview

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

Most of the samples that have been collected have been analyzed for asbestos by transmission electron microscopy (TEM) using either ISO 10312 (ISO 1995) or AHERA (AHERA 1986)

counting rules, as modified by site-specific modifications as described in modifications forms LB-000016 and LB-000031 (provided in Appendix B). In all cases, the data that are recorded during the analysis of a sample include the length, width and aspect ratio (length/width) of all particles that meet the counting rules specified for the analysis.

2.2 Data Presentation

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

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

3.0 RESULTS

3.1 Data Validation

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

3.2 Consolidated Data Set

Originally, most samples of air at Libby were analyzed using a counting rule based on a fiber aspect ratio of 5:1. More recently, most air samples are counted using an aspect ratio rule of 3:1. Because this rule has varied over time, Libby-specific laboratory modifications LB-000016 and

LB-000031 (see Attachment 1) were created to document the historic modifications and instructions that laboratories have followed throughout the Libby program.

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

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

3.3 Frequency of Complex Structures

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

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

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

3.4 Comparisons of Stratified Data Sets

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

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

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

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

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

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

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

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

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

4.0 SUMMARY

Particle size data are available for nearly 30,000 LA structures that have been observed in air samples collected at the Libby Asbestos Superfund site. Most (about 80%) LA particles are fibers, with less than 20% complex structures (bundles, clusters, or matrices). LA particle

lengths typically range from a little less than 1 um up to 20-30 um, and occasionally higher. The average length is about 7 um. Thicknesses typically range from about 0.1 um up to about 2 um, with an average of about 0.5 um. Although some variations occur, particle size distributions are generally similar between different locations and between different types of samples.

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APPENDIX A

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

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

See attached compact disc.

Table A-1. Structure Type Assignments

Counting Rule	Structure Type	Structure Class (a)	Fiber?	Notes
AHERA/ASTM	B	B		
	C	C		
	F	F	Y	
	M	(F)	Y	
	MD	(F)	Y	**recorded using ISO structure type, assumed to be disperse matrix
	MD11	(F)	Y	**recorded using ISO structure type, assumed to be disperse matrix
	MF	(F)	Y	**recorded using ISO structure type, assumed to be matrix w/fiber protrusion
ISO 10312	B	B		
	C	C		**recorded using AHERA structure type, assumed to be compact cluster
	CB	B		
	CF	F	Y	
	DM10	F	Y	**assumed to be fiber within a matrix (MF)
	F	F	Y	
	FM	F	Y	**assumed to be fiber within a matrix (MF)
	M	M		**recorded using AHERA structure type, assumed to be compact matrix
	MB	B		
	MB10	B		**assumed to be bundle within a matrix (MB)
	MC	M		**assumed to be a compact matrix
	MC+0	M		
	MC0	M		**assumed to be a compact matrix
	MC10	M		**assumed to be a compact matrix
	MD	F	Y	**assumed to be fiber within a matrix (MF)
	MD10	F	Y	**assumed to be fiber within a matrix (MF)
	MD11	F	Y	**assumed to be fiber within a matrix (MF)
	MF	F	Y	
	MF1	F	Y	**assumed to be fiber within a matrix (MF)
	MF10	F	Y	**assumed to be fiber within a matrix (MF)
	MF2	F	Y	**assumed to be fiber within a matrix (MF)
	ND10	F	Y	**typo MD10; assumed to be fiber within a matrix (MF)

** Structure Type is not valid

(a) For matrices recorded by AHERA counting rules, assumed that all matrices had fiber protrusions.

APPENDIX B

LIBBY-SPECIFIC LABORATORY MODIFICATION FORMS

LB-000016
LB-000031

Table 1. Air Sample Collection Programs

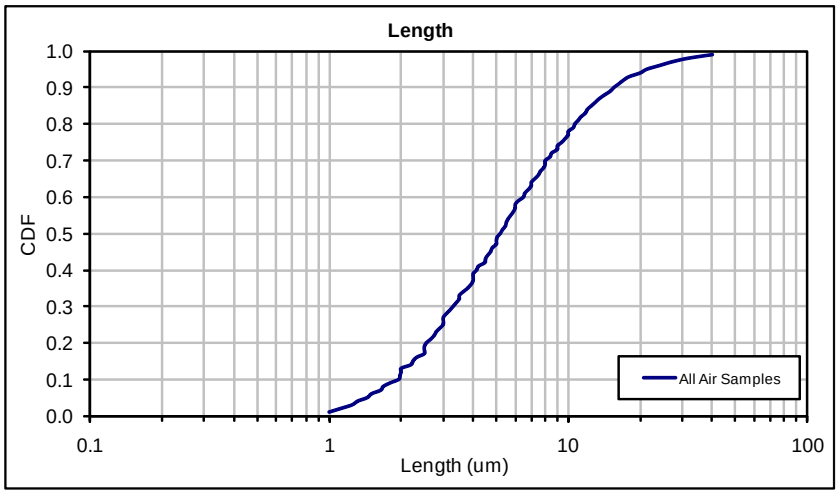
Program	Program Description	Program Date Range	Sampling and Analysis Plan (s)	Number of LA Structures [(a)]
Phase 1	Initial investigation sampling to assess nature and extent of potential contamination. Includes source areas (e.g., screening plant, export plant), commercial buildings, and residential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

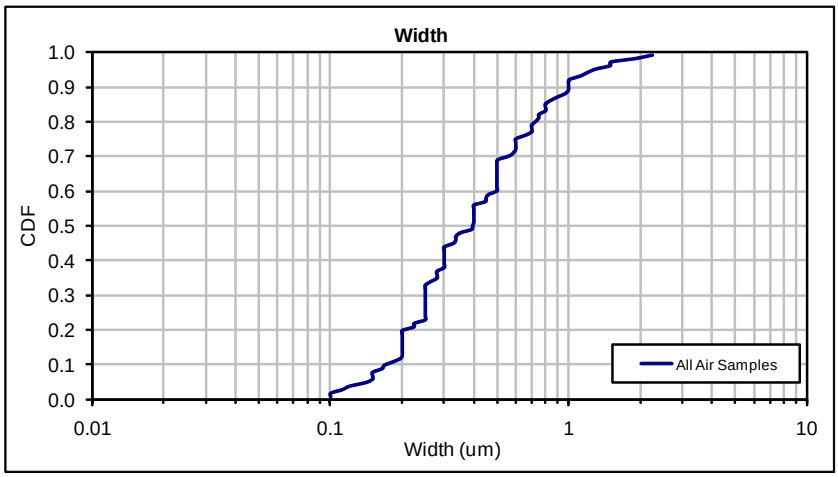
(a) Restricted to LA structures recorded in accordance with a 5:1 aspect ratio rule.

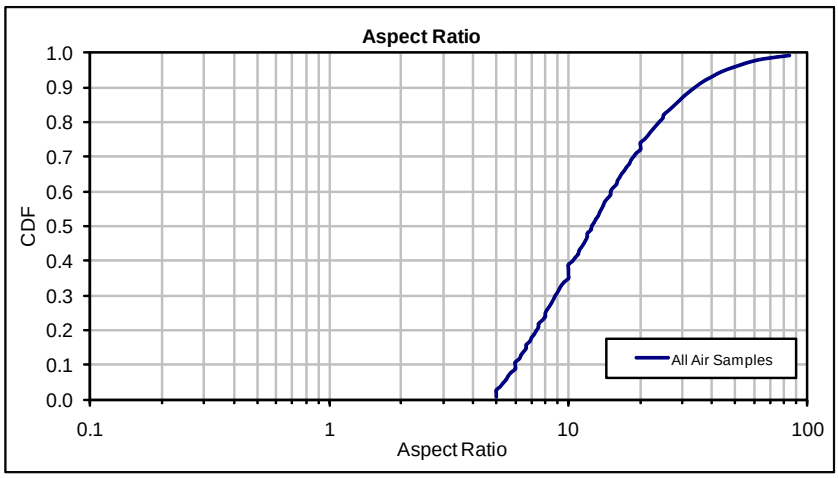
LA structure counts are based on a download of Libby 2DB performed on 12-8-09 and the Libby OU3 DB on 2-9-10.

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

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





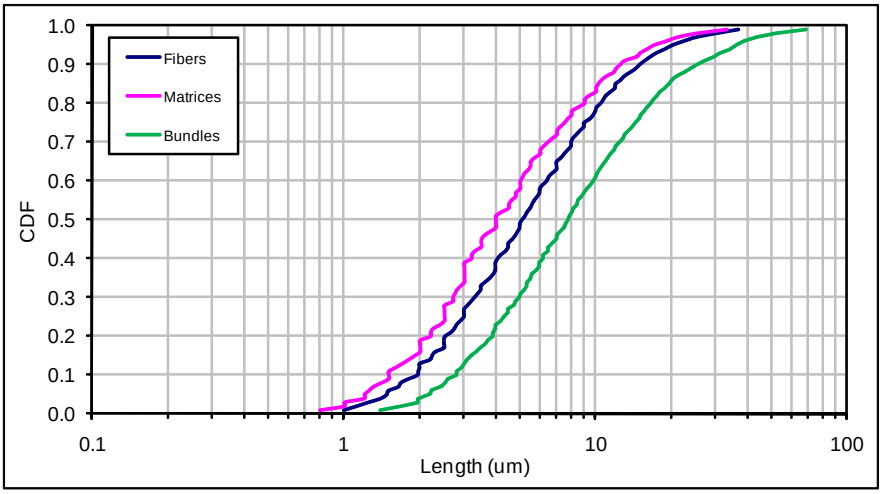


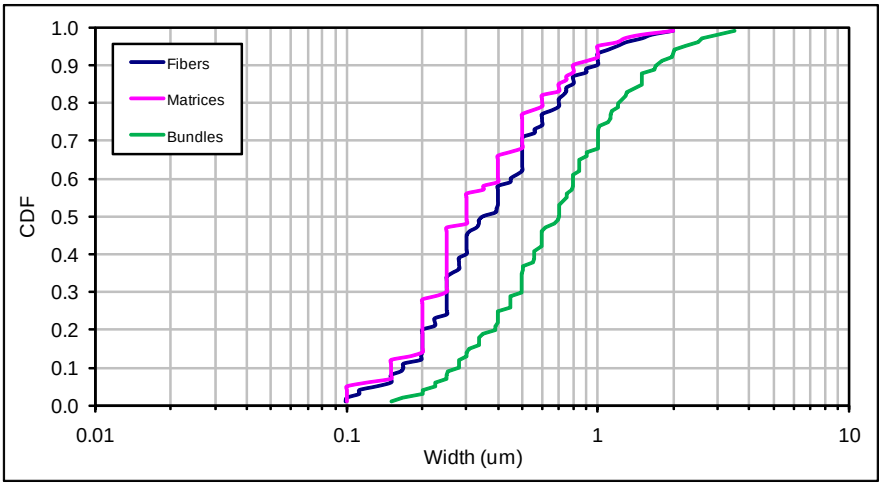
Data are based on a download of Libby 2DB performed on 12-8-09 and the Libby OU3 DB on 2-9-10.

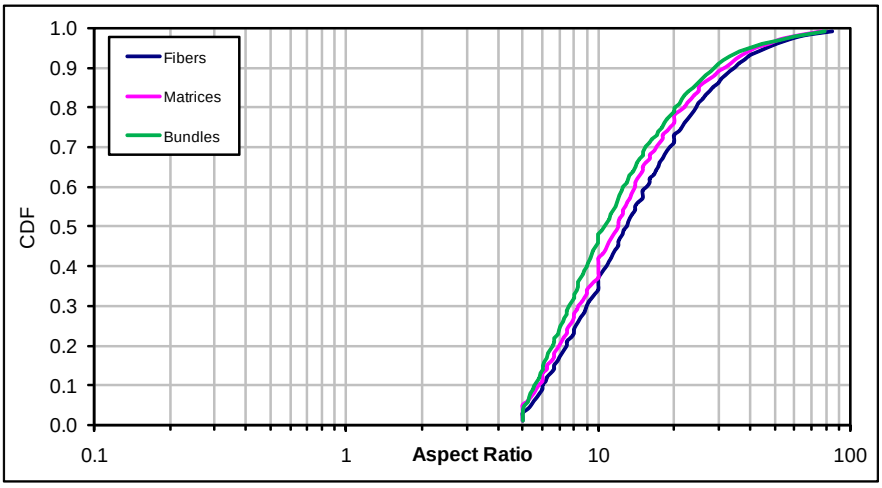
All Air Samples

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

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





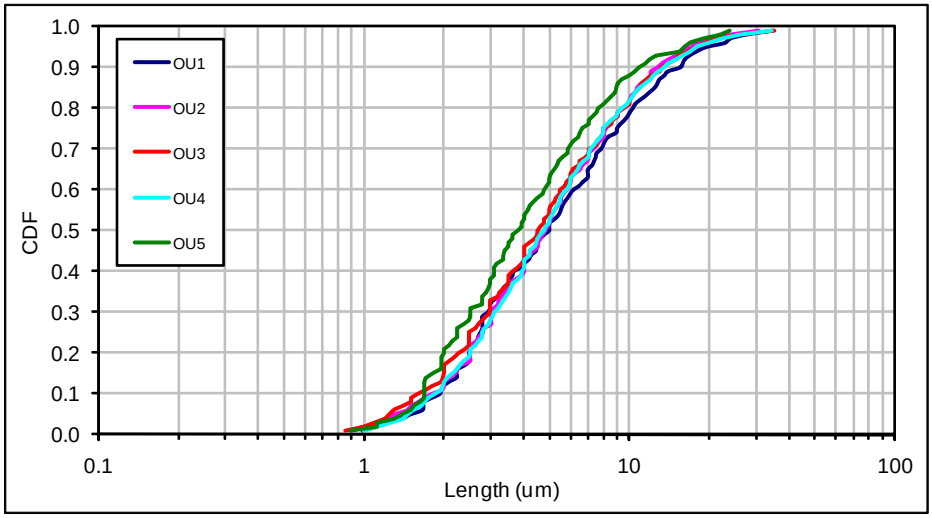


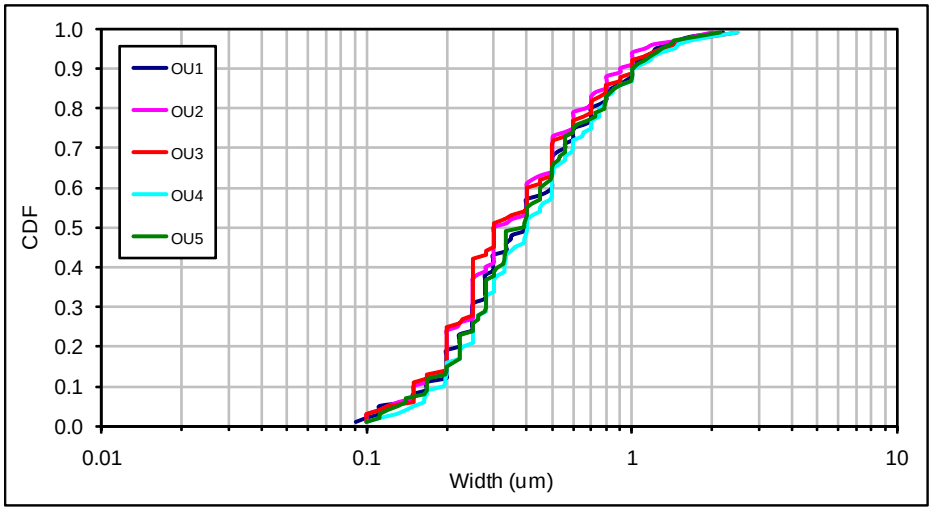
Data are based on a download of Libby 2DB performed on 12-8-09 and the Libby OU3 DB on 2-9-10.

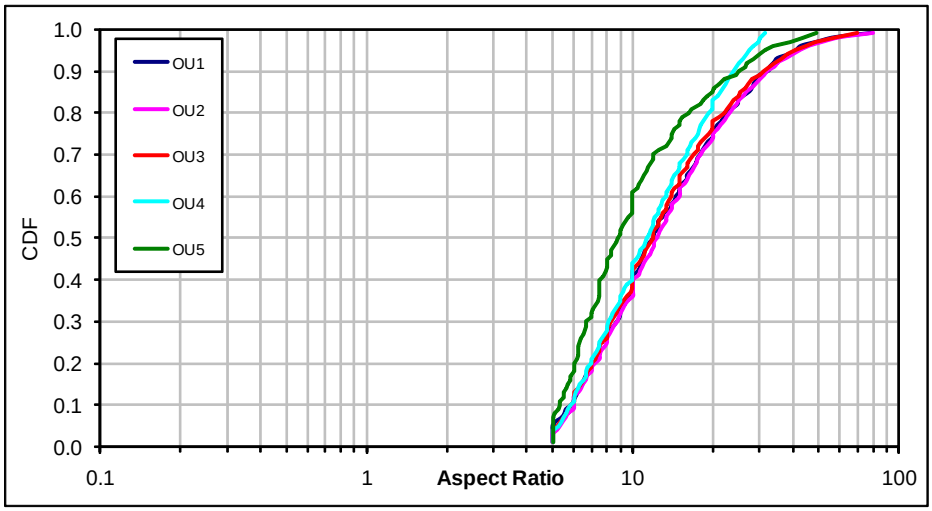
Structure Type	N Structures
F	23,933
B	2,366
M	3,150

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

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



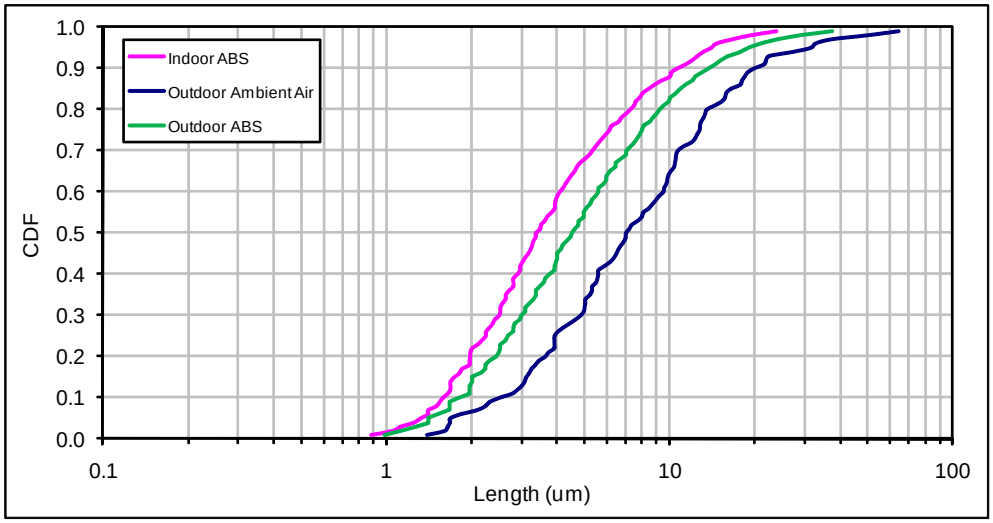


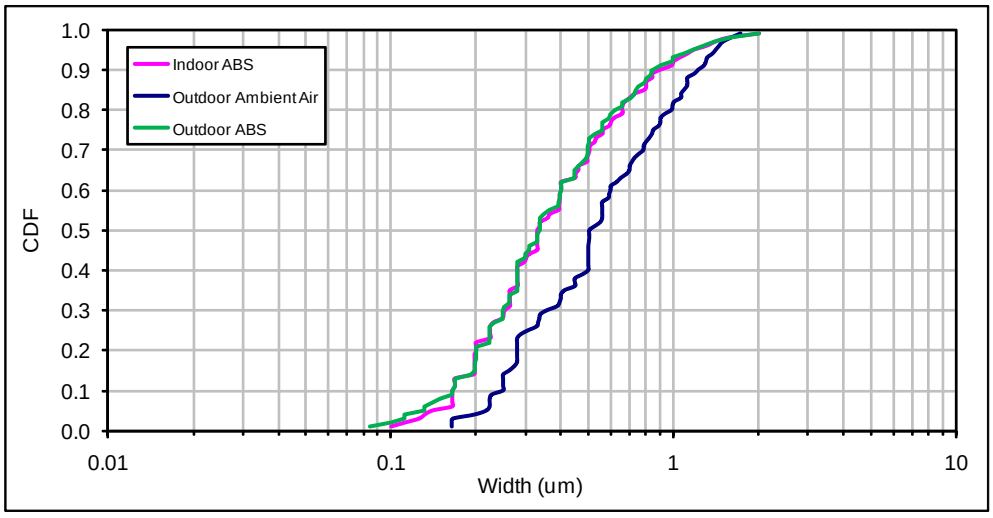


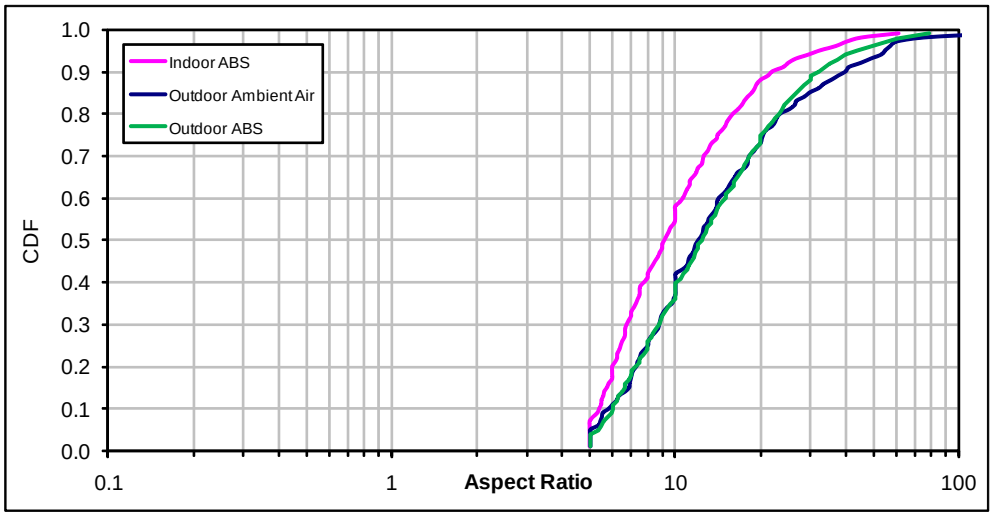
Data are based on a download of Libby 2DB performed on 12-8-09 and the Libby OU3 DB on 2-9-10.

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

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



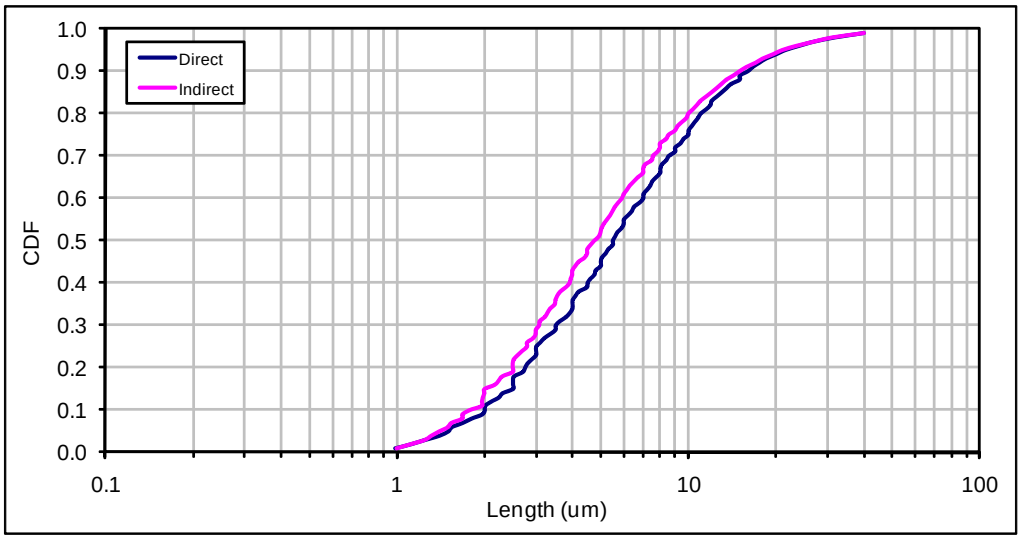


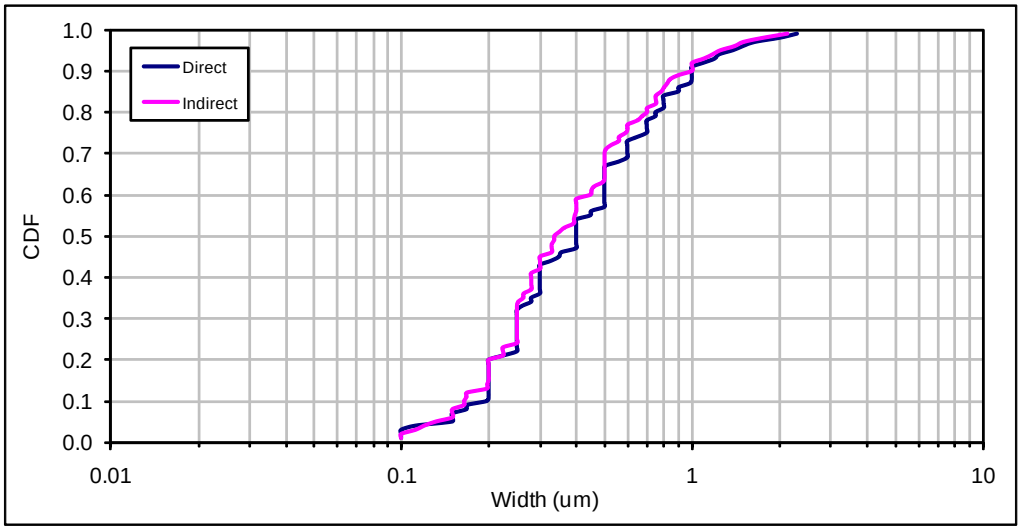


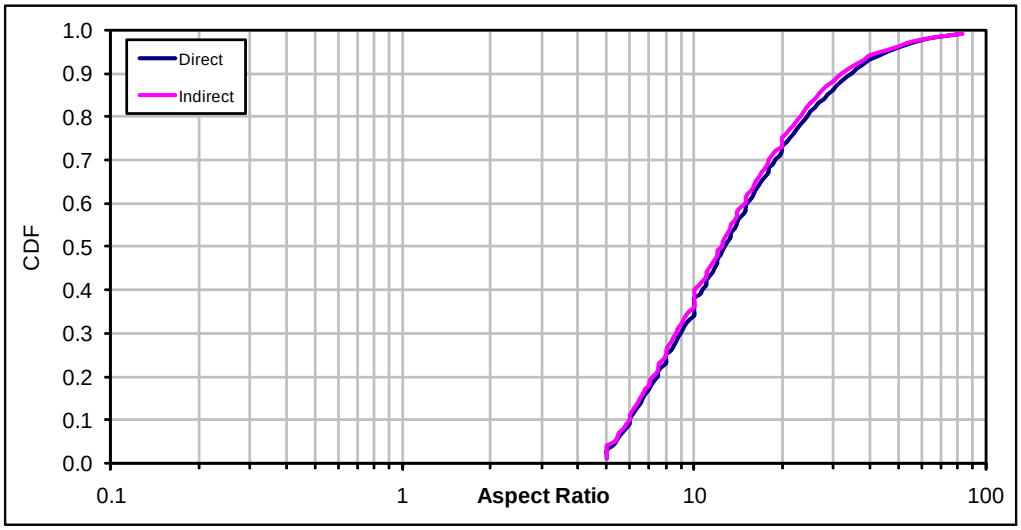
Data are based on a download of Libby 2DB performed on 12-8-09 and the Libby OU3 DB on 2-9-10.

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

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



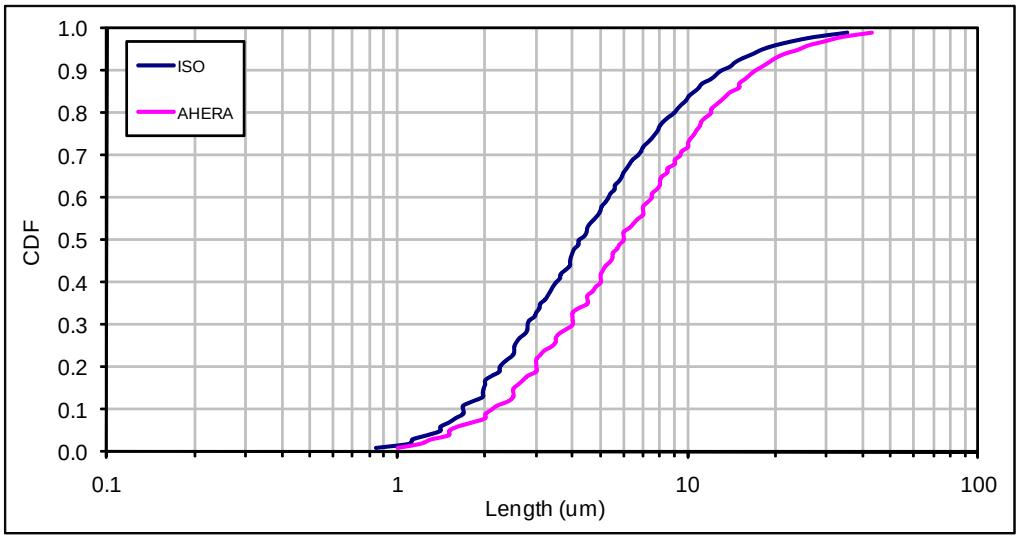


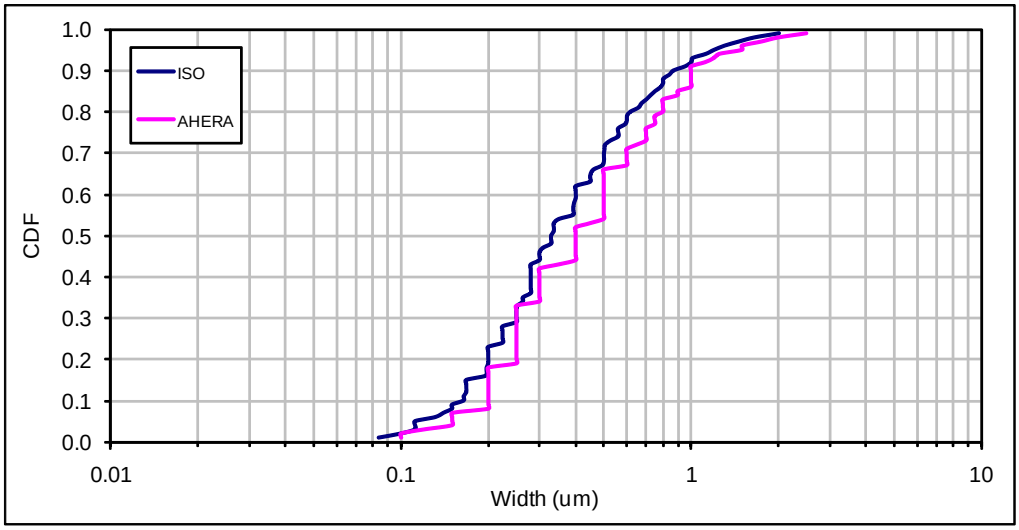


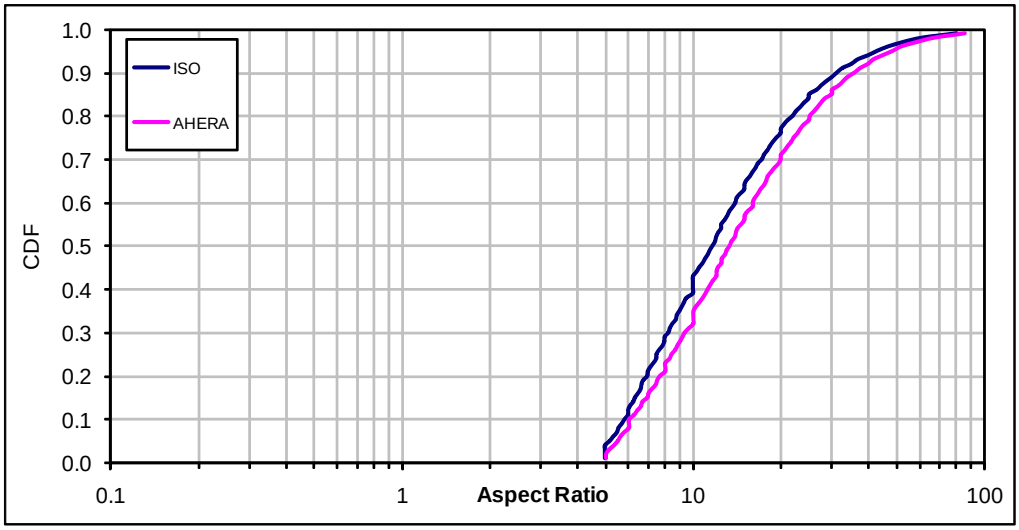
Data are based on a download of Libby 2DB performed on 12-8-09 and the Libby OU3 DB on 2-9-10.

Preparation	N Structures
Direct	17,578
Indirect	11,926

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







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

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

Request for Modification
to
Laboratory Activities
LB-000016A

Instructions to Requester: E-mail form to contacts at bottom of form for review and approval.
File approved copy with Data Manager (CDM). Data Manager distributes approved forms as follows:
All Labs Applicable forms – copies to: EPA, Volpe, CDM, All project labs
Individual Labs Applicable forms – copies to: EPA, Volpe, CDM, Initiating Lab

Method (circle one/those applicable): TEM-AHERA [TEM-ISO 10312] PCM-NIOSH 7400 NIOSH 9002
EPA/600/R-93/116 ASTM D5755 EPA/540/2-90/005a SRC-LIBBY-03
Other: _____

Requester: Lynn Woodbury Title: Technical Consultant
Company: Syracuse Research Corporation Date: April 10, 2008

Description of Modification:
Permanent modifications and clarifications to the Transmission Electron Microscopy analysis of air and dust samples using ISO 10312. The purpose of the attached is to document historic modifications & clarifications, and provide additional permanent clarifications.

Reason for Modification:
To optimize the efficiency of air and dust sample analysis and to provide consistency in analytical procedures and data recording in the project laboratories.

Potential Implications of this Modification:
Modifications reflect changes necessary to clarify ISO requirements in relation to project-specific issues. Negative implications - comparisons of the Total # of LA structures between historical results and current results may be biased (high or low) due to differences in recording rules with regard to aspect ratio criteria. Positive implications - consistency in procedures between and within project laboratories and documentation of those procedures.

Laboratory Applicability (circle one): [All] Individual(s) _____

This laboratory modification is (circle one): **NEW** **APPENDS to** _____ **[SUPERCEDES]** **LB-000016**

Duration of Modification (circle one):
Temporary Date(s): _____
Analytical Batch ID: _____
Temporary Modification Forms – Attach legible copies of approved form w/ all associated raw data packages

[Permanent] (Complete Proposed Modification Section) Effective Date: HISTORIC
Permanent Modification Forms – Maintain legible copies of approved form in a binder that can be accessed by analysts.

Data Quality Indicator (circle one) – Please reference definitions on reverse side for direction on selecting data quality indicators:

Not Applicable **Reject** **[Low Bias]** **Estimate** **[High Bias]** **No Bias**

Proposed Modification to Method (attach additional sheets if necessary; state section and page numbers of Method when applicable):
See attached sheets for the description of the TEM-ISO clarifications/modifications.

Technical Review: _____ Date: _____
(Laboratory Manager or designate)

Project Review and Approval: _____ Date: _____
(Volpe: Project Technical Lead or designate)

Approved By: _____ Date: _____
(USEPA: Project Chemist or designate)

DATA QUALITY INDICATOR DEFINITIONS

Reject - Samples associated with this modification form are not useable. The conditions outlined in the modification form adversely effect the associated sample to such a degree that the data are not reliable.

Low Bias - Samples associated with this modification form are useable, but results are likely to be biased low. The conditions outlined in the modification form suggest that associated sample data are reliable, but estimated low.

Estimate - Samples associated with this modification form are useable, but results should be considered approximations. The conditions outlined in the modification form suggest that associated sample data are reliable, but estimates.

High Bias - Samples associated with this modification form are useable, but results are likely to be biased high. The conditions outlined in the modification form suggest that associated sample data are reliable, but estimated high.

No Bias - Samples associated with this modification form are useable as reported. The conditions outlined in the modification form suggest that associated sample data are reliable as reported.

ISO 10312 MODIFICATIONS AND CLARIFICATIONS

1. **Overloading Modification:**

   The ISO method requirement states that if the specimen grid exhibits more than approximately 10% obscuration on the majority of the grid openings, the specimen shall be designated as overloaded. A rejection criteria of >25% obscuration and <50% intact grid openings will be used for this project. The 25% overload criteria resulted from various communications that took place 29 December 1999 between EPA Region 8, Camp Dresser McKee, Volpe Center, and Reservoirs.

2. **Indirect Preparation of Air Samples Modification:**

   ISO 10312 is a direct preparation method. If the sample is visibly overloaded or contains loose debris, it will be prepared indirectly according to procedures provided in SOP EPA-Libby-08. Secondary filters will be analyzed according to the ISO counting rules for this project. Calculations will be adjusted to contain a dilution factor. This indirect preparation procedure will enable the capture of data from samples that otherwise would be rejected.

3. **Stopping Rule Clarification:**

   Stopping rules for ISO analyses are completion of the grid opening on which the 100^{th} asbestos structure has been recorded, or a minimum of four grid openings. For this project, a maximum of ten grid openings will be read unless specifically instructed otherwise.

4. **Abundant Chrysotile Modification:**

   If abundant chrysotile is present, the chrysotile count may be terminated in accordance with the counting rules specified in LB-000039.

5. **Structure Counting and Recording Modifications and Clarifications:**

   a. Non-asbestos material (NAM) structures are not being recorded, unless identified as a "close call" (see LB-000066 for details). This project-specific modification stems from the need only to quantify levels of contaminants of concern (i.e., asbestos) at a given sample location.

   b. Recording rules will be as described in the ISO method except that the aspect ratio requirement will depend upon the classification of the sample as "investigative" or "non-investigative", as specified in LB-000053. If samples are classified as investigative, the aspect ratio requirement will be 3:1, rather than 5:1, unless program-specific sampling and analysis plans (SAPs) specify otherwise or specifically requested otherwise. Thus, fibers (either individual fibers or fibers within disperse matrices or clusters) shall only be recorded if the length is greater than or equal to 0.5 um and the aspect ratio is greater than or equal to the appropriate criterion. Bundles shall only be recorded if they contain individual constituent fibers with an aspect ratio greater than or equal to the appropriate criterion. The aspect ratio criterion does not apply to compact clusters, compact matrices, or residuals. The overall aspect ratio of a bundle, compact cluster, compact matrix, or residual may have any value.

   c. The definition of a PCM equivalent (PCME) structure is as follows: Any fiber, bundle, matrix, or cluster with an aspect ratio of 3:1 or greater, length longer than 5 um, and width greater than or equal to 0.25 um.

   d. The overall dimensions of disperse clusters (CD) and disperse matrices (MD) will not be recorded in two perpendicular directions. The matrix type and individual sub-structures associated with the matrix or cluster will be recorded as described in the ISO method.

   e. Structures that intersect a non-countable grid bar (i.e., top and left grid bars) will be recorded on the count sheet but excluded from the structure density and concentration calculations. These non-countable structures will be denoted with a zero in the Total column.

   f. If a structure originates in one grid opening and extends into an adjacent grid opening, providing that it does not intersect a non-counting grid bar, the entire length of the fiber is recorded.

g. If a structure intersects both a countable and a non-countable grid bar, the observed length of the structure will be recorded.

h. See Attachment A for detailed examples of how to record specific structure types that may be encountered in Libby samples.

These modifications and clarifications in structure counting and recording are to provide consistency in analytical procedures and data recording in the project laboratories.

OVERVIEW OF HISTORICAL RECORDING CRITERIA

At the beginning of the Libby project, analytical laboratories (primarily EMSL and RESI) were following the ISO method with regard to structure recording (i.e., recording only those structures meeting an aspect ratio of greater than or equal to 5:1).

Approximately the time of the Phase 2 Investigation (late Spring 2001), project laboratories were instructed by Chris Weis (EPA, Region 8) to record all structures regardless of minimum length or aspect ratio. This recording rule change enabled data users to gain a better understanding of the dimension attributes for structures at the Libby site and allowed for the calculation of PCM equivalent (PCME) structures. In the ISO report generated by the TEM EDD spreadsheet, structures with an aspect ratio less than 5:1 were counted in Bin A and structures with a length less than 0.5 um were counted in Bin B. Also at this time, the TEM EDD spreadsheet was modified to allow for the capture of the raw structure data, as entered from the laboratory bench sheet, into the Libby site database.

Although it is uncertain exactly when the recording rules changed after the Phase 2 Investigation, based on analyst interviews, project laboratories reverted back to following the ISO method (i.e., recording only those structures meeting an aspect ratio of greater than or equal to 5:1) beginning approximately December 2001, unless specifically requested otherwise in project-specific SAPs and/or QAPPs (e.g., the Supplemental Remedial Investigation samples collected under the SQAPP specified an aspect ratio criterion of greater than or equal to 3:1).

Laboratory modifications LB-000016B through 16F (provided as Attachment B) document the historical laboratory and analyst-specific deviations in recording/counting rules for ISO based on analyst interviews conducted in August and September 2006.

Beginning August 29, 2006, all project laboratories began utilizing an aspect ratio criterion of 3:1, unless specifically requested otherwise.

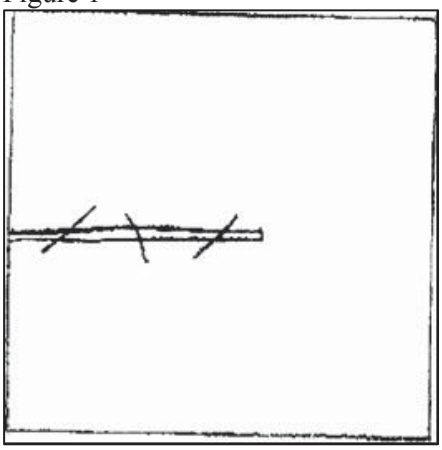
Preparation techniques and recording rules were further refined as part of LB-000053 (effective date: December 21, 2006), whereby all Libby samples were classified as “investigative” and “non-investigative”. Samples classified as “investigative” were to utilize an aspect ratio criterion of 3:1, and samples classified as non-investigative were to utilize an aspect ratio criterion of 5:1, unless program-specific sampling and analysis plans (SAPs) specify otherwise or specifically requested otherwise.

Because of the differences in recording rules for ISO analyses across time, data users should be cautious when making comparisons across samples based on the total number of LA structures. The binned metric of total number of LA structures may differ depending upon the recording rule in place at the time.

ATTACHMENT A

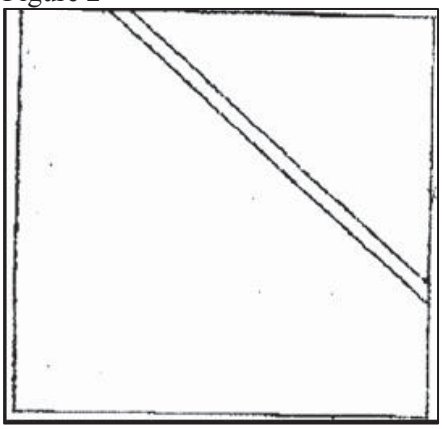
STRUCTURE-SPECIFIC EXAMPLES OF DATA RECORDING

Figure 1



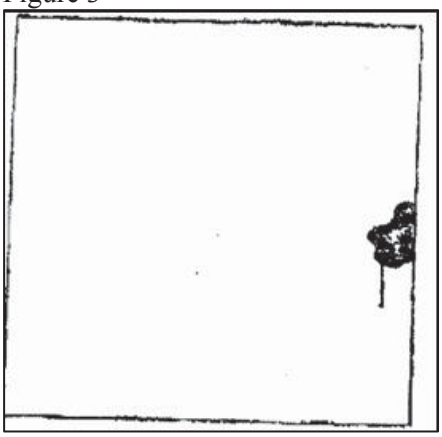
Count as three fibers (F). The large structure is excluded because it crosses a non-countable grid bar (left grid bar).

Figure 2



Count as one fiber (F). Record the length as that observed without doubling.

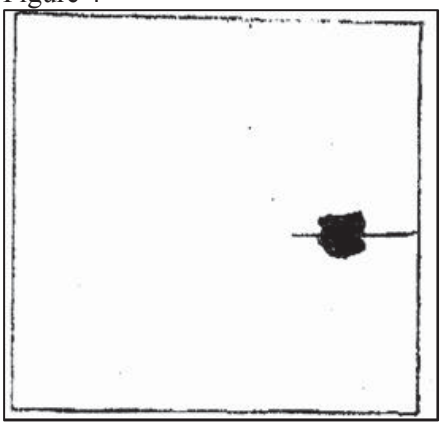
Figure 3



Count as disperse matrix, consisting of one fiber longer than 5 um.

Record as MD11, followed by one fiber (MF). When recording the MF, do not double the length.

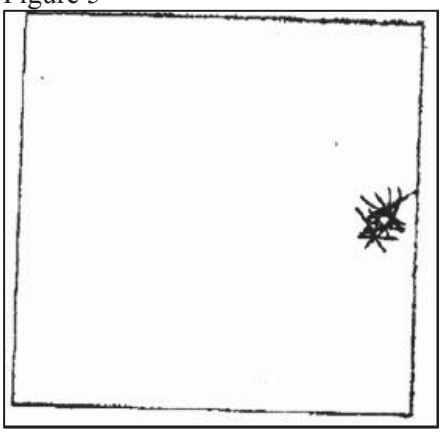
Figure 4



Count as disperse matrix, consisting of one fiber longer than 5 um.

Record as MD11, followed by one fiber (MF). When recording the MF, double the length of the observed fiber.

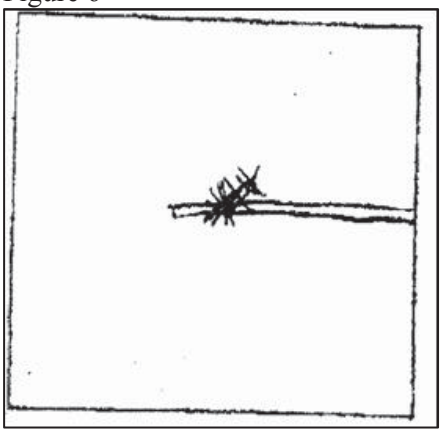
Figure 5



Count as one compact cluster containing more than 9 fibers, which includes one fiber that is longer than 5 um.

Record as CC+1. When recording the CC, record the length of the cluster as double the length of the observed fiber longer than 5 um.

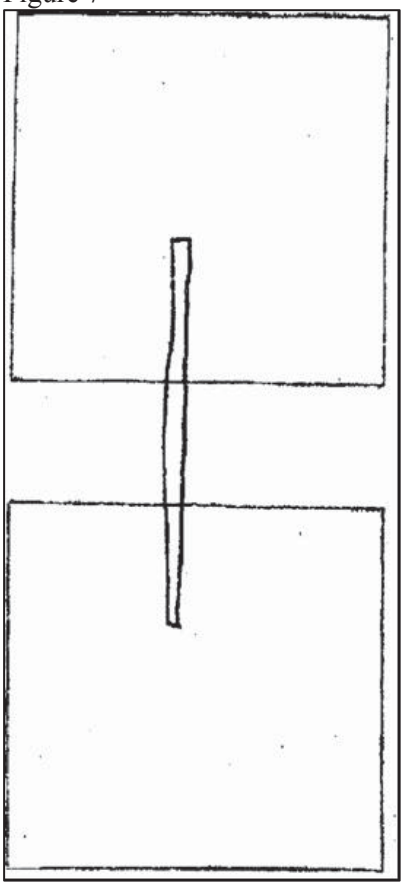
Figure 6



Count as disperse cluster, consisting of one fiber which is longer than 5 um and one compact cluster residual containing more than 9 fibers.

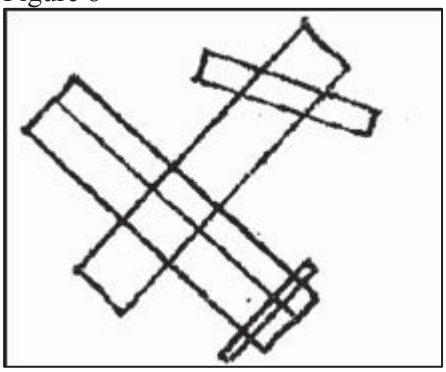
Record as CD+1, followed by one CF and one CR+0. When recording the CF intersecting grid bar, double the length.

Figure 7



Count as one fiber (F). Record the actual length, including protrusion into adjacent grid opening.

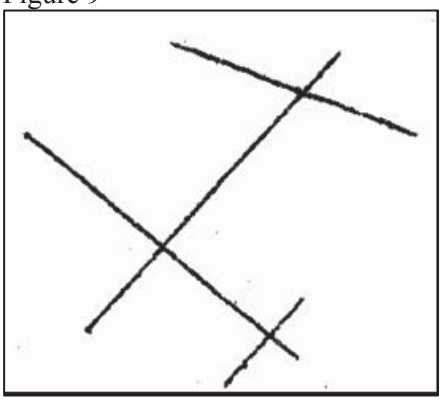
Figure 8



Count as disperse cluster, consisting of four fibers each longer than 5 um.

Record as CD44, followed by four CFs.

Figure 9



Count as disperse cluster, consisting of four fibers each longer than 5 um.

Record as CD44, followed by four CFs.

ATTACHMENT B

LABORATORY AND ANALYST-SPECIFIC DEVIATIONS IN ISO 10312 RECORDING AND COUNTING RULES PRIOR TO AUGUST 2006 (LB-000016B through 16F)

LB-000016B - Batta
LB-000016C - EMSL
LB-000016D - Hygeia
LB-000016E - MAS
LB-000016F - RESI

Request for Modification
to
Laboratory Activities
LB-000016B

Instructions to Requester: E-mail form to contacts at bottom of form for review and approval.
File approved copy with Data Manager (CDM). Data Manager distributes approved forms as follows:
All Labs Applicable forms – copies to: EPA, Volpe, CDM, All project labs
Individual Labs Applicable forms – copies to: EPA, Volpe, CDM, Initiating Lab

Method (circle one/those applicable): TEM-AHERA [TEM-ISO 10312] PCM-NIOSH 7400 NIOSH 9002
EPA/600/R-93/116 ASTM D5755 EPA/540/2-90/005a SRC-LIBBY-03
Other: _____

Requester: Bo Li Title: Manager of Microscopy Services
Company: Batta Laboratories, Inc. Date: September 26, 2006

Description of Modification:
Laboratory-specific clarification of potential inconsistencies among analysts when recording structures using ISO 10312, as modified by LB-000016.

Reason for Modification:
To document potential past differences between analysts and laboratories in recording structures using ISO 10312, as modified by LB-000016, and provide a historical timeline of potential changes in aspect ratio recording rules.

Potential Implications of this Modification:
None.

Laboratory Applicability (circle one): All [Individual](s) Batta Laboratories, Inc.

This laboratory modification is (circle one): **NEW** **[APPENDS] to LB-000016A** **SUPERCEDES** _____

Duration of Modification (circle one):
Temporary Date(s): _____
Analytical Batch ID: _____
Temporary Modification Forms – Attach legible copies of approved form w/ all associated raw data packages

[Permanent] (Complete Proposed Modification Section) Effective Date: HISTORIC
Permanent Modification Forms – Maintain legible copies of approved form in a binder that can be accessed by analysts.

Data Quality Indicator (circle one) – Please reference definitions on reverse side for direction on selecting data quality indicators:

Not Applicable **Reject** **Low Bias** **Estimate** **[High Bias]** **No Bias**

Proposed Modification to Method (attach additional sheets if necessary; state section and page numbers of Method when applicable):

Technical Review: _____ Date: _____
(Laboratory Manager or designate)

Project Review and Approval: _____ Date: _____
(Volpe: Project Technical Lead or designate)

Approved By: _____ Date: _____
(USEPA: Project Chemist or designate)

DATA QUALITY INDICATOR DEFINITIONS

Reject - Samples associated with this modification form are not useable. The conditions outlined in the modification form adversely effect the associated sample to such a degree that the data are not reliable.

Low Bias - Samples associated with this modification form are useable, but results are likely to be biased low. The conditions outlined in the modification form suggest that associated sample data are reliable, but estimated low.

Estimate - Samples associated with this modification form are useable, but results should be considered approximations. The conditions outlined in the modification form suggest that associated sample data are reliable, but estimates.

High Bias - Samples associated with this modification form are useable, but results are likely to be biased high. The conditions outlined in the modification form suggest that associated sample data are reliable, but estimated high.

No Bias - Samples associated with this modification form are useable as reported. The conditions outlined in the modification form suggest that associated sample data are reliable as reported.

HISTORIC INFORMATION ON ASPECT RATIO RECORDING RULES

Beginning May 2002 (when Batta Laboratories began analyzing Libby samples), all analysts recorded structures based on ISO definitions (i.e., aspect ratio criterion of ≥ 5:1). However, when PCM-equivalent structures were encountered (length > 5 µm and an aspect ratio ≥ 3:1), they were recorded and marked as countable. The same recording rule was applied to clusters, bundles and matrices that contained PCME structures.

Starting September 11, 2006 (beginning with Lab Job # QC-27, Index ID SQ-00208), recording rules were changed to utilize a length criterion of > 0.5 µm and an aspect ratio criterion of ≥ 3:1 in accordance with the email direction from Anni Autio (CDM).

DEVIATIONS FROM LAB MODIFICATION LB-000016

Section 4A – Recording of NAM Structures

Analysts were instructed in May 2007 not to record NAMs. However, analysts may occasionally record as NAM if the analyst thought there would be a chance that such a structure might likely be mistaken by a second analyst as a possible asbestos structure. In such a case, "0" was assigned to both primary and total structure columns.

Section 4B – Recording Dimensions for Disperse Clusters (CD) and Matrices (MD)

Dimensions for disperse clusters (CD) and matrices (MD) were measured at two perpendicular directions across the structure. The longest length was defined first, and then the width perpendicular to the length.

Section 4C – Recording Structures Crossing Non-Countable Grid Bars

Before March 2006, structures intersecting the adjacent grid bars on the lower left corner were counted and those intersecting the adjacent bars on the upper right were rejected. After March 2006, this practice was corrected to comply with ISO rules: only those fibers interesting or touching the lower right corner grid bars were counted and others were rejected.

Section 4D – Recording Structures Crossing Multiple Grid Openings

ISO rules on structures touching grid bars were followed.

Section 4E – Recording Structures Crossing Non-Countable and Countable Grid Bars

Refer to Section 4C above.

Request for Modification
to
Laboratory Activities
LB-000016C

Instructions to Requester: E-mail form to contacts at bottom of form for review and approval.
File approved copy with Data Manager (CDM). Data Manager distributes approved forms as follows:
All Labs Applicable forms – copies to: EPA, Volpe, CDM, All project labs
Individual Labs Applicable forms – copies to: EPA, Volpe, CDM, Initiating Lab

Method (circle one/those applicable): TEM-AHERA [TEM-ISO 10312] PCM-NIOSH 7400 NIOSH 9002
EPA/600/R-93/116 ASTM D5755 EPA/540/2-90/005a SRC-LIBBY-03
Other: _____

Requester: Ed Cahill Title: National Director
Company: EMSL Analytical, Inc. Date: September 27, 2006

Description of Modification:
Laboratory-specific clarification of potential inconsistencies among analysts when recording structures using ISO 10312, as modified by LB-000016.

Reason for Modification:
To document potential past differences between analysts and laboratories in recording structures using ISO 10312, as modified by LB-000016, and provide a historical timeline for each Libby laboratory of potential changes in aspect ratio recording rules.

Potential Implications of this Modification:
None.

Laboratory Applicability (circle one): All [Individual](s) EMSL

This laboratory modification is (circle one): **NEW** **[APPENDS] to LB-000016A** **SUPERCEDES** _____

Duration of Modification (circle one):
Temporary Date(s): _____
Analytical Batch ID: _____
Temporary Modification Forms – Attach legible copies of approved form w/ all associated raw data packages

[Permanent] (Complete Proposed Modification Section) Effective Date: HISTORIC
Permanent Modification Forms – Maintain legible copies of approved form in a binder that can be accessed by analysts.

Data Quality Indicator (circle one) – Please reference definitions on reverse side for direction on selecting data quality indicators:

Not Applicable **Reject** **Low Bias** **Estimate** **High Bias** **[No Bias]**

Proposed Modification to Method (attach additional sheets if necessary; state section and page numbers of Method when applicable):

Technical Review: _____ Date: _____
(Laboratory Manager or designate)

Project Review and Approval: _____ Date: _____
(Volpe: Project Technical Lead or designate)

Approved By: _____ Date: _____
(USEPA: Project Chemist or designate)

DATA QUALITY INDICATOR DEFINITIONS

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No Bias - Samples associated with this modification form are useable as reported. The conditions outlined in the modification form suggest that associated sample data are reliable as reported.

Analysts Interviewed
Jodie Bourgerie
Ed Cahill
Robyn Denton
Bob Georgens
Richard Harding
Ken Klutts
Brett Macey
Ron Mahoney

Ex Employees (not interviewed)
Duane Salinas
Thomas Ferrante
Richard White
Anant Samudra
Adrian Arav

HISTORIC INFORMATION ON ASPECT RATIO RECORDING RULES

Beginning in approximately late 1999 (when EMSL Analytical began analyzing Libby samples), all analysts interviewed applied a 5:1 aspect ratio and the counting rules outlined in the ISO method. Sometime during the spring of 2001, verbal directions were given to record all structures, regardless of aspect ratio. Before, during and after this time, if any other aspect ratio than > 5:1 was recorded, it was due to a written or verbal project specific directive (i.e. SQAPP and/or Phase 2 project samples).

DEVIATIONS FROM LAB MODIFICATION LB-000016

All analysts followed ISO method recording rules, as well as the guidance in Laboratory Mod LB-000016 except as noted below:

Section 4A – Recording of NAM Structures

All analysts in compliance.

Section 4B – Recording Dimensions for Disperse Clusters (CD) and Matrices (MD)

All analysts in compliance.

Section 4C – Recording Structures Crossing Non-Countable Grid Bars

Robyn Denton: Has not been adhering to Section 4C which called for recording asbestos structures even when they originated from non-countable grid bars.

Section 4D – Recording Structures Crossing Multiple Grid Openings

All analysts in compliance.

Section 4E – Recording Structures Crossing Non-Countable and Countable Grid Bars

All analysts in compliance.

Request for Modification
to
Laboratory Activities
LB-000016D

Instructions to Requester: E-mail form to contacts at bottom of form for review and approval.
File approved copy with Data Manager (CDM). Data Manager distributes approved forms as follows:
All Labs Applicable forms – copies to: EPA, Volpe, CDM, All project labs
Individual Labs Applicable forms – copies to: EPA, Volpe, CDM, Initiating Lab

Method (circle one/those applicable): TEM-AHERA [TEM-ISO 10312] PCM-NIOSH 7400 NIOSH 9002
EPA/600/R-93/116 ASTM D5755 EPA/540/2-90/005a SRC-LIBBY-03
Other: _____

Requester: Kyeong Corbin Title: TEM Laboratory Supervisor
Company: Hygeia Laboratories Inc. Date: September 22, 2006

Description of Modification:
Laboratory-specific clarification of potential inconsistencies among analysts when recording structures using ISO 10312, as modified by LB-000016.

Reason for Modification:
To document potential past differences between analysts and laboratories in recording structures using ISO 10312, as modified by LB-000016, and provide a historical timeline for each Libby laboratory of potential changes in aspect ratio recording rules.

Potential Implications of this Modification:
None.

Laboratory Applicability (circle one): All [Individual](s) Hygeia Laboratories Inc.

This laboratory modification is (circle one): **NEW** **[APPENDS] to LB-000016A** **SUPERCEDES** _____

Duration of Modification (circle one):
Temporary Date(s): _____
Analytical Batch ID: _____
Temporary Modification Forms – Attach legible copies of approved form w/ all associated raw data packages

[Permanent] (Complete Proposed Modification Section) Effective Date: HISTORIC
Permanent Modification Forms – Maintain legible copies of approved form in a binder that can be accessed by analysts.

Data Quality Indicator (circle one) – Please reference definitions on reverse side for direction on selecting data quality indicators:

Not Applicable **Reject** **Low Bias** **Estimate** **High Bias** **[No Bias]**

Proposed Modification to Method (attach additional sheets if necessary; state section and page numbers of Method when applicable):

Technical Review: _____ Date: _____
(Laboratory Manager or designate)

Project Review and Approval: _____ Date: _____
(Volpe: Project Technical Lead or designate)

Approved By: _____ Date: _____
(USEPA: Project Chemist or designate)

DATA QUALITY INDICATOR DEFINITIONS

Reject - Samples associated with this modification form are not useable. The conditions outlined in the modification form adversely effect the associated sample to such a degree that the data are not reliable.

Low Bias - Samples associated with this modification form are useable, but results are likely to be biased low. The conditions outlined in the modification form suggest that associated sample data are reliable, but estimated low.

Estimate - Samples associated with this modification form are useable, but results should be considered approximations. The conditions outlined in the modification form suggest that associated sample data are reliable, but estimates.

High Bias - Samples associated with this modification form are useable, but results are likely to be biased high. The conditions outlined in the modification form suggest that associated sample data are reliable, but estimated high.

No Bias - Samples associated with this modification form are useable as reported. The conditions outlined in the modification form suggest that associated sample data are reliable as reported.

HISTORIC INFORMATION ON ASPECT RATIO RECORDING RULES

Hygeia Laboratories Inc. received the first batch of ISO 10312 samples on May 30, 2002. Two analysts, Kyeong Corbin and Quynh Trieu, were involved in analyzing all Libby project samples. All ISO samples were counted and recorded for asbestos structures utilizing an aspect ratio criterion of 5:1 or greater, unless the project-specific requirements stated otherwise. For example, all SQAPP samples submitted (first job submitted in June 20, 2005) and all settled dust samples (SRC-Libby-07 method; first job submitted in June 23, 2005) for ISO 10312 method were analyzed for aspect ratio 3:1 or greater.

DEVIATIONS FROM LAB MODIFICATION LB-000016

Both analysts agree on the counting rules mentioned in LB-000016 and clarifications stated below:

1. Hygeia recorded no asbestos detected grid opening as “NSD” instead of “ND” as requested during the period of 6/1/02 to 11/30/02. The Lab Mod LB-000023 was filed.

2. Project-specific stopping rules or target analytical sensitivity superseded the ISO 10312 method stopping rules.

Section 4A – Recording of NAM Structures

NAM structures were not recorded as of August 6, 2002. At times, NAM structures were still recorded if the analysts thought it was necessary and marked as such on the data sheet and on the EDD. (If recorded, NAM structures were noted as non-countable on the data sheet and EDD.)

Section 4B – Recording Dimensions for Disperse Clusters (CD) and Matrices (MD)

All analysts in compliance.

Section 4C – Recording Structures Crossing Non-Countable Grid Bars

All structures intersecting countable grid bars (bottom/south and right/east) were counted and the lengths were doubled. Doubled length was indicated as “X” on the data sheet and indicated as “doubled length” on the comment field of EDD. In general, structures intersecting non-countable grid bars were recorded and indicated as non-countable on the data sheet and EDD. Intersecting grid bar was also indicated on the EDD comment field as crossing E, W, S, N grid bar, i.e. “Non-countable; CWGB,” or “CSGB; Doubled length.”

Section 4D – Recording Structures Crossing Multiple Grid Openings

All analysts in compliance (see text in Section 4C above).

Section 4E – Recording Structures Crossing Non-Countable and Countable Grid Bars

All analysts in compliance (see text in Section 4C above).

Request for Modification
to
Laboratory Activities
LB-000016E

Instructions to Requester: E-mail form to contacts at bottom of form for review and approval.
File approved copy with Data Manager (CDM). Data Manager distributes approved forms as follows:
All Labs Applicable forms – copies to: EPA, Volpe, CDM, All project labs
Individual Labs Applicable forms – copies to: EPA, Volpe, CDM, Initiating Lab

Method (circle one/those applicable): TEM-AHERA [TEM-ISO 10312] PCM-NIOSH 7400 NIOSH 9002
EPA/600/R-93/116 ASTM D5755 EPA/540/2-90/005a SRC-LIBBY-03
Other: _____

Requester: Michael D. Mount Title: EM Manager
Company: MAS, LLC Date: December 7, 2006

Description of Modification:
Laboratory-specific clarification of potential inconsistencies among analysts when recording structures using ISO 10312, as modified by LB-000016.

Reason for Modification:
To document potential past differences between analysts and laboratories in recording structures using ISO 10312, as modified by LB-000016, and provide a historical timeline for each Libby laboratory of potential changes in aspect ratio recording rules.

Potential Implications of this Modification:
None.

Laboratory Applicability (circle one): All [Individual](s) MAS

This laboratory modification is (circle one): **NEW** **[APPENDS] to LB-000016A** **SUPERCEDES** _____

Duration of Modification (circle one):
Temporary Date(s): _____
Analytical Batch ID: _____
Temporary Modification Forms – Attach legible copies of approved form w/ all associated raw data packages

[Permanent] (Complete Proposed Modification Section) Effective Date: HISTORIC
Permanent Modification Forms – Maintain legible copies of approved form in a binder that can be accessed by analysts.

Data Quality Indicator (circle one) – Please reference definitions on reverse side for direction on selecting data quality indicators:

Not Applicable **Reject** **Low Bias** **Estimate** **High Bias** **[No Bias]**

Proposed Modification to Method (attach additional sheets if necessary; state section and page numbers of Method when applicable):

Technical Review: _____ Date: _____
(Laboratory Manager or designate)

Project Review and Approval: _____ Date: _____
(Volpe: Project Technical Lead or designate)

Approved By: _____ Date: _____
(USEPA: Project Chemist or designate)

DATA QUALITY INDICATOR DEFINITIONS

Reject - Samples associated with this modification form are not useable. The conditions outlined in the modification form adversely effect the associated sample to such a degree that the data are not reliable.

Low Bias - Samples associated with this modification form are useable, but results are likely to be biased low. The conditions outlined in the modification form suggest that associated sample data are reliable, but estimated low.

Estimate - Samples associated with this modification form are useable, but results should be considered approximations. The conditions outlined in the modification form suggest that associated sample data are reliable, but estimates.

High Bias - Samples associated with this modification form are useable, but results are likely to be biased high. The conditions outlined in the modification form suggest that associated sample data are reliable, but estimated high.

No Bias - Samples associated with this modification form are useable as reported. The conditions outlined in the modification form suggest that associated sample data are reliable as reported.

HISTORIC INFORMATION ON ASPECT RATIO RECORDING RULES

MAS currently has four analysts (Mike Mount, Kevin Simpson, Mehrdad Motamedi and Will Stark) performing ISO 10312 analyses of Libby samples. The first set of Libby ISO samples (dust samples) were received on 04/03/03. At this time analyst performing analysis were Will Stark, Ding Qian and Jayme Callan. All ISO samples were counted and recorded for asbestos structures utilizing an aspect ratio criterion of 5:1 or greater, unless the project-specific requirements stated otherwise. SQAPP samples and settled dust samples for ISO 10312 submitted since that time (generally around June 2005) methods were analyzed for aspect ratio 3:1 or greater.

DEVIATIONS FROM LAB MODIFICATION LB-000016

All analysts followed ISO method recording rules, as well as the guidance in Laboratory Mod LB-000016 except as noted below:

Section 4A – Recording of NAM Structures

On some occasions one analyst (KS) has recorded non-asbestos structures (NAM) that he deemed significant. However, when NAM structures were recorded, they were always noted as non-countable structures (i.e., placed a “0” in the Total column).

Section 4B – Recording Dimensions for Disperse Clusters (CD) and Matrices (MD)

MAS analysts (MDM and others) may have recorded the overall dimensions of the matrix or cluster rather than the dimensions of the sub-structures.

Section 4C – Recording Structures Crossing Non-Countable Grid Bars

All analysts in compliance. MAS records asbestos structures that are deemed non-countable due to an intersection of the north and west grid bars and places a “0” in the structure count column.

Section 4D – Recording Structures Crossing Multiple Grid Openings

All analysts in compliance. MAS records the entire length of a structure that extends into an adjacent grid opening.

Section 4E – Recording Structures Crossing Non-Countable and Countable Grid Bars

All analysts in compliance. MAS records the entire length of a structure that crosses a non-countable grid bar and a countable grid bar.

Request for Modification
to
Laboratory Activities
LB-000016F

Instructions to Requester: E-mail form to contacts at bottom of form for review and approval.
File approved copy with Data Manager (CDM). Data Manager distributes approved forms as follows:
All Labs Applicable forms – copies to: EPA, Volpe, CDM, All project labs
Individual Labs Applicable forms – copies to: EPA, Volpe, CDM, Initiating Lab

Method (circle one/those applicable): TEM-AHERA [TEM-ISO 10312] PCM-NIOSH 7400 NIOSH 9002
EPA/600/R-93/116 ASTM D5755 EPA/540/2-90/005a SRC-LIBBY-03
Other: _____

Requester: Jeanne Orr Title: President
Company: RESI Date: December 12, 2006

Description of Modification:
Laboratory-specific clarification of potential inconsistencies among analysts when recording structures using ISO 10312, as modified by LB-000016.

Reason for Modification:
To document potential past differences between analysts and laboratories in recording structures using ISO 10312, as modified by LB-000016, and provide a historical timeline for each Libby laboratory of potential changes in aspect ratio recording rules.

Potential Implications of this Modification:
None.

Laboratory Applicability (circle one): All [Individual](s) RESI

This laboratory modification is (circle one): **NEW** **[APPENDS] to LB-000016A** **SUPERCEDES** _____

Duration of Modification (circle one):
Temporary Date(s): _____
Analytical Batch ID: _____
Temporary Modification Forms – Attach legible copies of approved form w/ all associated raw data packages

[Permanent] (Complete Proposed Modification Section) Effective Date: HISTORIC
Permanent Modification Forms – Maintain legible copies of approved form in a binder that can be accessed by analysts.

Data Quality Indicator (circle one) – Please reference definitions on reverse side for direction on selecting data quality indicators:

Not Applicable **Reject** **Low Bias** **Estimate** **High Bias** **[No Bias]**

Proposed Modification to Method (attach additional sheets if necessary; state section and page numbers of Method when applicable):

Technical Review: _____ Date: _____
(Laboratory Manager or designate)

Project Review and Approval: _____ Date: _____
(Volpe: Project Technical Lead or designate)

Approved By: _____ Date: _____
(USEPA: Project Chemist or designate)

DATA QUALITY INDICATOR DEFINITIONS

Reject - Samples associated with this modification form are not useable. The conditions outlined in the modification form adversely effect the associated sample to such a degree that the data are not reliable.

Low Bias - Samples associated with this modification form are useable, but results are likely to be biased low. The conditions outlined in the modification form suggest that associated sample data are reliable, but estimated low.

Estimate - Samples associated with this modification form are useable, but results should be considered approximations. The conditions outlined in the modification form suggest that associated sample data are reliable, but estimates.

High Bias - Samples associated with this modification form are useable, but results are likely to be biased high. The conditions outlined in the modification form suggest that associated sample data are reliable, but estimated high.

No Bias - Samples associated with this modification form are useable as reported. The conditions outlined in the modification form suggest that associated sample data are reliable as reported.

HISTORIC INFORMATION ON ASPECT RATIO RECORDING RULES

Reservoirs Environmental began analyzing samples for the Libby Project in November, 1999. Analysts applied an aspect ratio of 5:1 to the countable structures unless project specific requirements stated otherwise. The samples with a prefix of “SQ-“ or “2-“ were analyzed with an aspect ratio of 3:1 as requested. Current aspect ratio rules are outlined in LB-000053 and are delineated by the classification of “investigative” or “non-investigative”.

DEVIATIONS FROM LAB MODIFICATION LB-000016

All analysts followed ISO method recording rules to the best of their ability, as well as the guidance in Laboratory Mod LB-000016. Samples counted in 1999 and 2000 on historical laboratory bench sheets are identified in LB-000001 through LB-000014.

Section 4A – Recording of NAM Structures

Reservoirs has recorded NAM structures if the analyst determined the structure had morphology similar to an asbestos structure. NAM structures have always been marked as non-countable on the data sheet. The requirement to record non close-call NAM structures such as gypsum or glass was removed after August, 2006.

Section 4B – Recording Dimensions for Disperse Clusters (CD) and Matrices (MD)

All analysts in compliance.

Section 4C – Recording Structures Crossing Non-Countable Grid Bars

All analysts in compliance.

Section 4D – Recording Structures Crossing Multiple Grid Openings

All analysts in compliance.

Section 4E – Recording Structures Crossing Non-Countable and Countable Grid Bars

All analysts in compliance.

Request for Modification
to
Laboratory Activities
LB-000031A

Instructions to Requester: E-mail form to contacts at bottom of form for review and approval.
File approved copy with Data Manager (CDM). Data Manager distributes approved forms as follows:
All Labs Applicable forms – copies to: EPA, Volpe, CDM, All project labs
Individual Labs Applicable forms – copies to: EPA, Volpe, CDM, Initiating Lab

Method (circle one/those applicable): [TEM-AHERA] TEM-ISO 10312 PCM-NIOSH 7400 NIOSH 9002
EPA/600/R-93/116 [ASTM D5755] EPA/540/2-90/005a SRC-LIBBY-03
Other: _____

Requester: Lynn Woodbury Title: Technical Consultant
Company: Syracuse Research Corporation Date: January 18, 2008

Description of Modification:
Permanent modifications and clarifications to the Transmission Electron Microscopy analysis of air samples using AHERA and dust samples using ASTM. The purpose of the attached is to document historic modifications & clarifications, and provide additional permanent clarifications.

Reason for Modification:
To optimize the efficiency of air and dust sample analysis and to provide consistency in analytical procedures and data recording in the project laboratories.

Potential Implications of this Modification:
Modifications reflect changes necessary to clarify ISO requirements in relation to project-specific issues. Negative implications - comparisons of the Total # of LA structures between historical results and current results may be biased (high or low) due to differences in recording rules with regard to aspect ratio criteria. Positive implications - consistency in procedures between and within project laboratories and documentation of those procedures.

Laboratory Applicability (circle one): [All] Individual(s) _____

This laboratory modification is (circle one): **NEW** **APPENDS to** _____ **[SUPERCEDES] LB-000017, LB-000017A, LB-000031**

Duration of Modification (circle one):
Temporary Date(s): _____
Analytical Batch ID: _____
Temporary Modification Forms – Attach legible copies of approved form w/ all associated raw data packages

[Permanent] (Complete Proposed Modification Section) Effective Date: HISTORIC
Permanent Modification Forms – Maintain legible copies of approved form in a binder that can be accessed by analysts.

Data Quality Indicator (circle one) – Please reference definitions on reverse side for direction on selecting data quality indicators:

Not Applicable **Reject** **[Low Bias]** **Estimate** **[High Bias]** **No Bias**

Proposed Modification to Method (attach additional sheets if necessary; state section and page numbers of Method when applicable):

_____

_____

Technical Review: _____ Date: _____
(Laboratory Manager or designate)

Project Review and Approval: _____ Date: _____

(Volpe: Project Technical Lead or designate)

Approved By:_____ Date: _____

(USEPA: Project Chemist or designate)

DATA QUALITY INDICATOR DEFINITIONS

Reject - Samples associated with this modification form are not useable. The conditions outlined in the modification form adversely effect the associated sample to such a degree that the data are not reliable.

Low Bias - Samples associated with this modification form are useable, but results are likely to be biased low. The conditions outlined in the modification form suggest that associated sample data are reliable, but estimated low.

Estimate - Samples associated with this modification form are useable, but results should be considered approximations. The conditions outlined in the modification form suggest that associated sample data are reliable, but estimates.

High Bias - Samples associated with this modification form are useable, but results are likely to be biased high. The conditions outlined in the modification form suggest that associated sample data are reliable, but estimated high.

No Bias - Samples associated with this modification form are useable as reported. The conditions outlined in the modification form suggest that associated sample data are reliable as reported.

AHERA/ASTM MODIFICATIONS AND CLARIFICATIONS

1. Overloading Modification:

A rejection criteria of >25% obscuration will be used for this project. The 25% overload criteria resulted from various communications that took place 29 December 1999 between EPA Region 8, Camp Dresser McKee (CDM), Volpe Center, and Reservoirs (RESI). [The AHERA method grid rejection of 10% has been established and clarified by NVLAP Lab Bulletin 7-2002 – July 12, 2002].

2. Indirect Preparation Of Air Samples Modification:

If the sample is visibly overloaded or contains loose debris, it will be prepared indirectly according to procedures provided in SOP EPA-Libby-08. Secondary filters will be analyzed according to the AHERA/ASTM counting rules for this project. Calculations will be adjusted to contain a dilution factor. This indirect preparation procedure will enable the capture of data from samples that otherwise would be rejected.

3. Stopping Rule Clarification:

For this project, a maximum of ten grid openings will be read unless specifically instructed otherwise.

4. Abundant Chrysotile Modification:

If abundant chrysotile is present, the chrysotile count may be terminated in accordance with the counting rules specified in LB-000039.

5. Cassette Modification:

Cassettes with a 0.8 µm pore size and no 5.0 µm diffuser filter (PCM cassettes) are primarily used for AHERA/ASTM sample collection.

6. Structure Counting and Recording Modifications and Clarifications:

a. All structures will be recorded with the following "Structure Type" designations on the EPA Region 8 spreadsheet:

Fiber	F
Bundle	B
Cluster	C
Matrix	M

If the analyst determines that additional information is needed to describe a structure, comments pertaining to the structure in additional to a sketch will be recorded in the structure comments column.

b. Non-asbestos material (NAM) structures are not being recorded, unless identified as a "close call" (see LB-000066 for details). This project-specific modification stems from the need only to quantify levels of contaminants of concern (i.e., asbestos) at a given sample location.

c. For the Libby project, a designation of "ND" (none detected) will be used to document when no structures are detected for the grid opening.

d. Recording rules will be as described in the AHERA method except that the aspect ratio requirement will depend upon the classification of the sample as "investigative" or "non-investigative", as specified in LB-000053. If samples are classified as investigative, the aspect ratio requirement will be 3:1, rather than 5:1, unless program-specific sampling and analysis plans (SAPs) specify otherwise or specifically requested otherwise. Thus, fibers shall only be recorded if the aspect ratio is greater than or equal to the appropriate criterion. Bundles, clusters, and matrices shall only be recorded if they contain individual constituent fibers with an aspect ratio greater than or equal to the appropriate criterion. The overall aspect ratio of a bundle, cluster, or matrix may have any value.

e. Structures that are non-countable (e.g., aspect ratio does not meet the appropriate criterion, matrices without an

exposed termination) should be recorded for informational purposes, but identified as non-countable, to ensure they are excluded from structure density and concentration calculations. These non-countable structures will be denoted with a zero in the Total column.

f. If a structure originates in one grid opening and extends into an adjacent grid opening, the entire length of the fiber is recorded.

g. The AHERA method requires the analyst to "record the length category and structure type classification non the count sheet after the field number and fiber number". As a clarification to this, the actual length and width of individual fibers, bundles, compact clusters, and compact matrices will be recorded. For disperse clusters and matrices, the length of only the longest protruding structure will be recorded. It is not appropriate to record all sub-structures as in the ISO 10312 method. Structure dimensions may be recorded in microns (μm) or screen units provided that the scaling factors are recorded. See Attachment A for detailed examples of how to record specific structure types that may be encountered in Libby samples.

h. In the AHERA method, one of the provided illustrations for bundles is unclear (i.e., the bundle appears as three fibers). The AHERA written definition for bundles will be utilized.

These modifications and clarifications in structure counting and recording are to provide consistency in analytical procedures and data recording in the project laboratories.

OVERVIEW OF HISTORICAL RECORDING CRITERIA

At the beginning of the Libby project, analytical laboratories (primarily EMSL and RESI) were following the AHERA method with regard to structure recording (i.e., recording only those structures meeting an aspect ratio of greater than or equal to 5:1).

Approximately the time of the Phase 2 Investigation (late Spring 2001), project laboratories were instructed by Chris Weis (EPA, Region 8) to record all structures regardless of minimum length or aspect ratio. This recording rule change enabled data users to gain a better understanding of the dimension attributes for structures at the Libby site and allowed for the calculation of PCM equivalent (PCME) structures.

Although it is uncertain exactly when the recording rules changed after the Phase 2 Investigation, based on analyst interviews, project laboratories reverted back to following the AHERA method (i.e., recording only those structures meeting an aspect ratio of greater than or equal to 5:1) beginning approximately in late 2001 to early 2002.

Laboratory modifications LB-000031B through 31F (provided as Attachment B) document the historical laboratory and analyst-specific deviations in recording/counting rules for AHERA/ASTM based on analyst interviews conducted in August and September 2006. Beginning August 29, 2006, all project laboratories were instructed to utilize an aspect ratio criterion of 5:1 for AHERA/ASTM analyses, unless specifically requested otherwise.

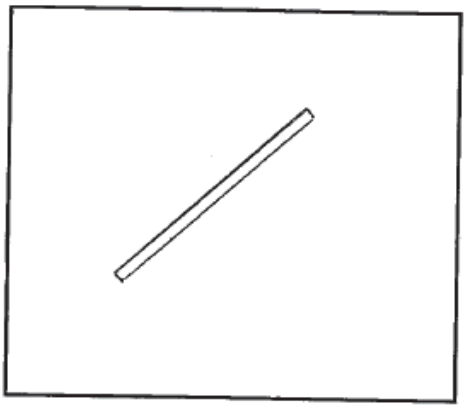
Beginning April 24, 2007, all project laboratories were instructed to utilize an aspect ratio criterion of 3:1 for AHERA/ASTM analyses of "investigative" samples. Instruction regarding classification of samples as "investigative" and "non-investigative" was provided as part of LB-000053 (effective date: December 21, 2006. Samples classified as "non-investigative" were to utilize an aspect ratio criterion of 5:1, unless program-specific sampling and analysis plans (SAPs) specify otherwise or specifically requested otherwise.

Because of the differences in recording rules for AHERA/ASTM analyses across time, data users should be cautious when making comparisons across samples based on the total number of LA structures. The binned metric of total number of LA structures may differ depending upon the recording rule in place at the time.

ATTACHMENT A

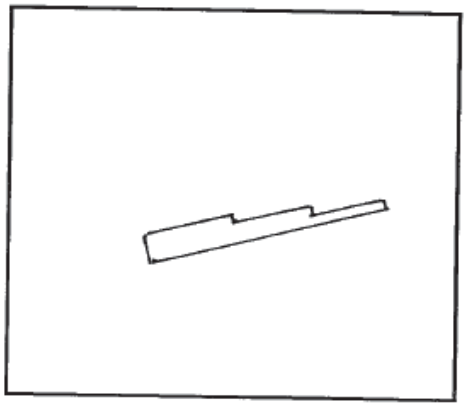
STRUCTURE-SPECIFIC EXAMPLES OF DATA RECORDING

Structure 1:



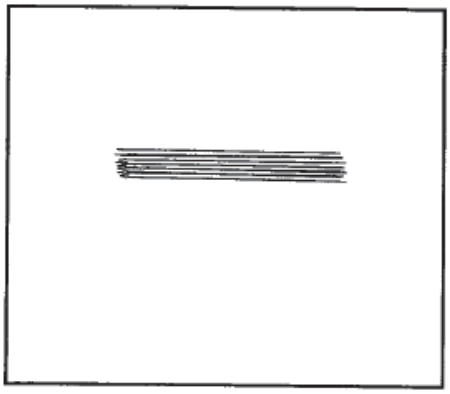
Simple fiber – Record length and width. Structure must meet AHERA length and aspect ratio criteria.

Structure 2:



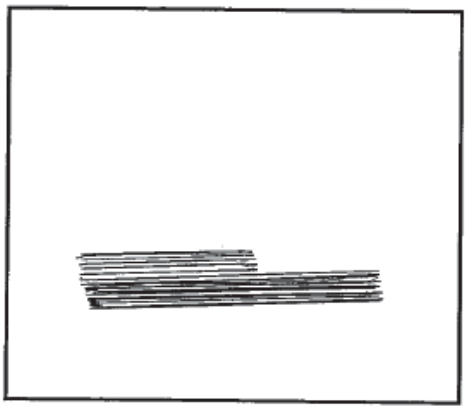
Stepped fiber – Record length. Record width as a best estimate of the average width. Structure must meet AHERA length and aspect ratio criteria.

Structure 3:



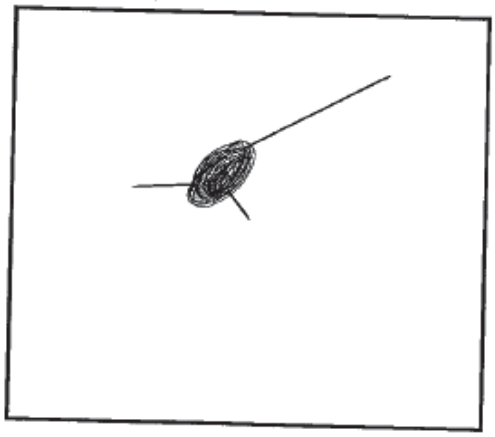
Bundle – Record length and width of bundle. The aspect ratio of the overall structure is not a factor. At least three individual sub-structures in parallel arrangement separated by less than one sub-structure diameter, adequate to meet AHERA bundle definition, must meet AHERA length and aspect ratio criteria.

Structure 4:



Stepped bundle – Record longest length of bundle. Record width as a best estimate of the average width. The aspect ratio of the overall structure is not a factor. At least three individual sub-structures in parallel arrangement separated by less than one sub-structure diameter, adequate to meet AHERA bundle definition, must meet AHERA length and aspect ratio criteria.

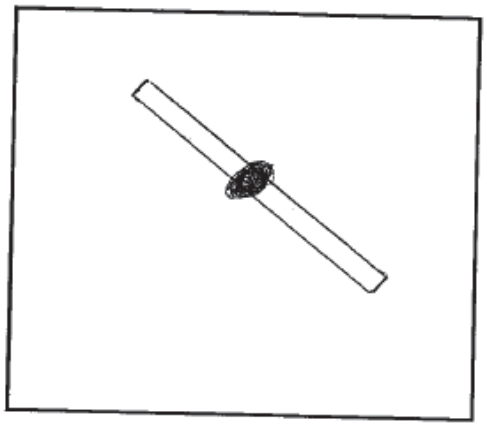
Structure 5:



Matrix – Record length of longest exposed structure and its width. Structure must meet AHERA length and aspect ratio criteria.

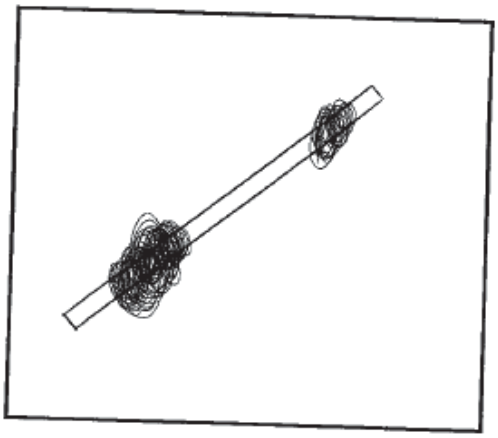
[Do not record the dimensions of the matrix, only the longest protruding structure.]

Structure 6:



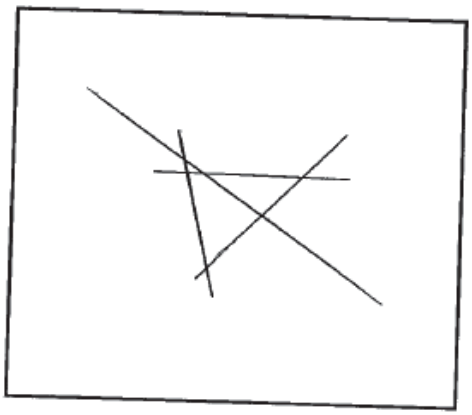
Fiber with adhering matrix material - This structure does not fall into the matrix category as defined in that both ends are exposed (definition 14, AHERA) - Record length and width of the fiber. Structure must meet AHERA length and aspect ratio criteria.

Structure 7:



Structure with protrusions < aspect ratio criterion but an overall aspect ratio meeting criterion. Provided that the structure can be observed to be continuous through the adhering material, count as a fiber. Structure must meet AHERA length and aspect ratio criteria. If the structure cannot be observed to be continuous through the adhering material, do not count.

Structure 8:



Cluster – Record the length of the longest observable sub-structure. Record width as a best estimate of the average width of the overall structure, not the individual sub-structures. The aspect ratio of the overall structure is not a factor. There must be at least three intersections comprised of individual sub-structures that meet AHERA length and aspect ratio criteria to meet cluster definition.

ATTACHMENT B

LABORATORY AND ANALYST-SPECIFIC DEVIATIONS IN AHERA/ASTM RECORDING AND COUNTING RULES PRIOR TO AUGUST 2006 (LB-000031B through 31F)

LB-000031B - Batta
LB-000031C - EMSL
LB-000031D - Hygeia
LB-000031E - MAS
LB-000031F - RESI

Request for Modification
to
Laboratory Activities
LB-000031X

Instructions to Requester: E-mail form to contacts at bottom of form for review and approval.
File approved copy with Data Manager (CDM). Data Manager distributes approved forms as follows:
All Labs Applicable forms – copies to: EPA, Volpe, CDM, All project labs
Individual Labs Applicable forms – copies to: EPA, Volpe, CDM, Initiating Lab

Method (circle one/those applicable): [TEM-AHERA] TEM-ISO 10312 PCM-NIOSH 7400 NIOSH 9002
EPA/600/R-93/116 [ASTM D5755] EPA/540/2-90/005a SRC-LIBBY-03
Other: _____

Requester: Bo Li Title: Manager of Microscopy Services
Company: Batta Laboratories, Inc. Date: September 26, 2006

Description of Modification:
Laboratory-specific clarification of potential inconsistencies among analysts when recording structures using AHERA/ASTM, as modified by LB-000017, LB-000017A, and LB-000031.

Reason for Modification:
To document potential past differences between analysts and laboratories in recording structures using AHERA/ASTM, as modified by LB-000017, LB-000017A, and LB-000031, and provide a historical timeline for each Libby laboratory of potential changes in aspect ratio recording rules.

Potential Implications of this Modification:
None.

Laboratory Applicability (circle one): All [Individual](s) Batta Laboratories, Inc.

This laboratory modification is (circle one): **NEW** **[APPENDS] to LB-000031A** **SUPERCEDES** _____

Duration of Modification (circle one):
Temporary Date(s): _____
Analytical Batch ID: _____
Temporary Modification Forms – Attach legible copies of approved form w/ all associated raw data packages

[Permanent] (Complete Proposed Modification Section) Effective Date: HISTORIC
Permanent Modification Forms – Maintain legible copies of approved form in a binder that can be accessed by analysts.

Data Quality Indicator (circle one) – Please reference definitions on reverse side for direction on selecting data quality indicators:

Not Applicable **Reject** **[Low Bias]** **Estimate** **[High Bias]** **No Bias**

Proposed Modification to Method (attach additional sheets if necessary; state section and page numbers of Method when applicable):

Technical Review: _____ Date: _____
(Laboratory Manager or designate)

Project Review and Approval: _____ Date: _____
(Volpe: Project Technical Lead or designate)

Approved By: _____ Date: _____
(USEPA: Project Chemist or designate)

DATA QUALITY INDICATOR DEFINITIONS

Reject - Samples associated with this modification form are not useable. The conditions outlined in the modification form adversely effect the associated sample to such a degree that the data are not reliable.

Low Bias - Samples associated with this modification form are useable, but results are likely to be biased low. The conditions outlined in the modification form suggest that associated sample data are reliable, but estimated low.

Estimate - Samples associated with this modification form are useable, but results should be considered approximations. The conditions outlined in the modification form suggest that associated sample data are reliable, but estimates.

High Bias - Samples associated with this modification form are useable, but results are likely to be biased high. The conditions outlined in the modification form suggest that associated sample data are reliable, but estimated high.

No Bias - Samples associated with this modification form are useable as reported. The conditions outlined in the modification form suggest that associated sample data are reliable as reported.

HISTORIC INFORMATION ON ASPECT RATIO RECORDING RULES

Beginning May 2002 (when Batta Laboratories began analyzing Libby samples), all analysts used fiber definition of ≥ 5:1 aspect ratio and ≥ 0.5 µm length for all AHERA analyses, and any project-specific requirements regarding the aspect ratio were incorporated into AHREA/ASTM (dust) analyses as available through various lab modifications.

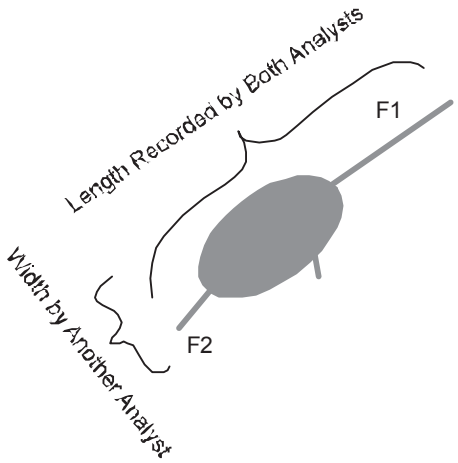
DEVIATIONS FROM LAB MODIFICATIONS LB-000017, LB-000017A, LB-000031

Prior to LB-000066, NAM structures were recorded by all analysts when deemed necessary by the analysts. Inconsistencies regarding the measurement and recording of clusters and matrices began as early as May, 2003 when compared with the guidelines outlined in LB-000031). See Attachments #1 through #4 for clarifications and illustrations. Figure numbers in the following attachments are corresponding to structure examples provided in LB-000031.

Batta Laboratories, Inc. began to comply with LB-000031 among analysts beginning August 23, 2006, with sample batch CDM-91 (EPA Job# L10972).

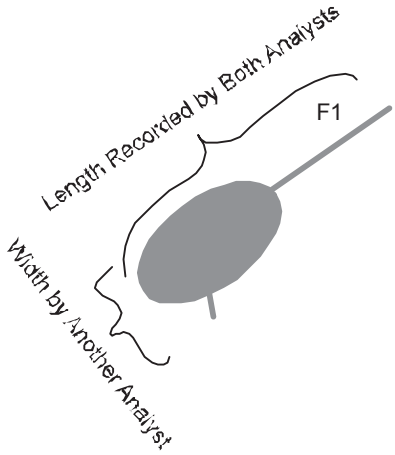
Attachment #1

Figure 5: Matrix



Batta recorded as one matrix:

width: one analyst took the average of F1 and F2 (if both are within the fiber definition), and the other took the overall width of the entire structure as illustrated.

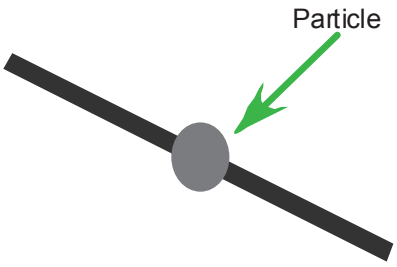


Batta recorded as one matrix:

width: refer to above.

Attachment #2

Figure 6

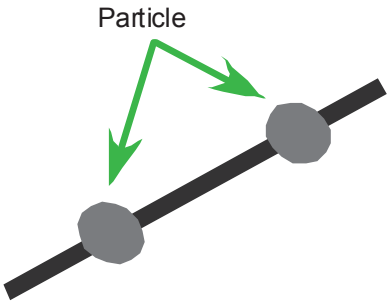


Batta recorded as either as one fiber or one matrix:

1) Matrix: particle size is equal or greater than 0.5 micron.

2) Fiber: particle size is less than 0.5 micron.

Figure 7



Batta recorded as either a fiber or a matrix:

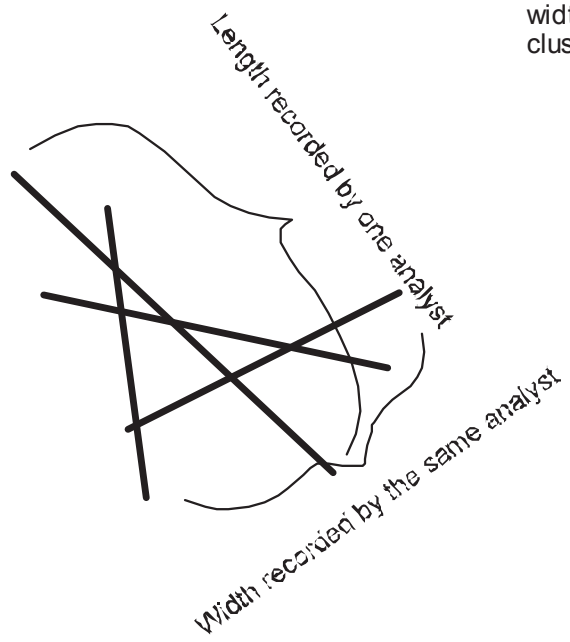
1) Fiber: both particles are less than 0.5 micron

2) Matrix: any one of the particles is equal or greater than 0.5 micron

3) Not a structure: both exposed fiber ends do not meet the fiber definition and both particles are equal or greater than 0.5 micron

Attachment #3

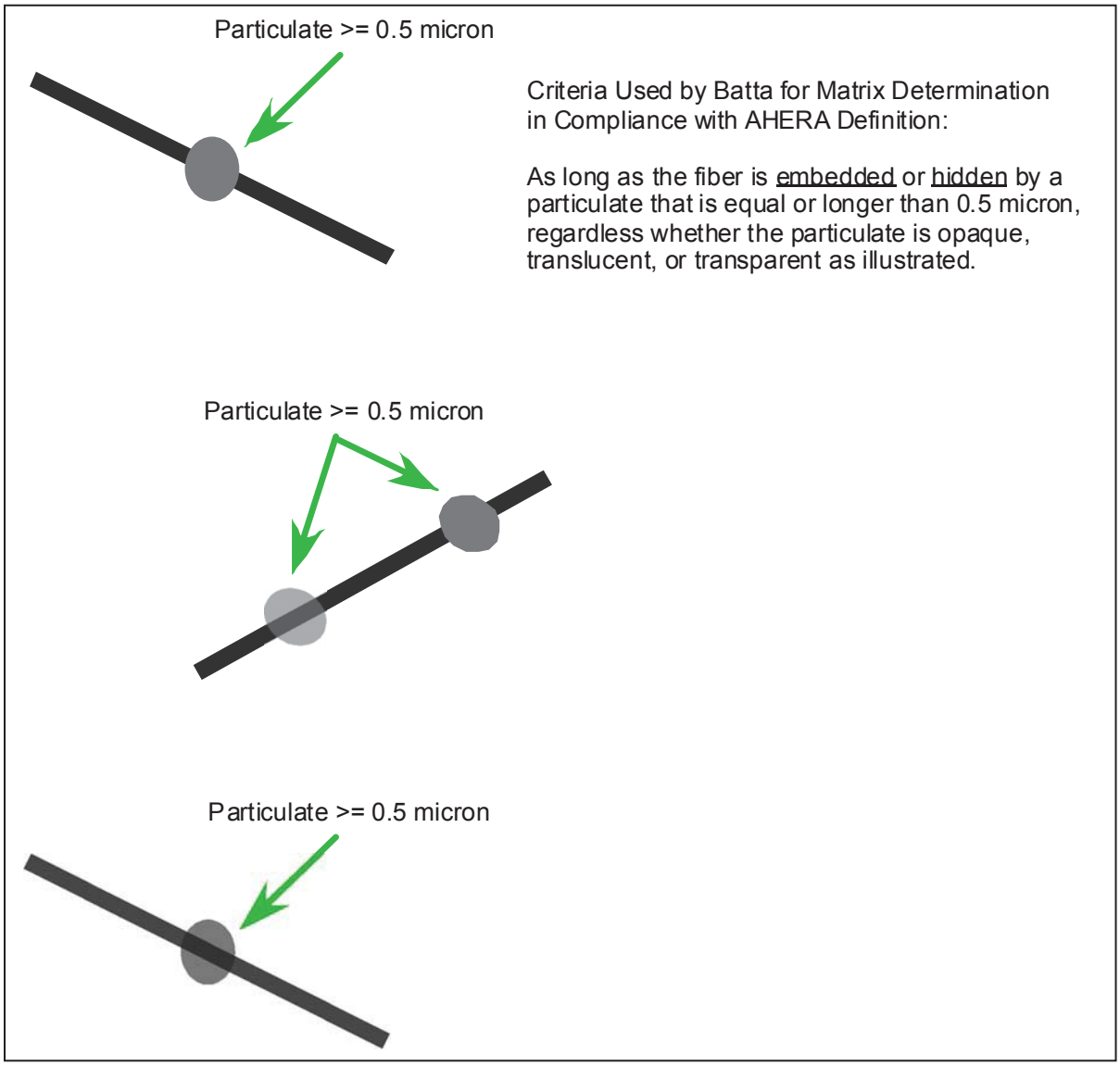
Figure 8: Cluster



Batta has internal discrepancies in recording the dimension of the this structure:

One analyst recorded as illustrated; the other recorded as the following:
length = the longest fiber within the cluster
width = average width of all fibers within the cluster

Attachment #4



Request for Modification
to
Laboratory Activities
LB-000031C

Instructions to Requester: E-mail form to contacts at bottom of form for review and approval.
File approved copy with Data Manager (CDM). Data Manager distributes approved forms as follows:
All Labs Applicable forms – copies to: EPA, Volpe, CDM, All project labs
Individual Labs Applicable forms – copies to: EPA, Volpe, CDM, Initiating Lab

Method (circle one/those applicable): [TEM-AHERA] TEM-ISO 10312 PCM-NIOSH 7400 NIOSH 9002
EPA/600/R-93/116 [ASTM D5755] EPA/540/2-90/005a SRC-LIBBY-03
Other: _____

Requester: Ed Cahill Title: National Director
Company: EMSL Analytical Date: September 26, 2006

Description of Modification:
Laboratory-specific clarification of potential inconsistencies among analysts when recording structures using AHERA/ASTM, as modified by LB-000017, LB-000017A, and LB-000031.

Reason for Modification:
To document potential past differences between analysts and laboratories in recording structures using AHERA/ASTM, as modified by LB-000017, LB-000017A, and LB-000031, and provide a historical timeline for each Libby laboratory of potential changes in aspect ratio recording rules.

Potential Implications of this Modification:
None.

Laboratory Applicability (circle one): All [Individual](s) EMSL Analytical

This laboratory modification is (circle one): **NEW** **[APPENDS] to LB-000031A** **SUPERCEDES** _____

Duration of Modification (circle one):
Temporary Date(s): _____
Analytical Batch ID: _____
Temporary Modification Forms – Attach legible copies of approved form w/ all associated raw data packages

[Permanent] (Complete Proposed Modification Section) Effective Date: HISTORIC
Permanent Modification Forms – Maintain legible copies of approved form in a binder that can be accessed by analysts.

Data Quality Indicator (circle one) – Please reference definitions on reverse side for direction on selecting data quality indicators:

Not Applicable **Reject** **Low Bias** **Estimate** **High Bias** **[No Bias]**

Proposed Modification to Method (attach additional sheets if necessary; state section and page numbers of Method when applicable):

Technical Review: _____ Date: _____
(Laboratory Manager or designate)

Project Review and Approval: _____ Date: _____
(Volpe: Project Technical Lead or designate)

Approved By: _____ Date: _____
(USEPA: Project Chemist or designate)

DATA QUALITY INDICATOR DEFINITIONS

Reject - Samples associated with this modification form are not useable. The conditions outlined in the modification form adversely effect the associated sample to such a degree that the data are not reliable.

Low Bias - Samples associated with this modification form are useable, but results are likely to be biased low. The conditions outlined in the modification form suggest that associated sample data are reliable, but estimated low.

Estimate - Samples associated with this modification form are useable, but results should be considered approximations. The conditions outlined in the modification form suggest that associated sample data are reliable, but estimates.

High Bias - Samples associated with this modification form are useable, but results are likely to be biased high. The conditions outlined in the modification form suggest that associated sample data are reliable, but estimated high.

No Bias - Samples associated with this modification form are useable as reported. The conditions outlined in the modification form suggest that associated sample data are reliable as reported.

Analysts Interviewed
Steve Bennett
Jodie Bourgerie (August 2001 in Libby and 5 times after)
Ed Cahill
Joe Centifonti
Robyn Denton (late 2002 and 2003)
Bob Georgens
Richard Harding
Ken Klutts
Brett Macey
Ron Mahoney
Anant Samudra
Paul Senne (in Libby 2003, 2004, 2005)

Ex Employees (not interviewed)
Adrian Arav (whereabouts unknown)
Duane Salinas (whereabouts unknown)
Tom Ferrante (deceased)
Richard White (whereabouts unknown)

HISTORIC INFORMATION ON ASPECT RATIO RECORDING RULES

Beginning in late 1999, the aspect ratio applied by EMSL was greater than or equal to 5:1. Sometime in the spring of 2001, analysts received verbal direction to record structures regardless of aspect ratio. In late 2001 or early 2002, project analysts reverted back to 5:1. EMSL analyst interviews were conducted in August and September 2006. On August 29, 2006, all laboratories were instructed to use 5:1 for AHERA/ASTM analyses.

DEVIATIONS FROM LAB MODIFICATIONS LB-000017, LB-000017A, LB-000031

All analysts followed AHERA/ASTM method recording rules, as well as the guidance in the above laboratory modifications, except as noted below. Figure numbers in the following attachments are corresponding to structure examples provided in LB-000031.

structure	Steve Bennett
2	record longest L and maximum width
3	as stated in Mod 31
4	record longest L and maximum width
8	record longest sub-structure L and maximum width perpendicular to that sub-structure

structure	Joe Centifonti
2	Maximum width
3	As stated in Mod 31, BUT AR of whole bundle is used as criterium
4	Maximum width
5	Add ALL fiber Lengths and average fiber width
6	As stated in Mod 31, BUT Matrix
7	As stated in Mod 31, BUT Matrix
8	L=longest fiber BUT W=average width

structure	Robyn Denton (late 2002 and 2003)
5	Pre 2005 L=add up all sub structure L. W=average W of sub structure fibers. From 2005 on, overall L and W was recorded.
6	Matrix. Pre 2005 L=add up all sub structure L W=average W of sub structure fibers. From 2005 on overall L and W was recorded.
7	would call Matrix

structure	Bob Georgens
2	record longest L and maximum width
4	record longest L and maximum width

6	matrix not fiber. Record total L and max width
7	matrix not fiber. Record total L and max width
8	record longest sub-structure L and widest sub-structure W

structure	Ken Klutts
3	As stated in Mod 31, UNLESS AR of bundle <5 the record average width of component fibers
4	As stated in Mod 31, UNLESS AR of bundle <5 the record average width of component fibers
5	Add ALL AHERA countable fiber Lengths and average fiber width
8	L = longest fiber W = average fiber width

structure	Brett Macey
3	as stated in Mod 31 BUT AR of whole bundle is used as criterion
5	Add ALL fiber Lengths and average fiber width
6	as stated in Mod 31 BUT Matrix
7	as stated in Mod 31 BUT Matrix
8	L=longest fiber BUT W=maximum width

structure	Anant Samudra
8	record longest sub-structure L and maximum width perpendicular to that sub-structure ***At times, recorded AHERA analyses in ISO 10312 format*

structure	Paul Senne (in Libby 2003, 2004, 2005)
6	Matrix if matrix material is >0.5 microns

Request for Modification
to
Laboratory Activities
LB-000031D

Instructions to Requester: E-mail form to contacts at bottom of form for review and approval.
File approved copy with Data Manager (CDM). Data Manager distributes approved forms as follows:
All Labs Applicable forms – copies to: EPA, Volpe, CDM, All project labs
Individual Labs Applicable forms – copies to: EPA, Volpe, CDM, Initiating Lab

Method (circle one/those applicable): [TEM-AHERA] TEM-ISO 10312 PCM-NIOSH 7400 NIOSH 9002
EPA/600/R-93/116 [ASTM D5755] EPA/540/2-90/005a SRC-LIBBY-03
Other: _____

Requester: Kyeong Corbin Title: TEM Laboratory Supervisor
Company: Hygeia Laboratories Inc. Date: September 20, 2006

Description of Modification:
Laboratory-specific clarification of potential inconsistencies among analysts when recording structures using AHERA/ASTM, as modified by LB-000017, LB-000017A, and LB-000031.

Reason for Modification:
To document potential past differences between analysts and laboratories in recording structures using AHERA/ASTM, as modified by LB-000017, LB-000017A, and LB-000031, and provide a historical timeline for each Libby laboratory of potential changes in aspect ratio recording rules.

Potential Implications of this Modification:
None.

Laboratory Applicability (circle one): All [Individual](s) Hygeia Laboratories Inc.

This laboratory modification is (circle one): **NEW** **[APPENDS] to LB-000031A** **SUPERCEDES** _____

Duration of Modification (circle one):
Temporary Date(s): _____
Analytical Batch ID: _____
Temporary Modification Forms – Attach legible copies of approved form w/ all associated raw data packages

[Permanent] (Complete Proposed Modification Section) Effective Date: HISTORIC
Permanent Modification Forms – Maintain legible copies of approved form in a binder that can be accessed by analysts.

Data Quality Indicator (circle one) – Please reference definitions on reverse side for direction on selecting data quality indicators:

Not Applicable **Reject** **Low Bias** **Estimate** **High Bias** **No Bias**

Proposed Modification to Method (attach additional sheets if necessary; state section and page numbers of Method when applicable):

Technical Review: _____ Date: _____
(Laboratory Manager or designate)

Project Review and Approval: _____ Date: _____
(Volpe: Project Technical Lead or designate)

Approved By: _____ Date: _____
(USEPA: Project Chemist or designate)

DATA QUALITY INDICATOR DEFINITIONS

Reject - Samples associated with this modification form are not useable. The conditions outlined in the modification form adversely effect the associated sample to such a degree that the data are not reliable.

Low Bias - Samples associated with this modification form are useable, but results are likely to be biased low. The conditions outlined in the modification form suggest that associated sample data are reliable, but estimated low.

Estimate - Samples associated with this modification form are useable, but results should be considered approximations. The conditions outlined in the modification form suggest that associated sample data are reliable, but estimates.

High Bias - Samples associated with this modification form are useable, but results are likely to be biased high. The conditions outlined in the modification form suggest that associated sample data are reliable, but estimated high.

No Bias - Samples associated with this modification form are useable as reported. The conditions outlined in the modification form suggest that associated sample data are reliable as reported.

HISTORIC INFORMATION ON ASPECT RATIO RECORDING RULES

Hygeia Laboratories Inc. received the first batch of AHERA samples on September 16, 2002. Two analysts, Kyeong Corbin and Quynh Trieu, were involved in analyzing all Libby project samples. All AHERA samples were analyzed according to the AHERA counting rules (aspect ratio 5:1 or greater) and any project-specific requirements were incorporated as available. At times, asbestos structures with an aspect ratio of at least 3:1 were recorded by the analyst. These were indicated as such on the data sheet and on the EDD, and were recorded as non-countable (i.e., total column populated with a zero).

DEVIATIONS FROM LAB MODIFICATIONS LB-000017, LB-000017A, LB-000031

Both analysts agree on the counting rules mentioned in LB-000017, LB-000017a, and LB-000031 and clarifications stated below:

1. Hygeia recorded no asbestos detected grid opening as “NSD” as expressed in the AHERA instead of “ND” as requested by project modification during the period of 6/1/02 to 11/30/02. The Lab Mod LB-000023 was filed.

2. As results of August 6, 2002 teleconference, the following instructions were given to the analysts:
   - Do not count NAM structures. At times, NAM structures were still recorded if the analyst thought it was necessary and marked as such on the data sheet and on the EDD, and were recorded as non-countable (i.e., total column populated with a zero).
   - Record fiber, bundle, cluster, and matrix as F, B, C, M as indicated by AHERA. (Do not record matrix as MF, MB, MC, F/M, B/M, or C/M.)

3. As results of August 13, 2002 teleconference, the following instructions were given to the analysts:
   - Measure only visible portion of the fiber or bundle sticking out of the matrix. (Prior to this date, any matrix components that were embedded in opaque matrix were measured by doubling length or to the end of matrix depending on the matrix size.)
   - It is a non-countable structure if both ends were embedded in the matrix. (In general, non-countable structures were recorded and indicated as such on the data sheet and on the EDD.)
   - Intersection is defined as stated on the AHERA, i.e. Non-parallel toughing or crossing of fibers, with the projection having an aspect ratio 5:1 or greater. (If <5:1 projection, it was considered no intersection.)

4. As results of September 9 and September 13, 2003 teleconferences, the following clarifications were given to the analysts as of October 2003:
   - No doubling of length measurement when crossing grid bars (different from ISO, i.e. ISO requires length to be doubled);
   - Count all grid bars;
   - Measure visible portion only;
   - For C or M, record the dominant/longest sub-structure’s dimension;
   - Do not use F/m, B/m, or C/m classification; just record it as M, matrix.

5. Stopping rules for chrysotile structures were changed from 100 structures to 50 structures in October 2003. The laboratory was instructed to file an individual lab mod for these cases.

Request for Modification
to
Laboratory Activities
LB-000031E

Instructions to Requester: E-mail form to contacts at bottom of form for review and approval.
File approved copy with Data Manager (CDM). Data Manager distributes approved forms as follows:
All Labs Applicable forms – copies to: EPA, Volpe, CDM, All project labs
Individual Labs Applicable forms – copies to: EPA, Volpe, CDM, Initiating Lab

Method (circle one/those applicable): [TEM-AHERA] TEM-ISO 10312 PCM-NIOSH 7400 NIOSH 9002
EPA/600/R-93/116 [ASTM D5755] EPA/540/2-90/005a SRC-LIBBY-03
Other: _____

Requester: Michael D. Mount Title: EM Manager
Company: Materials Analytical Services Date: September 25, 2006

Description of Modification:
Laboratory-specific clarification of potential inconsistencies among analysts when recording structures using AHERA/ASTM, as modified by LB-000017, LB-000017A, and LB-000031.

Reason for Modification:
To document potential past differences between analysts and laboratories in recording structures using AHERA/ASTM, as modified by LB-000017, LB-000017A, and LB-000031, and provide a historical timeline for each Libby laboratory of potential changes in aspect ratio recording rules.

Potential Implications of this Modification:
None.

Laboratory Applicability (circle one): All [Individual](s) Materials Analytical Services

This laboratory modification is (circle one): **NEW** **[APPENDS] to LB-000031A** **SUPERCEDES** _____

Duration of Modification (circle one):
Temporary Date(s): _____
Analytical Batch ID: _____
Temporary Modification Forms – Attach legible copies of approved form w/ all associated raw data packages

[Permanent] (Complete Proposed Modification Section) Effective Date: HISTORIC
Permanent Modification Forms – Maintain legible copies of approved form in a binder that can be accessed by analysts.

Data Quality Indicator (circle one) – Please reference definitions on reverse side for direction on selecting data quality indicators:

Not Applicable **Reject** **Low Bias** **Estimate** **High Bias** **[No Bias]**

Proposed Modification to Method (attach additional sheets if necessary; state section and page numbers of Method when applicable):

Technical Review: _____ Date: _____
(Laboratory Manager or designate)

Project Review and Approval: _____ Date: _____
(Volpe: Project Technical Lead or designate)

Approved By: _____ Date: _____
(USEPA: Project Chemist or designate)

DATA QUALITY INDICATOR DEFINITIONS

Reject - Samples associated with this modification form are not useable. The conditions outlined in the modification form adversely effect the associated sample to such a degree that the data are not reliable.

Low Bias - Samples associated with this modification form are useable, but results are likely to be biased low. The conditions outlined in the modification form suggest that associated sample data are reliable, but estimated low.

Estimate - Samples associated with this modification form are useable, but results should be considered approximations. The conditions outlined in the modification form suggest that associated sample data are reliable, but estimates.

High Bias - Samples associated with this modification form are useable, but results are likely to be biased high. The conditions outlined in the modification form suggest that associated sample data are reliable, but estimated high.

No Bias - Samples associated with this modification form are useable as reported. The conditions outlined in the modification form suggest that associated sample data are reliable as reported.

HISTORIC INFORMATION ON ASPECT RATIO RECORDING RULES

MAS currently has four analysts (Mike Mount, Kevin Simpson, Mehrdad Motamedi, and Will Stark) performing ISO 10312 analyses of Libby samples. The first set of Libby AHERA samples (dust samples) were received on 10/08/04. At this time, analyst performing TEM analysis were Will Stark, Ding Qian and Kevin Simpson. AHERA/ASTM method dust samples were counted and recorded for asbestos structures utilizing an aspect ratio criterion of 5:1 or greater, unless the project-specific requirements stated otherwise.

DEVIATIONS FROM LAB MODIFICATIONS LB-000017, LB-000017A, LB-000031

All analysts followed AHERA/ASTM method recording rules, as well as the guidance in the above laboratory modifications, except as noted below:

- Between 1/1/06 to 8/31/06, TEM analysts Mike Mount and Mehrdad Motamedi, recorded asbestos fibers and bundles with visible ends as a matrix structure instead of a fiber or bundle.

Request for Modification
to
Laboratory Activities
LB-000031F

Instructions to Requester: E-mail form to contacts at bottom of form for review and approval.
File approved copy with Data Manager (CDM). Data Manager distributes approved forms as follows:
All Labs Applicable forms – copies to: EPA, Volpe, CDM, All project labs
Individual Labs Applicable forms – copies to: EPA, Volpe, CDM, Initiating Lab

Method (circle one/those applicable): [TEM-AHERA] TEM-ISO 10312 PCM-NIOSH 7400 NIOSH 9002
EPA/600/R-93/116 [ASTM D5755] EPA/540/2-90/005a SRC-LIBBY-03
Other: _____

Requester: Jeanne Orr Title: President
Company: Reservoirs Environmental, Inc. Date: September 25, 2006

Description of Modification:
Laboratory-specific clarification of potential inconsistencies among analysts when recording structures using AHERA/ASTM, as modified by LB-000017, LB-000017A, and LB-000031.

Reason for Modification:
To document potential past differences between analysts and laboratories in recording structures using AHERA/ASTM, as modified by LB-000017, LB-000017A, and LB-000031, and provide a historical timeline for each Libby laboratory of potential changes in aspect ratio recording rules.

Potential Implications of this Modification:
None.

Laboratory Applicability (circle one): All [Individual](s) Reservoirs Environmental, Inc.

This laboratory modification is (circle one): **NEW** **[APPENDS] to LB-000031A** **SUPERCEDES** _____

Duration of Modification (circle one):
Temporary Date(s): _____
Analytical Batch ID: _____
Temporary Modification Forms – Attach legible copies of approved form w/ all associated raw data packages

[Permanent] (Complete Proposed Modification Section) Effective Date: HISTORIC
Permanent Modification Forms – Maintain legible copies of approved form in a binder that can be accessed by analysts.

Data Quality Indicator (circle one) – Please reference definitions on reverse side for direction on selecting data quality indicators:

Not Applicable **Reject** **Low Bias** **Estimate** **High Bias** **[No Bias]**

Proposed Modification to Method (attach additional sheets if necessary; state section and page numbers of Method when applicable):

Technical Review: _____ Date: _____
(Laboratory Manager or designate)

Project Review and Approval: _____ Date: _____
(Volpe: Project Technical Lead or designate)

Approved By: _____ Date: _____
(USEPA: Project Chemist or designate)

DATA QUALITY INDICATOR DEFINITIONS

Reject - Samples associated with this modification form are not useable. The conditions outlined in the modification form adversely effect the associated sample to such a degree that the data are not reliable.

Low Bias - Samples associated with this modification form are useable, but results are likely to be biased low. The conditions outlined in the modification form suggest that associated sample data are reliable, but estimated low.

Estimate - Samples associated with this modification form are useable, but results should be considered approximations. The conditions outlined in the modification form suggest that associated sample data are reliable, but estimates.

High Bias - Samples associated with this modification form are useable, but results are likely to be biased high. The conditions outlined in the modification form suggest that associated sample data are reliable, but estimated high.

No Bias - Samples associated with this modification form are useable as reported. The conditions outlined in the modification form suggest that associated sample data are reliable as reported.

HISTORIC INFORMATION ON ASPECT RATIO RECORDING RULES

Reservoirs Environmental began analyzing samples for the Libby Project in November, 1999. Analysts applied an aspect ratio of 5:1 to the countable structures unless project specific requirements stated otherwise.

DEVIATIONS FROM LAB MODIFICATIONS LB-000017, LB-000017A, LB-000031

All analysts followed AHERA/ASTM method recording rules, as well as the guidance in the above laboratory modifications, except as noted below:

- Analysts at Reservoirs have historically characterized a fiber with both ends visible and matrix in the middle as a matrix, whereas LB-000031 designates this type of structure as a fiber.
- Samples counted in 1999 and 2000 were recorded on historical laboratory bench sheets and are identified in LB-000001 through LB-000014.
- In August, 2002 the project no longer required that NAM structures be recorded. On occasion, analysts recorded NAM structures when the analyst found the structure notable. The NAM structure was noted as non-countable by recording a zero in the total column.
- Excluded structures, such as a fiber with both ends obscured by matrix or a fiber with less than the required aspect ratio, were recorded and designated as non-countable by recording a zero in the total column.

Appendix C. Characterization of Amphibole Fibers from ore originating from Libby, Montana; Louisa County, Virginia; and Palabora, Republic of South Africa.

By:

David L. Berry, Ph.D.

U.S. EPA Region 8
Ecosystems Protection and Remediation
1595 Wynkoop Street [8EPR-PS]
Denver, CO 80202-1129

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

EPA Region 8 obtained samples of ore from Libby, South Africa, and Virginia from Dr. James Lockey, University of Cincinnati, and analyzed the samples to determine mineralogy and particle size distribution (length, width, and aspect ratio) using transmission electron microscopy and energy dispersive spectroscopy to identify the nature of the amphibole fibers. Dr. Lockey obtained the South African and Virginia ore samples from the Marysville facility in 1980 and the Libby ore [Libby #3ore] from an expansion plant in Salt Lake City, Utah, in 1981. Region 8 was unable to obtain vermiculite or ore from the Enoree, South Carolina mine complex.

The ore from the Rainey Creek complex [Vermiculite Mountain Mine, Libby, Montana] resides in large ultramafic intrusive bodies that are rich in biotite, pyroxenite, and biotitite, a rock comprised of almost pure biotite. The ultramafic intrusions are cut by deposits of syenite and carbonatite and much of the biotite has been hydrothermally altered to hydrobiotite and vermiculite [Frank and Edmond, 2001, Meeker, et. al. 2003]. The pyroxenite has been altered to fibrous soda-rich amphiboles and contacts with pyroxenite surrounding the biotitite contain the vermiculite ore zone containing diopside, hydrobiotite and apatite. Fibrous and non-fibrous amphiboles are located in both veins and disseminated throughout the intrusive rock along cleavage planes of pyroxene. Amphiboles from Vermiculite Mountain had been referred to as soda tremolite, richterite, soda-rich tremolite, tremolite asbestos, and richterite asbestos by a number of investigators. In 2000, Wylie and Verkouteren [2000] identified winchite as the principle amphibole in the Vermiculite Mountain deposit based on chemical investigation referencing the classification system of Leake et al. [1997] and optical properties. Meeker et al. [2003] investigated amphibole types from the mine complex using electron probe microanalysis and X-ray diffraction analysis and reported the presence of winchite, richterite, tremolite, and magnesioriebeckite. Magnesio-arfvedsonite and edenite were detected in low abundance. The amphibole composition of the Libby Amphiboles is roughly winchite, richterite, tremolite, magnesio-riebeckite, magnesio-arfvedsonite, and edenite [84:11:6:<1:<1:<1]. The O. M. Scott

facility received ore from the Vermiculite Mountain Mine complex, Libby, Montana from 1959 through 1980.

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

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

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

There is limited information on the asbestos content of the ores from the Louisa deposit. Rohl and Langer [1977] reported both chrysotile and amphibole fibers in six ore samples from the Louisa deposit. The chrysotile was reported as fibers and bundles while the amphiboles were described as widely composed with most of the fibers classified as actinolite. Moatamed et. al. [1986] analyzed a Virginia ore sample collected at a processing plant in Salt Lake City, Utah and reported traces of fibrous amphibole asbestos identified as actionlite in the form of cleavage fragments having low aspect ratios. Amphibole content for both unexfoliated and exfoliated ores ranged up to 1.3 % amphibole asbestos.

Ores from the Enoree, South Carolina deposits are primarily hydrobiotite and biotite in origin. Fluroapatite is a common mineral collocated with the hydrobiotite. Zircon is also widely

dispersed throughout the plutons along with minor accessory minerals including talc, chlorite, chromite, rutile, titanite, corundum, anatase, and amphibole asbestos [Hunter, 1950]. The amphibole asbestos identified in the vermiculite deposit at Enoree has been classified as tremolite [Libby, 1955].

As previously noted, EPA Region 8 obtained samples of ore from Libby, South Africa, and Virginia from Dr. James Lockey, University of Cincinnati, and analyzed the samples to determine the particle size distribution (length, width, and aspect ratio) using transmission electron microscopy and energy dispersive spectroscopy to identify the mineral composition of the amphibole fibers. Region 8 was unable to acquire a sample of ore from the South Carolina Enoree mine complex for analysis. Region 8 conducted analysis of the ore and exfoliated materials to connect the exposures of workers to mineral fibers in Marysville, OH to the ore originating in Libby, MT. The connection is based on fiber morphology, mineralogy, and fiber size similarities.

In order to analyze the fibers from the ore and vermiculite bulk material, the fibers must be loaded onto filters and prepared for analysis by transmission electron microscopy [TEM]. Three potential methods were considered for transferring the fibers from the bulk material to filters: water elutriation, glove-box transfer, and the fluidized bed asbestos segregator [FBAS]. Of these three methods, the glove-box and FBAS involved physical disturbance of the bulk material to elutriate fibers into the air that might be similar to handling and processing of ore in the Marysville plant. Due to the limited quantity of test material available for analysis, Region 8 employed the FBAS as an analytical instrument to load the mineral fibers onto filters for TEM analysis

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

The laboratory followed fiber counting rules detailed in the Quality Assurance Project Plan for the specific study using Libby-specific laboratory modifications. Total amphibole fibers and Phase Contrast Microscopy equivalent [PCMe] fibers were counted for each of the ore/vermiculite samples as described in Appendix B. A total of 1.0 mm^2 area or a total of 200 asbestos structures were counted to achieve the desired analytical sensitivity [1/g; 1.5E+4]. Energy dispersive spectroscopy [EDS] was performed on selected samples from each of the vermiculite/ore samples to provide mineral characterization of individual fibers. Fiber counts were recorded on NADES data sheets for further analysis. Only the Libby vermiculite and Libby ore samples had sufficient fibers detected to construct a fiber size distribution.

Fiber counts were determined by counting fiber numbers for a specific area of the filter grid or a specific number of grid openings [which ever was achieved first] to determine total fibers present. As shown in Table C-1, the number of fibers for the test materials varied greatly depending on the source and the grid area measurement was exceeded prior to the fiber count metric [167 grid openings~1.0 mm^2].

Table C-1 Fiber Detected in Ore and Expanded Product

		Structures Counted			Concentration [s/g]		
Sample Type	**Grid Openings**	**LA**	**OA**	**C**	**LA**	**OA**	**C**
Virginia Ore	167	0	0	0	0	0	0
Virginia Expanded	167	1	0	0	13,008	0	0
South Africa Ore	167	2	0	2	26,403	0	26,403
South Africa Expanded	167	0	0	0	0	0	0
Libby # 3 Ore	167	320	0	0	1,393,873	0	0
Libby Expanded	167	100	0	0	468,213	0	0

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

The Libby #3 ore and the Libby #3 expanded material contained the greatest number of fibers both in fiber counts on the filters and in calculated structures per gram of bulk material. Virginia expanded and South African ore contain amphibole structures represented by low fiber counts. South African ore also contained chrysotile fibers as determined by morphology and EDS analysis. The absence of fibers detected in the Virginia ore and the South African expanded materials probably represents actual low fiber content of the ore and is a function of the detection limit for the structure analysis. The estimation of structures per gram of material indicated that there were 13- to 26 thousand fibers per gram of bulk material which was approximately 18 times lower than the Libby ore samples. The decrease in fibers found in the Marysville facility

after 1980 when only ore from Virginia, Palabora, and South Carolina was used (Appendix F) is consistent with the findings of low fiber counts for the Virginia and Palabora materials. In addition, numerous non asbestiform minerals were also detected including biotite, micas, and pyroxenes in the bulk materials from Virginia and South Africa.

Amphiboles are a complex group of minerals characterized by double chains of silicate tetrahedral and the generic chemical formula of: $A_{0-1}B_2C_5T_8O_{22}[OH]_2$ where A, B, C, and T represent the various cations. The modern classification system of amphiboles is described in: Leake et al. [1997]. To classify the mineral species of the amphibole, it is not sufficient to determine its composition; the various cations must be assigned to the specific A, B, C, and T sites. The cutoffs of the compositional ranges allowed for each amphibole mineral species are based on the number of the cations in the various sites. The methodology to classify an amphibole is to first determine its elemental compositions [e.g., as expressed as weight percent oxide for each element or as atomic percent for each element]. Then a normalized routine is applied to the raw elemental measurements to calculate the number of each of the cations contained in one formula unit. [This is a simple arithmetic calculation since the cation percents have been measured and the stoichiometry must balance the charges of the cations and anions.] Generally, one formula unit is assumed to contain 23 oxygens. Next the sites are filled up by assigning cations to them subsequently, specifically:

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

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

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

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

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

The Libby amphibole group of minerals is a complex group of amphiboles consisting of 6 minerals:

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

- Edenite $NaCa_2Mg_5Si_7AlO_{22}[OH]_2$

Libby amphibole is characterized by a low amount of Al in the T site [and a correspondingly high Si content] so according to Leake's classification, if the Si [expressed as atoms per formula unit, apfu] is at least 7.5 and Al content in the T site is <0.5, all 6 Libby amphibole types can be plotted on a graph of Na content of the B site versus the [Na + K] content in the A site. This approach was described by Meeker et al. [2003] for the Rainy Creek complex.

EDS spectra [TEM/EDS] were collected from all amphibole fibers found in the South Africa and Virginia samples, and 6 randomly-selected LA fibers in each of the Libby ore and Libby expanded samples. Two bundles of asbestiform serpentine [chrysotile] were found in the South Africa ore sample. EDS spectra were collected for one of the bundles. The chemical formula of serpentine is $Mg_3Si_2O_5[OH]_4$. The EDS software package collected and summarized each spectrum to determine the atomic percent of each element of interest.

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

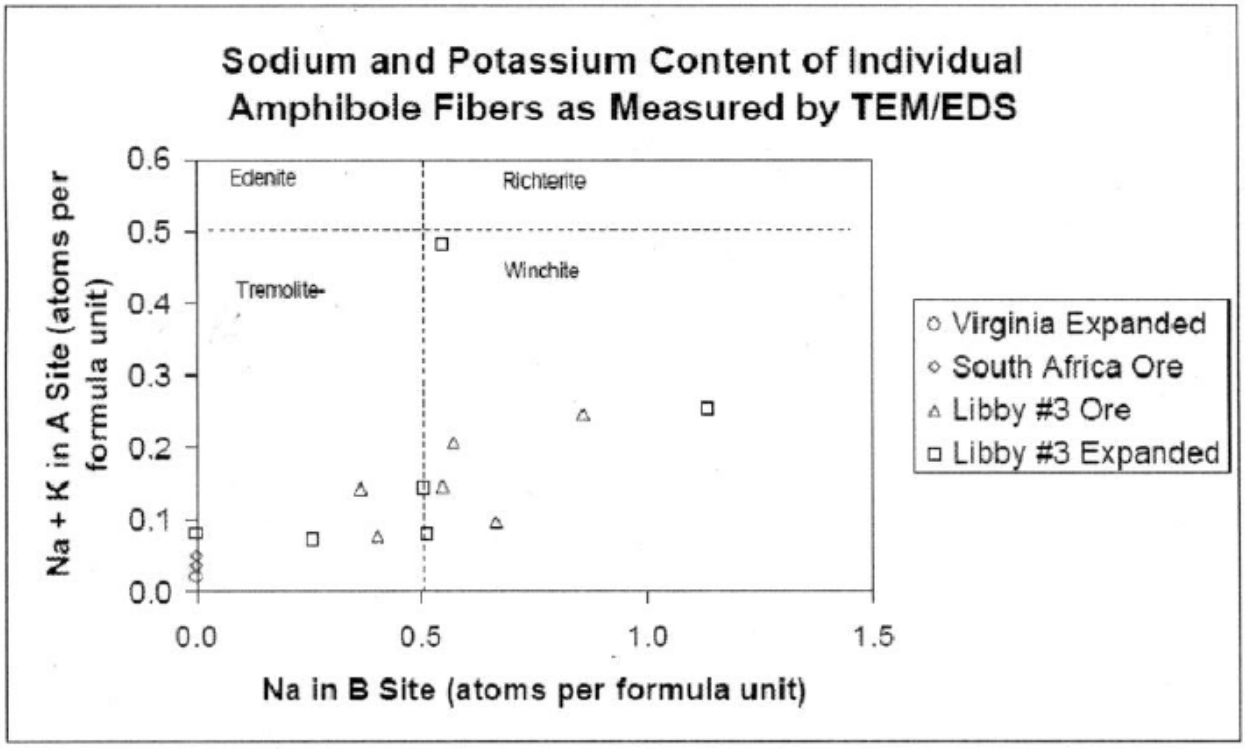
1) Numbers of cations per formula unit are calculated on the basis of 23 oxygens. This may or may not be correct, since an [OH] site in the amphibole crystal can be occupied by either OH^-, F^-, Cl^-, or O^{2-}. The calculated cation numbers will be affected if a significant quantity of O^{2-} is in the OH site.
2) A persistent problem with amphiboles is that they can contain both ferric [3+] and ferrous [2+] iron in the same crystal. For the purposes of this report all Fe was assumed to be Fe^{2+}. A routine for calculating the ratio of Fe^{2+} to Fe^{3+} is described in Leake et al. [1997] but it is very complex, applies to polished sections, and was not attempted for this report.
3) For the purposes of this report, the T sites were assumed to be filled completely full to 8 apfu and the C sites were assumed to be completely full to 5 apfu. All Ca and any Mg, Fe, and Mn remaining after the C site was full were then assigned to the B site. Next, Na was assigned to the B site until it was full [2 apfu], then any remaining Na and all K was assigned to the A site.

   Applying these assumptions to the TEM/EDS data produce a useable graph of the Na and K content of the amphibole fibers. As shown in Figure C-1, Libby #3 ore and Libby #3 Expanded amphiboles were characteristic of winchite and tremolite. Virginia Expanded and South African ore both contained amphibole fibers characteristic of non-Libby [Na and K negative] in the tremolite series.

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

- The single Virginia amphibole asbestos fiber is an actinolite
- Both of the South African amphibole fibers are tremolite
- 8 of the LA fibers from Libby are winchite
- 4 of the LA fibers from Libby are Tremolite

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

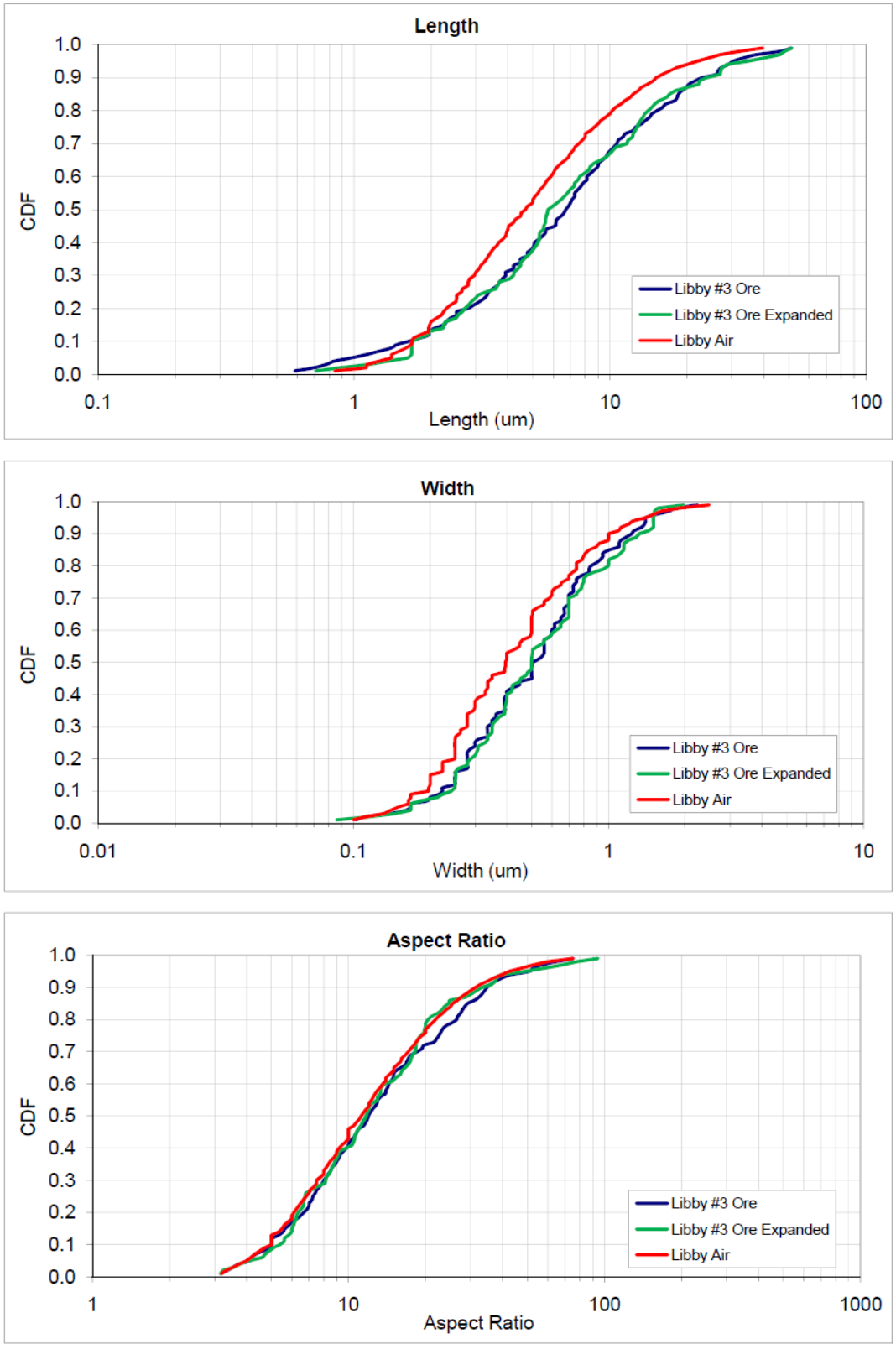


Fiber size distributions for amphibole fibers from the Libby #3 ore and Libby #3 Expanded sources were conducted on the fibers counted during the TEM analysis of the filter grids. Due to the low fiber count detected in the Virginia and South Africa sources, it was not possible to develop a fiber size distribution for these fibers. The LA fiber size data were plotted as a cumulative distribution frequency for fiber length, fiber width, and aspect ratio. These data were compared to LA fibers collected in Libby as part of EPA's ongoing ambient air monitoring program and the Libby Asbestos Superfund site [Appendix B]. The Libby ore and expanded

material showed an increased frequency of longer and wider fibers than the fibers from the Libby ambient air sampling program. Aspect ratios were nearly identical. The differences between the length and width frequency were not outside of the expected range for LA fibers and were consistent with fiber size distributions for soil activity-based-sampling data from Libby.

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

Figure C-2. Fiber size Distribution of LA amphiboles



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APPENDIX D: Analysis of Subchronic and Chronic Studies and Cancer Bioassays in Animals and Mechanistic Studies

D.1 Subchronic and Chronic Studies and Cancer Bioassays

D.1.1 Oral

McConnell et al. (1983a) describe part of a National Toxicology Program study (NTP, 1990a) performed to evaluate the toxicity and carcinogenicity of ingestion of several minerals. This study examined chrysotile and amosite in both hamsters and rats, and crocidolite and tremolite only in rats. This chronic bioassay was designed to encompass the lifetime of the animal, including exposure of the dams from which the test animals were derived. Although the study examined chrysotile, amosite, crocidolite, and tremolite, for the purposes of this document, the focus is on the results from exposure to tremolite. The tremolite (Governeur Talc Co, Governeur, New York) used was not fibrous. Instead, the material was crystalline, as this form was a common contaminant in talc at the time of these studies (McConnell et al., 1983a) (Table D-1). Citing the Stanton (1981) paper, McConnell et al. (1983a) stated that crystalline tremolite can become fibrous upon grinding. Tremolite was incorporated by 1% weight into NIH-31 feed and given to 250 male and female F344 rats from birth until death (118 male and female controls).

Table D-1. Fiber characteristics and distribution of fibers analyzed in feed studies in F344 rats

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

[a]Average groups, more detailed in primary paper.
Source: McConnell et al. (1983a).

No significant tumor induction was observed in the animals with oral exposure to tremolite animals. Although non-neoplastic lesions were observed in many of the aging rats,

these were mostly in the stomach and occurred in both controls and exposed animals. The lesions included chronic inflammation, ulceration, and necrosis of the stomach (McConnell et al., 1983a). McConnell et al. (1983a) suggested that nonfibrous tremolite could account for the lack of toxicity following exposure in this group of animals. Also, oral studies of asbestos, in general, show decreased toxicity and carcinogenicity as compared to inhalation and implantation/injection studies.

D.1.2 Inhalation

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

Table D-2. Pulmonary fibrosis and irregular alveolar wall thickening produced by tremolite exposure

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

[a]Percentage of 100 squares counted in lung tissue area.
[b]Percentage of total lung tissue area.
SD = standard deviation
Source: Adapted from Davis et al. (1985).

Table D-3. Tumors (benign and malignant) produced by tremolite exposure

Tumor site	Control (n = 36)	Tremolite (n = 39)
Pulmonary		
Adenomas	0	2
Adenocarcinomas	0	8
Squamous carcinomas	0	8

Mesotheliomas	0	2
Other organ systems		
Digestive/peritoneal	5	3
Urinogenital	3	1
Endocrine	3	5
Musculoskeletal, integumentary	5	5
Reticuloendothelial/vascular	20	15

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

Although Davis et al. (1985) did not describe the data, the difference between tremolite and chrysotile was stated to be statistically significant, with tremolite exposure inducing more fibrotic and carcinogenic lesions (Table D-2). These results show that rats exposed to tremolite exhibited increased numbers of pulmonary lesions and tumors. Tumors observed in other organ systems are also listed in Table 4-24 and appear to be unrelated to exposure. Although a method for an injection study is described in Davis (1985), only the inhalation results are presented. This same tremolite was used in later intraperitoneal injection experiments (Davis et al., 1991) and might be what the authors are referring to in this article.

Wistar rats were exposed for 13 consecutive weeks (6 hours per day, 5 days per week) to either Calidria chrysotile asbestos or tremolite asbestos in a flow-past, nose-only inhalation study (Bernstein et al., 2003) (Table D-4). The long-term effects from the same exposure were described in Bernstein et al. (2005) (6 hours per day, 5 days per week). This study describes the full results through 1 year after cessation of tremolite exposure in Wistar rats (n = 56). The tremolite samples were chosen to have 100 fibers/mL of fibers longer than 20 μm present in the exposure aerosol. Fibers were defined as any object with an aspect ratio >3:1, length ≥5 μm, and diameter ≤3 μm, and all other objects were considered nonfibrous particles. Counting was stopped when nonfibrous particle counts reached 30, and fiber counting was stopped at 500 with length ≥5 μm, diameter ≤3 μm, or a total of 1,000 fibers and nonfibrous particles were recorded (Bernstein et al., 2003). Lung tissue and associated lymph nodes were examined by histopathology following tissue digestion. Associated lymph nodes showed erythrophagocytosis (minimal severity) in one animal at all time points, compared to chrysotile and control, which showed erythrophagocytosis (minimal severity) only at 180 days.

Table D-4. Chrysotile and tremolite fiber characteristics of fibers used in inhalation exposure studies in rats

Fiber type	Mean no. fibers evaluated	Mean no. total fibers/mL	Mean % total fibers, >20 μm length	Mean diameter (μm) ± SD	Mean length (μm) ± SD	Diameter range (μm)	Length range (μm)

Chrysotile	2,016	48,343.2	0.4	0.08 ± 0.07	3.61 ± 7.37	0.02–0.7	0.07–37.6
Tremolite	1,627	3,128.1	3.4	0.32 ± 3.52	5.49 ± 13.97	0.1–3.7	0.9–75

Source: Bernstein et al. (2003).

Table D-4 shows the comparison of number, concentration, and mean size distribution of fibers used in this study. Note that the mean tremolite fiber diameter and length are much greater than those of chrysotile, but the size ranges do overlap somewhat (Bernstein et al., 2003). The long tremolite fibers, once deposited in the lung, remain throughout the rat's lifetime. Even the shorter fibers, following early clearance, remain with no dissolution or additional removal. At 365 days post exposure, the mean lung burden was 0.5 million tremolite fibers >20-µm long and 7 million fibers 5–20-µm long with a total mean lung burden of 19.6 million tremolite fibers. The tremolite-exposed rats showed a pronounced inflammatory response in the lung as early as 1 day post exposure, with the rapid development of granulomas (1 day post exposure) followed by the development of pulmonary fibrosis characterized by collagen deposition within the granulomas. Increases in alveolar macrophages and granulomas were observed at all time points (1, 2, 14, 90, and 180 days) measured except 365 days. Pulmonary fibrosis increased starting at 14 days and continued to be observed for up to 365 days. Slight interstitial fibrosis also was observed, but only at 90 and 180 days post exposure. This study demonstrates that tremolite exposure leads to pronounced inflammation and fibrosis (Bernstein et al., 2006). Tumors were not observed in this study, which is a consistent observation with the time frame observed in other studies (i.e., 1 year post exposure) (Smith, 1978).

D.1. 3 Intratracheal Instillation

A recent study by Putnam et al. (2008) was designed to explore gene-environment interactions in the development of asbestos-related diseases. C57Bl/6 mice were exposed once to either Libby Amphibole asbestos (Six Mix) (100 µg via intratracheal instillation); crocidolite (100 µg via intratracheal instillation); or saline (30 µL via intratracheal instillation). Characteristics of fibers are described in Table D-5. Animals were sacrificed, and the lungs harvested 6 months post-instillation. The left lung was used for ribonucleic acid (RNA) isolation, and the right lung was used for histology (personal communication, e-mail from E. Putnam [University of Montana] to M. Gwinn [U.S. EPA] 02/26/09). Histology on mouse lungs from each treatment group demonstrated an increase in fibrosis, as viewed by Gomori's trichrome staining, following exposure to crocidolite and, to a lesser extent, Libby Amphibole asbestos. Histologic tissue was also exposed to Lucifer Yellow stain to further analyze

Table D-5. Fiber characteristics for intratracheal instillation studies in mice.

Material	Diameter	Length	Aspect Ratio
Libby Amphibole asbestos (Six Mix)	0.61 ± 1.22 μm	7.21 ± 7.01 μm	22.52 ± 22.87
Crocidolite	0.16 ± 0.09 μm	4.59 ± 4.22 μm	34.05 ± 43.29

Source: Blake et al. (2007, 2008); Putnam et al. (2008); Smartt et al. (2009).

variability in collagen following exposure. Lucifer Yellow staining revealed an increase in collagen following exposure to both crocidolite and Libby Amphibole asbestos, but only crocidolite exposure led to a statistically significant increase ($p < 0.05$). RNA was isolated from homogenized lungs and purified for use in microarray analysis. Pooled RNA samples from mice in each exposure group were analyzed on a 0K element mouse oligonucleotide array (MWG Biotech), and expression was compared to a mouse reference standard RNA. Gene expression results were analyzed by GO Miner, and genes exhibiting at least 1.25-fold up- or down-regulation in treated lungs were described. These included genes involved in membrane transport, signal transduction, epidermal growth factor signaling, and calcium regulation for both crocidolite and Libby Amphibole asbestos exposures, which supports the increase in collagen observed above. Some limitations to this study are the use of a standard reference for gene expression comparisons (as opposed to the saline controls), the practice of describing genes only if a greater than two-fold difference in expression is observed, and the use of pooled samples of homogenized whole lung that in some cases could dilute variability between different areas of exposed lung (different lobes, fibrotic versus nonfibrotic).

A follow-up paper to Putnam et al. (2008), prepared by Smartt et al. (2009), examined the increase of collagen in C57Bl/6 mouse lung following exposure to crocidolite or Libby Amphibole asbestos and also examined a few specific gene alterations by quantitative reverse transcription polymerase chain reaction (RT-PCR). Animals (n = 3 to 6 mice per group) were dosed with the same samples (Table D-5) as described above (Putnam et al., 2008) but were euthanized at 1 week, 1 month, and 3 months post-instillation. Treated mice were then divided into two groups, with the left lung from the first group used for RNA isolation and the right lung used for histology. The lungs from the second group were used for protein isolation and hydroxyproline assay (personal communication, e-mail from E. Putnam [University of Montana] to M. Gwinn [U.S. EPA] 02/26/09). Similar to results from Putnam et al. (2008), Gomori's staining demonstrated increased collagen and inflammation at the airways in lungs of mice exposed to either Libby Amphibole asbestos or crocidolite. These results were similar following exposure to both amphiboles, with crocidolite effects appearing more severe at all time points examined. No changes at the pleura of the lungs that were indicative of potential mesothelioma

were observed; such changes, however, would not be expected in such a short time-frame. This study also examined severity of inflammation and found that, on average, crocidolite-exposed animals demonstrated minimal inflammation at 1 week post-instillation, which then progressively worsened at 1 and 3 months post-instillation. Although both asbestos exposures led to increased inflammation, Libby Amphibole asbestos exposure demonstrated minimal inflammation that did not progress in the time points examined. Gene expression alterations were measured by quantitative RT-PCR for genes involved in collagen accumulation and scar formation (Col1A1, Col1A2, Col3A1). Although exposure to both forms of asbestos at 1 week and 1 month post-instillation led to increased Col gene expression, the levels and subtypes altered varied. Libby Amphibole asbestos exposure led to increased gene expression of Col1A2 at 1 week post-instillation and Col3A1 at 1 month post exposure, while crocidolite led to no significant alterations in the expression of these genes. Both crocidolite and Libby Amphibole asbestos exposure led to increased Col1A1 gene expression as compared to saline control at 1 week and 1 month post exposure. Due to these differences in expression, the authors also examined the collagen protein levels in the lungs to compare to the gene expression changes. Total collagen content was determined by measuring the hydroxyproline content in the caudal aspect of the left lung. As compared to saline-exposed mice, a significant increase in hydroxyproline was observed at 1 week and 1 month following exposure to both crocidolite and Libby Amphibole asbestos; however, only lungs from crocidolite-exposed animals demonstrated a significant increase at 3 months post exposure. These studies demonstrate that exposure to Libby Amphibole asbestos lead to inflammation and fibrosis, although with differences in the time and level of response.

Shannahan et al. (2011) exposed two rat models of human cardiovascular disease to Libby Amphibole asbestos[1] to determine if the pre-existing cardiovascular disease in these models would impact the lung injury and inflammation following exposure. Healthy Wistar Kyoto (WKY) rats were compared to spontaneously hypertensive (SH) and spontaneously hypertensive heart failure (SHHF) rats following exposure. These rat models demonstrate pulmonary iron homeostasis dysregulation (Shannahan et al., 2010). All rats (male only) were exposed to 0, 0.25 or 1.0 mg/rat via intratracheal instillation and were examined at 1 d, 1 wk and 1 mo post-exposure. No changes were observed histopathologically, however, changes were observed in markers of homeostasis, inflammation and oxidative stress. Bronchoalveolar lavage fluid (BALF) protein was significantly increased in both the SH and SHHF rat models as compared to controls as early as 1 wk post-exposure. GGT activity was increased in a concentration-dependent manner with exposure to Libby Amphibole asbestos at the earliest

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

timepoint measured (1 d), and was more pronounced in WKY rats as compared to SH and SHHF rats. LDH activity was also elevated in all strains, but was more pronounced in the SHHF rat model. Neutrophil increases were observed following exposure in all strains, peaking at 1 d post-exposure in all strains and persisting in the SH and SHHF rats until 1 mo post-exposure. Macrophages showed similar results but persisted only in the SH rat model until 1 mo post-exposure. In order to determine any impact of exposure on iron homeostasis, BALF ferritin and transferrin levels were measured in the lung. Increases in ferritin and transferrin were observed in both SH and SHHF rats as compared to WKY controls. Non-heme iron was also observed to be increased in only the SH rats at 1 d and 1 wk post-exposure. Markers of inflammation (MIP-2) and oxidative stress (heme oxygenase-1, HO-1) were elevated in both SH and SHHF as compared to WKY rats at baseline, but limited exposure-related differences were observed. Limited changes were also observed in ascorbate and glutathione levels in BALF and lung tissue. While inflammation and cell injury were observed in all strains, no strain-related differences were observed following exposure to Libby Amphibole asbestos (Shannahan et al., 2011). In conclusion, this study showed the potential for population variability related to cardiac disease in response to exposure to Libby Amphibole asbestos, including markers of cellular injury, iron homeostasis and inflammation.

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

Blake et al. (2008) and Pfau et al. (2008) examined the role of asbestos in autoimmunity. Blake et al. (2008) performed in vitro assays with Libby Amphibole asbestos, and both studies performed the in vivo assays with tremolite. C57BL/6 mice were instilled intratracheally for a total of two doses each of 60-μg saline and wollastonite or Korean tremolite sonicated in sterile PBS, given 1 week apart in the first 2 weeks of a 7-month experiment. Detailed fiber characteristics were described in Blake et al. (2007) for wollastonite and Libby Amphibole asbestos, but not for Korean tremolite (Table D-5; wollastonite not shown).

Blake et al. (2008) described autoantibody production, monitored biweekly with blood samples from saphenous vein bleeds and then by cardiac puncture following euthanization. Specific autoantibodies were identified by immunoblotting with known nuclear antigens. These

autoantibodies were then incubated with murine macrophage cells previously exposed to Libby Amphibole asbestos, wollastonite, or vehicle. Only sera from mice exposed to tremolite showed antibody binding colocalized with SSA/Ro52 on the surface of apoptotic blebs (Blake et al., 2008).

In Pfau et al. (2008), collected serum samples and urine were checked for protein bi-weekly for 7 months. By 26 weeks, the tremolite-exposed animals had a significantly higher frequency of positive anti-nuclear antibody tests compared to wollastinate and saline. Most of the tests were positive for dsDNA and SSA/Ro52. Serum isotyping showed no major changes in immunoglobulin subclasses (IgG, IgA, IgM), but serum IgG in tremolite-exposed mice decreased overall. Further, IgG immune complex deposition in the kidneys increased, with abnormalities suggestive of glomerulonephritis. No increased proteinuria was observed during the course of the study. Local immunologic response was further studied on the cervical lymph nodes. Although total cell numbers and lymph-node size were significantly increased following exposure to tremolite, percentages of T- and B-cells did not significantly change. Because tremolite is part of the makeup of Libby Amphibole asbestos (6%), using tremolite-exposed mice might yield a similar response to Libby Amphibole asbestos-exposed mice. This same effect has been demonstrated following exposure to ultraviolet radiation in skin cells, suggesting a similar mechanism (Saegusa et al., 2002).

D.1.4 Injection/Implantation

LVG:LAK hamsters were intrapleurally injected with tremolite obtained from the Libby, MT mine in an unpublished study by Smith (1978) prepared for W.R. Grace & Company. These samples were identified as tremolite (22260p5; Sample 60) and 50% tremolite + 50% vermiculite (22263p2, Sample 63). Both fiber samples were measured by optical phase microscopy, and fibers were described as amorphous, irregularly shaped particles of about 5–15 μm diameter, with Sample 60 (tremolite) also containing the occasional fiber up to 30 μm long. Fiber size for Sample 60 (tremolite) also was measured by scanning electron microscopy (SEM) and was determined to have a geometric mean length of 2.07 μm, geometric mean diameter of 0.2 μm, and average aspect ratio of 10.36. Twenty-five milligrams of each of the two samples were individually injected intraperitoneally into the pleural cavity of LVG:LAK hamsters. Pathology was examined at approximately 3 months post exposure in 10 animals from each group, with the remaining animals observed until death, or 600 days post exposure, depending on the health of the animal. Average survivorship was 410, 445, and 421 days in groups exposed to Sample 60, Sample 63, and saline, respectively (Table D-6). Pleural fibrosis was observed 3 months post

exposure, and mesothelioma was observed in both treatment groups between 350 and 600 days post exposure, with no mesotheliomas in control groups.

Table D-6. Pleural adhesions and tumors following intraperitoneal injection exposure in LVG:LAK hamsters (25 mg)

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

[a]As analyzed in first group sacrificed (between 41 and 92 days post exposure).
[b]Rating for pleural adhesions: 0 = no adhesions; 1 = minimal adhesions; 4 = extensive adhesions.
[c]These include adrenal adenomas, adrenal adenocarcinomas, lymphoma, pulmonary adenocarcinoma, adrenal and salivary carcinoma, mesothelioma, rhabdomyosarcoma, hepatoma, thyroid carcinoma, subcutaneous carcinoma, and malignant melanoma.
Source: Smith (1978).

The Smith et al. (1979) study was designed to determine whether mesothelioma is a non-specific result of mesothelial cells trapped in fibrous pleural adhesions, occurring regardless of fiber type. Earlier studies by this group suggested that fibrosis and tumors resulting from fiber exposure (chrysotile or glass) were related to fiber dimensions (>20-μm long, >0.75-μm diameter) (Smith, 1974). Injected fibrous talc (FD-14) was used as a negative control in earlier studies and led to limited fibrosis and no tumor formation. The characteristics of the FD-14 sample are described in the proceedings of Smith (1974). No further information could be found on the characteristics of the samples used in this study.[2] Because the talc contained 50% tremolite, 35% talc, 10% antigorite, and 5% chlorite, it was considered a tremolite sample by Smith (1978). When the sample was later analyzed independently by Wylie et al. (1993), only 64 (12.8%) of 500 tremolite particles measured met the NIOSH definition of a fiber (≥3:1 aspect ratio). Wylie et al. (1993) note, however, that very long fibers of the mineral talc, with narrow widths and fibrillar structure, occur in this sample. A second tremolite sample (sample 275) used by Smith et al.(1979) was described as similar to FD-14, although no details were given. The last two samples were prepared from a deposit of tremolitic talc from the western

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

United States (sample 31) and from a specimen of asbestiform tremolite (sample 72),[3] respectively.

Each of the four samples was examined microscopically, although the data were not reported in the paper by Smith et al. (1979). The average fibers in sample 72 were long, thin, crystalline fibers (>20-μm long, 0.4-μm diameter). Sample 31 appeared to have fewer long, thin fibers than sample 72, and many of the fibers in this sample were acicular. The characteristics of the FD-14 sample were determined by phase microscopy (Smith, 1974), but no characterization method was reported for the other three samples in this study. Other samples used by this group have been analyzed by both optical and electron microscopy (Smith, 1974; Smith, 1978). The limited information on the fiber characteristics of the samples used in these studies is provided in Table D-7. Note that no information was provided confirming the presence or absence of particles or fibers less than 5 μm in length in any of the three papers by Smith (1974) or Smith et al. (1978, 1979). These data deficiencies limit the interpretation of results from this study.

Table D-7. Fiber characteristics and numbers of resulting tumors following intrapleural injection into Syrian hamsters of 10- or 25-mg fiber samples

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

[a]Although average length and diameter are reported, what range of fibers was counted is unclear. Smith, 1978 (unpublished) states that only fibers greater than 5 μm long are included. No other information is provided for these samples.
[b]Numerator = cumulative number of animals with tumors; denominator = number of survivors.
N/D = not described
Source: Smith et al. (1979); Smith (1974).

Following analysis of Syrian hamsters intrapleurally injected with 10 or 25 mg of each of the four samples of tremolite, Smith (1978) reported tumors at 350 days post exposure (25 mg) or 600 days postexposure (10 mg) for Samples 31 and 72 (Table D-7). Although number of animals was not provided by Smith et al. (1979), previous studies by these authors reported using 50 animals per exposure group (Smith et al., 1978; Smith, 1974). The results in Table D-7 present the cumulative number of tumors (numerator) at each time point analyzed over the

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

remaining survivors (denominator). The survival rate without tumor presentation was decreased for animals exposed to samples 72, 31, and 275. Smith et al. (1979) concluded that the FD-14 and 275 samples were noncarcinogenic, and sample 31 was less carcinogenic than sample 72. Hamsters exposed to sample 72 had extensive pleural fibrosis, which was observed to a lesser degree in hamsters exposed to the other samples (sample 72 > sample 31 > sample 275 = FD-14). No statistical information was reported for these results, and because the number of background tumors in control animals was not provided, no statistical analysis can be performed.

Both studies demonstrate that intrapleural injections of Libby Amphibole asbestos[4] leads to an increase in pleural fibrosis and mesothelioma in hamsters compared to controls or animals injected with less fibrous materials. The use of doses of equal mass for both studies makes it difficult to compare potency between samples, as each sample could have vastly different fiber number and total surface area. Although these studies clearly show the carcinogenic potential of Libby Amphibole asbestos fibers, intrapleural injections bypass the clearance and dissolution of fibers from the lung after inhalation exposures.

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

Wagner et al. (1982) examined three types of tremolite (California talc, Greenland, and Korea) using SPF Sprague-Dawley (n = 48) and Wistar (n = 32) rats, then followed up with a range of in vitro tests using the same fiber samples. Rats were injected intrapleurally (20 mg tremolite) at 8–10 weeks of age and allowed to live out their lives. Median survival times after injections were 644 days (California talc), 549 days (Greenland tremolite) and 557 days (Korean

[4] Assuming Smith et al. (1979) used Libby Amphibole asbestos.

tremolite). Positive controls had a decreased survival time due to an infection, which limits the interpretation of these data. Also, this study was performed separately using different rat strains for the three tremolite samples. The authors state that, although the decreased control survival time and use of different rat strains limit the usefulness of the study for quantitative analysis, the results can be described qualitatively. Of the three tremolites, only the Korean tremolite (Table D-9) showed carcinogenic activity producing mesothelioma (14/47 rats, 30%). Analysis of the fiber characteristics showed the Korean sample had fibers that were longer than 8 μm and a diameter less than 1.5 μm. The California talc and Greenland tremolite had little to no fibers in this size range (Table D-8). Follow-up in vitro assays in the sample publication (Wagner et al. 1982) confirmed the in vivo results, with the exposure to Korean tremolite resulting in increased lactic dehydrogenase (LDH) and β-glucuronidase (BGL) release, cytotoxicity, and giant-cell stimulation.

Table D-8. Fiber characteristics of three tremolite samples analyzed by in vivo and in vitro methods (TEM measurements)

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

TEM = transmission electron microscopy.
Source: Wagner et al. (1982).

Davis et al. (1991) examined six tremolites with differing morphologies through intraperitoneal injections with male SPF Wistar rats. Four of the tremolites were from Jamestown, California; Korea; Wales; and Italy; and two were from Scotland. Of these, the three from California, Korea, and Wales were asbestiform, and the other three were fiber bundles or prismatic (Table D-9). Rats were exposed (n = 33 or 36) with one intraperitoneal injection with samples that were 10-mg/2 mL sterile phosphate buffered saline (PBS). Animals were allowed to live out their full life spans or until signs of debility or tumor formation developed. Although exposure was performed based on sample weight, each sample was analyzed to determine the number of expected fibers per milligram, and, therefore, per exposure. These samples also were characterized further by counting fibers versus particles. Data were collected for all fibers

(aspect ratio >3:1) and particles (aspect ratio <3:1) of total fibers. A fiber was defined as any component ≥8-µm long and <0.25-µm diameter as measured by SEM (i.e., Stanton fibers).

Table D-9. Fiber characteristics in a 10-mg dose (as numbers of fibers)

Sample	No. of animals	No. of mesotheliomas	No. of fibers in 1 mg of injected dust ($\times 10^5$)	No. of fibers ≥8 µm long, <0.25 µm diameter[a] ($\times 10^5$)	No. of particles in 1 mg injected dust ($\times 10^5$)	Morphology
California	36	36	13,430	121	18,375	Asbestiform
Swansea	36	35	2,104	8	4,292	Asbestiform
Korea	36	32	7,791	48	13,435	Asbestiform
Italy	36	24	1,293	1	20,137	Fiber bundles
Carr Brae	33	4	8,99	0	9,490	Fiber bundles
Shinness	36	2	3,83	0	5,901	Prismatic

[a]Stanton fibers.
Source: Davis et al. (1991).

The authors' overall conclusions were that all materials studied could cause mesothelioma by this method of exposure and the number of Stanton fibers was not sufficient to explain the differences in response. Mesothelioma incidence was not correlated to Stanton fibers, total particles, or mass of dust. The best predictor of mesothelioma incidence was total fibers (Table D-9). Although three samples were considered asbestiform (California, Swansea, Korea), all samples had <1% of counted fibers defined as Stanton fibers. The highest mesothelioma incidence was observed for the California sample, which contained the most Stanton fibers (121 fibers per mg dust). The tremolite from Swansea, resulted in 97% mesothelioma incidence yet contained only 8 Stanton fibers per milligram (more than 90% less than in the California sample). In contrast, the Italy tremolite, although containing only 0.08% Stanton fibers, resulted in 67% mesothelioma incidence. Little is known, however, about the characteristics of particles or fibers <5-µm long. This study highlights two issues associated with all fiber studies: the limits of analytical techniques and the variability in response based on the metric used to measure exposure. This study also supports the premise that asbestos samples containing fibers that are not long and thin can be carcinogenic.

The Roller et al. (1996) study was designed to provide data on the dose-response of various fiber types in relation to their fiber dimensions (as measured by SEM). Fibers were defined in this study as having an aspect ratio of >5:1 for all lengths and widths. Female Wistar rats (n = 40) were given either one intraperitoneal injection of 3.3 mg or 15 mg of tremolite.

Rats were examined for tumors in the abdominal cavity following a lifetime (up to 30 months) of observation. This paper described the fiber dimensions in depth (Table D-10), while limited discussion is focused on the exposure results. This table shows the characteristics of the fibers

Table D-10. Characteristics of tremolite fibers intraperitoneally injected into Wistar rats

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

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

SEM = scanning transmission microscopy
Source: Roller et al. (1996).

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

D.2. Mechanistic Data and Other Studies in Support of the Mode of Action

D.2.1 In Vitro Studies – Libby Amphibole Asbestos

Hamilton et al. (2004) examined the potential for fibers, including Libby Amphibole asbestos, to modify the function of antigen-presenting cells (APC). Analysis was performed for 24 hours with two forms of asbestos (crocidolite [25 or 50 µg/mL] and Libby Amphibole

asbestos obtained from Site No. 30, Libby, MT [25 or 50 µg/mL]) and ultrafine particulate matter ($PM_{2.5}$ [particulate matter 2.5 microns diameter or less] [50 or 100 µg/mL]). Limited information is provided by Hamilton et al. (2004) on fiber characteristics. Samples from Site No. 30, however, are described as predominantly richterite and winchite by Meeker et al. (2003). Primary human alveolar macrophages were incubated for 24 hours with Libby Amphibole asbestos (25 or 50 µg/mL), crocidolite (25 or 50 µg/mL), or ultrafine particulate matter (50 or 100 µg/mL). Following incubation, cells were isolated from remaining particles and nonviable cells, after which 0.25×10^6 macrophages were co-cultured with autologous lymphocytes (1×10^6 cells) in an 11-day APC assay. This assay analyzes the antigen-presenting function of the pre-treated macrophages by stimulating the lymphocytes using tetanus toxoid as the antigen. The supernatant was assayed for cytokines at day 11, and Hamilton et al. (2004) found that pretreatment with either asbestos or $PM_{2.5}$ significantly upregulated both T_{H1} and T_{H2} cytokines (interferon gamma [IFNγ]; interleukin-4 [IL-4]; and interleukin-13 [IL-13]) ($p < 0.05$). Therefore, preexposure to either fibers or particles increased APC function, as reflected in increased cytokine release after tetanus challenge. No significant differences, however, were discernable between asbestos and $PM_{2.5}$ pretreatment. The authors speculated that the variability in response between samples assayed—presumably due to the use of primary cells—obscures statistical significance. Although this study supports a role for fibers and $PM_{2.5}$ in potentiating immune response, the implications of these findings to human health are unclear because many agents can activate macrophages prior to antigen challenge.

Recent studies (Blake et al., 2007, 2008) compared the response of murine macrophages (primary and cell line RAW264.7) to Libby Amphibole asbestos fibers and crocidolite asbestos fibers. The Libby Amphibole asbestos fibers (7.21 ± 7.01 µm long, 0.61 ± 1.22 µm diameter) used in these studies were obtained from the U.S. Geological Survey and were chemically representative of the Libby, MT mine (Meeker et al., 2003). The crocidolite fibers (4.59 ± 4.22 µm long, 0.16 ± 0.09 µm diameter) used in these studies were provided by Research Triangle Institute, North Carolina, and the noncytotoxic control fiber (wollastonite, 4.46 ± 5.53 µm long, 0.75 ± 1.02 µm diameter) was provided by NYCO Minerals, New York. Cells were exposed for 24 hours to fiber samples measured by relative mass (5 µg/cm^2), after which the cells were analyzed by transmission electron microscopy to measure internalization. The results of the first study (Blake et al., 2007) indicate that Libby Amphibole asbestos fibers can both attach to the plasma membrane and be internalized by macrophages, similar to the crocidolite fibers. These internalized fibers were primarily less than 2-µm long and were found localized in the cytoplasm, in cytoplasmic vacuoles, and near the nucleus following 3-hour exposure, 62.5 µg/cm^2. This same concentration (62.5 µg/cm^2) was selected for the remaining studies because cell viability was not decreased at this concentration for the

Libby Amphibole asbestos (92%); cell viability was decreased for crocidolite (62%), however, at this concentration. As a result, the remaining assays would be expected to have decreased viability following exposure to crocidolite, which may impact the levels of various responses. For example, the reactive oxygen species (ROS) measurement would increase with increased cell number; therefore, some of the quantitative results would be difficult to compare between fiber types unless normalized to cell number.

Oxidative stress was measured by the induction of ROS and the reduction in glutathione (GSH) levels. These two measurements generally complement each other, as GSH is used in cells to maintain intracellular redox balance in cells in response to increased ROS levels. Both Libby Amphibole asbestos and crocidolite fiber internalization generated a significant increase ($p < 0.05$) in intracellular ROS as quantified by the oxidation of 2,7-dichlorodihydrofluorescien (DCFH) to dichlorofluorescein with hourly readings on a fluorescent plate reader. Libby Amphibole asbestos exposure significantly increased ROS in a dose-dependent manner (6.25, 32.5, and 62.5 $\mu g/cm^2$), as early as 1 hour post exposure at the highest dose ($p < 0.05$), as compared to a no-treatment group. Only the highest concentration of crocidolite was tested. The lower concentrations of Libby Amphibole asbestos were not compared to crocidolite and wollastonite, but a comparison of the highest exposure concentrations (62.5 $\mu g/cm^2$) of Libby Amphibole asbestos, crocidolite, and wollastonite revealed greater ROS production following Libby Amphibole asbestos exposure (1 hour, $p < 0.05$). Blake et al. (2007) stated that similar results were seen in the primary cell line but did not report the data. To differentiate the type of ROS produced, dehydroergosterol (DHE) fluorescence intensity levels were used, revealing that superoxide anion was significantly increased following exposure to Libby Amphibole asbestos as compared to controls. This observation was further confirmed with use of a free radical scavenger (PEG-SOD [polyethylene glycol-superoxide dismutase]) specific to superoxide anion. This co-exposure of Libby Amphibole asbestos and PEG-SOD led to a significant decrease in ROS as compared to cells exposed only to Libby Amphibole asbestos ($p < 0.05$). Total intracellular superoxide dismutase (SOD) activity also was measured following exposure to Libby Amphibole asbestos and showed a decrease in activity at 3 hours post exposure as compared to controls ($p < 0.05$). Crocidolite appears to increase intracellular SOD activity at 24 hours post exposure. These three assays demonstrate that Libby Amphibole asbestos exposure leads to increased superoxide anion in macrophages, most likely by suppressing activity of intracellular SOD.

GSH levels were found to be decreased in response to Libby Amphibole asbestos and crocidolite exposure in the macrophage cell line as compared to unexposed cells ($p < 0.05$). The decreased GSH levels were more prominent following crocidolite exposure as compared to Libby Amphibole asbestos. Crocidolite exposure has been shown in other studies to lead to

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

To determine if the ROS production was related to fiber number for both Libby Amphibole asbestos and crocidolite, cell-fiber interactions and fiber internalization were measured following exposure to equal concentrations of crocidolite, Libby Amphibole asbestos, and wollastonite (62.5 $\mu g/cm^2$, 3 hours). With phase contrast light microscopy, the number of cells interacting with one or more fibers was counted (one hundred cells counted for each treatment). All murine macrophages bound or internalized at least one fiber from the Libby Amphibole asbestos sample (mean ± SD, 4.38 ± 1.06 internalized) or the crocidolite sample (3.28 ± 1.58 internalized), but not the wollastonite sample (Blake et al., 2007). No significant differences were observed in the responses to Libby Amphibole asbestos or crocidolite samples, suggesting that the differences in measured ROS were not related to cell number. Fiber sizes varied between the two samples, with the crocidolite sample containing a more homogeneous mixture of long fibers (exact size not given), while the Libby Amphibole asbestos sample contained a mixture of sizes and widths. These characteristics were not analyzed to determine what, if any, role they might play in the varied response.

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

the unexposed controls and wollastonite-exposed RAW264.7 murine macrophages, further confirming apoptosis.

The role of reactive oxygen species in chromosomal damage from asbestos was examined in a recent study of Libby Amphibole asbestos and UICC crocidolite in XRCC1-deficient human lung epithelial H460 cells (Pietruska et al., 2010). XRCC1 is involved in the repair mechanisms for oxidative DNA damage, particularly single strand breaks. This study examined the effect of XRCC1 deficiency (induced in cells by shRNA knockdown) following exposure to genotoxic (crocidolite and Libby Amphibole asbestos) and nongenotoxic compounds (wollastonite, titanium dioxide) on micronucleus formation. Cells were exposed to chemicals with known oxidants hydrogen peroxide (0–60µM) or bleomycin (0-10µg/ml) for 1 and 3 hrs, or the non-oxidant paclitaxel (0-5nM, 24hrs) to confirm the clonogenic survival of the knockout cells, and as positive and negative controls. Fiber size distribution for crocidolite and Libby Amphibole asbestos is shown in Table D-11. Micronuclei induction was measured following treatment of cells by controls as described above, and by 5µg/cm^2 fibers or TiO_2 particles for 24 hrs. Following treatment, cells were fixed, permeabilized, and blocked before exposed to anti-centromere antibodies, and micronuclei were counted and scored as centromere negative arising from DNA breaks (clastogenic) or centromere positive arising from chromosomal loss (aneugenic). Spontaneous micronuclei induction was increased in XRCC1-deficient cells as compared to control. Wollastonite and titanium dioxide did not induce micronuclei in either cell type. Crocidolite and Libby Amphibole asbestos induced dose-dependent increases in micronuclei formation in both cell types but with an increase in proportion of micronuclei in the XRCC1-deficient cells (Table D-12). Libby Amphibole asbestos exposure led to a decreased amount of micronuclei as compared to crocidolite. Specifically examining clastogenic versus aneugenic micronuclei, crocidolite exposure led to mainly clastogenic micronuclei while Libby Amphibole asbestos exposure led to a mixture of aneugenic and clastogenic micronuclei. Nuclear bud formation was also observed, but only with exposure to crocidolite and bleomycin. Western blot analysis was performed to analyze protein expression related to DNA damage repair (XRCC1) and cell cycle progression (p53, p21) (data not shown in publication). The differences observed between crocidolite and Libby Amphibole asbestos are most likely related to their physicochemical differences, particularly related to their iron content. However, these results support a genotoxic effect of exposure to both crocidolite and Libby Amphibole asbestos.

Table D-11. Size distribution of UICC crocidolite and Libby Amphibole asbestos used in Pietruska et al. (2010)[a]

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

[a]Distribution by diameter also given in original manuscript.
Source: Adapted from Supplemental Material of Pietruska et al. (2010).

Table D-12. Percent clastogenic micronuclei following exposure to Libby Amphibole asbestos or crocidolite

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

[a] $p < 0.05$ as compared to control cells.
Source: Pietruska et al. (2010).

Mechanisms of oxidative stress following exposure to Libby Amphibole asbestos were also studied in human mesothelial cells (Hillegass et al. 2010). Gene expression changes were measured with Affymetrix U133A microarrays (analysis with GeneSifter) following exposure to 15×10^6 µm^2/cm^2 Libby Amphibole asbestos[5] as compared to the non-pathogenic control (75×10^6 µm^2/cm^2 glass beads) in the human mesothelial cell line LP9/TERT-1 for 8 and 24 hrs. Gene expression of only one gene (manganese superoxide dismutase) was altered following exposure to Libby Amphibole asbestos for 8 hours, while 111 genes had an altered gene expression following exposure to Libby Amphibole asbestos at 24 hours (altered by at least 2-fold as compared to control).

[5] 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 non-toxic (15×10^6 µm^2/cm^2) or the toxic dose (75×10^6 µm^2/cm^2).

The gene for manganese superoxide dismutase (MnSOD; SOD2) was observed to be significantly upregulated at both time points ($p < 0.05$) as compared to non-pathogenic controls. This gene was confirmed in normal human pleural mesothelial cells (HKNM-2) by quantitative RT-PCR at 24 hours following exposure to the non-toxic dose of Libby Amphibole asbestos. Upregulation of three genes from this and previous studies by these authors were confirmed by quantitative RT-PCR (*SOD2, ATF,* and *IL8*) in HKNM-2 cells exposed to both Libby Amphibole and crocidolite asbestos. 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 one gene related to reactive oxygen species processing. Follow-up studies at both the 'non-toxic dose' (15×10^6 $\mu m^2/cm^2$) and the 'toxic dose' (75×10^6 $\mu m^2/cm^2$) exposure levels in LP9/TERT-1 cells examined SOD protein and activity, reactive oxygen species production and glutathione (GSH) levels. At 24 hours, SOD2 protein levels were increased following exposure to the toxic dose of Libby Amphibole asbestos ($p < 0.05$) but not at 8 hours. Cells exposed to all doses of Libby Amphibole and crocidolite asbestos also resulted in increases in copper-zinc superoxide dismutase (Cu/ZnSOD; SOD1) protein at 24 hours ($p < 0.05$) but not at 8 hours. Although total SOD activity remained unchanged, a dose-related SOD2 activity was observed following exposure to both doses of Libby Amphibole asbestos for 24 hours, but this appeared to be minimal and was not statistically significant (8 hours was not examined). Oxidative stress was measured by dichlorodihydrofluorescein diacetate (DCFDA) fluorescence staining detected by flow cytometry and was observed as both dose- and time-dependent in cells exposed to Libby Amphibole asbestos but was increased following exposure to the toxic dose of Libby Amphibole asbestos (statistical analysis not possible). Oxidative stress was further supported by analysis of gene expression of heme oxygenase 1 (HO-1) following exposure to Libby Amphibole asbestos in both LP9/TERT-1 and HKNM-2 cells for 8 and 24 hrs. HO-1 was significantly increased following exposure to the toxic dose of Libby Amphibole asbestos in both cell lines (p-value not given). GSH levels were transiently depleted following 2–8 hrs exposure to 75×10^6 $\mu m^2/cm^2$ levels of Libby Amphibole asbestos, with a gradual recovery up to 48hrs in LP9/TERT-1 cells (HKNM-2 not analyzed). Exposure to crocidolite asbestos at the toxic dose led to a significant GSH decrease at all times points up to 24 hrs exposure ($p < 0.05$). These studies demonstrate that Libby Amphibole asbestos 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 relative toxicity of Libby Amphibole asbestos was measured by gene expression changes of interleukin-8 (IL-8), cyclooxygenase-2 (COX-2), heme oxygenase (HO)-1 as well as other stress-responsive genes as compared to amosite (Research Triangle Institute) in primary

human airway epithelial cells (HAEC) in vitro. Comparisons were made with both fractionated (aerodynamic diameter ≤2.5μm) and unfractionated fiber samples (Duncan et al., 2010). Crocidolite (CRO) fibers (UICC) were also included in some portions of this study for comparison. Fractionation was performed using the water elutriation method (Webber et al., 2008) and characterized as described in Lowers and Bern (2009). Primary HAECs were exposed to 0, 2.64, 13.2, and 26.4 μg/cm^2 of crocidolite, amosite (AM), AM2.5 (fractionated), Libby Amphibole asbestos (LA), or LA 2.5 (fractionated) for 2 or 24 hours in cell culture. Confocal microscopy was used to determine fiber content in cells exposed for 4 or 24 hours to 26.4 μg/cm^2 AM2.5 or LA2.5 only. At 4h post-exposure, fibers were mainly localized on the periphery of the cell with some fibers internalized. By 24 h post-exposure, most fibers appeared to be internalized and localized by the nucleus. Cytotoxicity was determined by measurement of lactate dehydrogenase (LDH) from the maximum dose (26.4 μg/cm^2) of both amosite and Libby Amphibole asbestos samples, with less than 10% LDH present following exposure to all four samples. Cytotoxicity was also determined for just the fractionated samples of amosite and Libby Amphibole asbestos by measuring intracellular calcein fluorescence emitted by live cells and showed 95% and 99% viability for AM2.5 and Libby Amphibole asbestos 2.5, respectively. These results support a limited cytotoxicity of both amosite and Libby Amphibole asbestos under these concentrations and time frames.

Gene expression changes in specific inflammatory markers (IL-8, COX-2, HO-1) were analyzed by quantitative RT-PCR for AM, AM2.5, LA, LA2.5, and CRO at both 2 and 24h post-exposure (all doses). Minimal increases in gene expression of IL-8, COX-2 or HO-1 were observed at 2 h post-exposure to all five fiber types; at 24h post-exposure, however, a dose response was observed following exposure to all fiber types. The smaller size fractions resulted in differences in magnitude of gene expression changes between AM2.5 and LA2.5, with AM2.5 leading to greater induction of IL-8 and COX-2 as compared to LA2.5. HO-1 levels were comparable between the two samples (Table D-13). Gene expression of transforming growth factor (TGF)-B1 was also quantified, but only following exposure to AM2.5 and LA2.5 (all doses; data not shown in publication). Levels of IL-8 protein were also measured following 24 h exposure to AM2.5 and LA2.5 (all doses) and were statistically significant at the two highest exposures (13.2 and 26.4 μg/cm^2). Gene expression changes were also examined for 84 genes involved in cellular stress and toxicity using a 96-well RT-PCR array format following 24 h exposure to 13.2 μg/cm^2 AM, LA, AM2.5 or LA2.5 or to 26.4 μg/cm^2 LA2.5 only. The results show a pro-inflammatory gene expression response. Gene expression profiles were similar between AM and LA, but differences were observed between AM2.5 and LA2.5.

Table D-13. Gene expression changes following exposure to 26.4 μg/cm^2 amphibole asbestos for 24 hr[a]

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

[a]All results in fold change as compared to untreated control cells.
Source: Duncan et al. (2010).

To determine if surface iron on the fibers played a role in the inflammatory response, Duncan et al. (2010) also examined surface iron concentrations by two methodologies: inductively coupled plasma optical emission spectroscopy (ICP-OES) and citrate-bicarbonate-dithionite (CBD). Both assays determined AM2.5 appeared to have the greatest amount of surface iron, with both LA samples containing much lower levels of iron. Similar patterns of reactive oxygen species production were observed as measured by TBA-reactive product formation following exposure to AM, AM2.5, LA, and LA2.5. Both AM samples were found to generate the greatest amount of hydroxyl radicals compared to the two LA samples, with the fractionated AM2.5 and LA2.5 exhibiting small increases in ROS produced compared to the unfractionated samples.

D.2.2 In Vitro Studies - Tremolite

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

Cytotoxicity

Wagner et al. (1982) examined the in vitro cytotoxicity of three forms of tremolite (see Table D-8) used in their in vivo studies. LDH and BGL were measured in the medium following incubation of unactivated primary murine macrophages to 50, 100, and 150 μg/mL of each sample for 18 hours. Cytotoxicity of Chinese hamster lung fibroblasts V79-4 was measured by

methylene blue staining (fiber concentrations not given). Giant-cell formation in A549 human basal alveolar epithelial cell cultures was measured, using 100 and 200 μg/mL of each sample for 5 days. Crocidolite fibers were used as the positive control.

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

In a study to further elucidate the role of ROS following exposure to asbestos, Suzuki and Hei (1996) examined the role of heme oxygenase (HO) in response to asbestos. HO is induced in response to oxidative stress and functions to degrade heme; it might, therefore, prevent iron-mediated hydroxyl radical production. All fibers tested led to an increase in HO, though chrysotile (UICC) and crocidolite (UICC) led to a greater increase than tremolite (Metsovo, Greece) and erionite (Rome, Oregon). No statistics, however, are described for these results. This study focused on response to 20 and 40 μg/mL of chrysotile and then used doses that yielded 0.5 and 0.3 relative survival fractions for all other fibers (crocidolite, 20 and 40 μg/mL; tremolite, 150 and 300 μg/mL; erionite, 200 and 400 μg/mL). Fibers were not characterized in this paper. When normalized by survival fraction, the induction of HO above control was 3.89-, 3.86-, 2.75-, and 2.78-fold above background for chrysotile, crocidolite, tremolite, and erionite, respectively. Limited information is provided on the results of tremolite exposures beyond an increase in HO following an 8-hour exposure. This increased HO following exposure to tremolite demonstrates a response similar to that observed for crocidolite and chrysotile in this study. Crocidolite is further analyzed, with exposures to the antioxidants, superoxide dismutase and catalase, leading to a dose-dependent decrease in HO induction, which supports the role of HO in oxidative stress.

Wylie et al. (1997) examined the mineralogical features associated with cytotoxic and proliferative effects of asbestos in hamster tracheal epithelial (HTE) and rat pleural mesothelial (RPM) cells with a colony-forming efficiency assay. HTE cells are used because they give rise to tracheobronchial carcinoma, while RPM cells give rise to mesotheliomas. Cells were exposed to fibers by weight, number, and surface area (Table D-14).

Table D-14. Fiber characteristics of five fibers examined in vitro for cytotoxic (HTE cells) and proliferative effects (RPM cells)

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

NIEHS = National Institute of Environmental Health Sciences
Source: Wylie et al. (1997).

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

No proliferation was observed for either chrysotile or crocidolite asbestos fibers in RPM cells, but cytotoxicity was observed at concentrations greater than 0.05 $\mu g/cm^2$ ($p < 0.05$). All talc samples were less cytotoxic in both cell types. Comparing results of these samples when exposure is measured by fiber number, the same number of crocidolite asbestos fibers >5-µm long leads to proliferation in HTE cells, but proliferation did not occur for FD14 fibers. The other two talc samples showed both insignificant cytotoxicity (SI57) and significant cytotoxicity (CPS183, $p < 0.05$). Therefore, when measured by fiber number, the results show differential responses for the fibers analyzed, suggesting the mineralogy of the fibers is more important in determining the biological response to fibers. In the RPM cells, however, similar responses were seen for all fibers analyzed, except for the slight cytotoxicity of FD14 at 2.6 fibers/cm^2. This suggests that fiber number does play a role in biological response in this cell type.

Data analysis by surface area of these samples is shown in Table 4-29. The results of these samples in both cell lines demonstrated that the cellular responses seemed unrelated to the

surface area, which demonstrates the impact of the dose metric on data. Analyzing the data for cytotoxicity and proliferation based on the exposure measurement demonstrated differences in response depending solely on how the fibers were measured: by mass, number, or surface area. These results show variability in interpreting the results of the same assay based on the defined unit of exposure. Most early studies used mass as the measurement for exposure, which can impact how the results are interpreted. When possible, further analysis of fiber number and surface area would help elucidate the role of these metrics, particularly for in vivo studies.

Genotoxicity

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

Furthermore, this study demonstrated the clastogenic effects of tremolite, including chromosomal aberrations and micronuclei induction. Tremolite exposure (0–3.0 μg/cm^2) in Syrian hamster embryo (SHE) cells resulted in a statistically significant increase in chromosomal aberrations ($p < 0.02$) when all treatment groups were combined and then compared to controls; however, no clear dose-response relationship was evident (Athanasiou et al., 1992). Tremolite exposure in SHE cells did lead to a dose-dependent increase in chromosome aberrations that was statistically significant at the highest doses tested (1.0–3.0 μg/cm^2) ($p < 0.01$) (Table D-15).

Table D-15. Micronuclei induction (BPNi cells) and chromosomal aberrations (SHE cells) following exposure to tremolite for 24 hours

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

[a]Significantly different from control ($p < 0.05$).
[b]Significantly different from control ($p < 0.01$).
[c]Significantly different from control ($p < 0.02$).
Source: Athanasiou et al. 1992

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

To determine if tremolite has some tumor promoter characteristics, Athanasiou et al. (1992) further examined intercellular communication following exposure to 0–4.0 μg/cm^2 tremolite in both Chinese hamster lung fibroblasts (V79) and Syrian hamster embryo BPNi cells, which are sensitive to transformation. Inhibition of gap-junctional intercellular communication has been proposed to detect tumor-promoting activity of carcinogens (Trosko et al., 1982). No effect on the gap-junctional intercellular communication following tremolite exposure was observed.

Okayasu et al. (1999) analyzed the mutagenicity of Metsovo tremolite, erionite, and the man-made ceramic (RCF-1) fiber. Whether this tremolite is the same as that used in previous studies from this group is unclear. Tremolite from Metsovo, Greece, used in this study was characterized as 2.4 ± 3.1 μm long and 0.175 ± 0.13 μm diameter (arithmetic mean) with the number of fibers per microgram of sample equal to 1.05×10^5. Human-hamster hybrid A(L) cells contain a full set of hamster chromosomes and a single copy of human chromosome 11.

Mutagenesis of the CD59 locus on this chromosome is quantifiable by antibody complement-mediated cytotoxicity assay. The authors state that this is a highly sensitive mutagenicity assay, and previous studies have demonstrated mutagenicity of both crocidolite and chrysotile (Hei et al., 1992). The cytotoxicity analysis for mutagenicity was performed by exposing 1×10^5 A(L) cells to a range of concentrations of fibers as measured by weight (0–400 μg/mL or 0–80 μg/cm^2) for 24 hours at 37°C. CD59 mutant induction showed a dose-dependent increase in mutation induction for erionite and tremolite, but RCF-1 did not.

Summary:

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

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

Appendix E. Evaluation of Exposure-Response Data for Discrete Pleural Thickening in Workers from the Marysville Cohort

1. STATISTICAL ANALYSIS OF THE 2004 POST 1972 DATA SET

All analyses were performed using SAS® statistical software v. 9.1. BMDLs were obtained by the profile likelihood method as recommended by Crump and Howe (1985) using the NLMIXED procedure in SAS (Wheeler, 2005).

Investigation of Explanatory Variables

Dichotomous statistical models describing the probability of individual response as a function of cumulative exposure as measured by CHEEC in the units of fibers-yr/cc. In order to investigate the key explanatory variables for analysis, a forward selection process was used to evaluate the association of each of the potential covariates with odds of discrete pleural thickening, controlling for CHEEC. Covariates considered for inclusion in the model were time since first exposure, age at x-ray, gender, smoking history and BMI. This initial modeling was done using a standard logistic regression model as commonly applied in analysis of epidemiological data. The base model was a logistic regression model with cumulative exposure (natural log transformed) as the independent variable. This model provided an adequate fit to the data (Hosmer-Lemeshow p-value of 0.7073), and the exposure variable was statistically significantly associated with the outcome (beta [SE] = 0.5398 [0.2374], p-value=0.0230). Covariates were evaluated according to whether inclusion of the covariate improved model fit as assessed by the AIC, and statistical significance of the covariate. When controlling for cumulative exposure, inclusion of each of the covariates increased the AIC for the model, and none were associated with odds of discrete pleural thickening: time since first exposure -- p-value=0.9350; age at x-ray -- p-value=0.6822; gender – p-value=0.7734; smoking -- p-value=0.1905; BMI -- p-value=0.3206. Therefore, only exposure (CHEEC) was included in further analyses. See Table E-1.

TABLE E-1 Evaluation of covariates for the 2004 post 1972 set

Covariate	Wald p-value for beta coefficient corresponding to covariate	Wald p-value for beta coefficient corresponding to exposure	AIC
Base model (only ln(CHEEC))	--	0.0230	76.2
Time since first exposure	0.9350	0.0375	78.2
Age at x-ray	0.6822	0.0219	78.0
Gender	0.7734	0.0236	78.1
Smoking history	0.1905	0.0298	76.3
BMI*	0.3206	0.0110	57.4

*Note that only 98 observations used, due to missing values (AIC not comparable)

Investigation of Candidate Models

The candidate models were: logistic (with CHEEC considered as continuous and continuous with a natural logarithm transformation), probit (with CHEEC considered as continuous and continuous with a natural logarithm transformation), 3-parameter log-logistic, dichotomous Hill, and dichotomous Michaelis-Menten models. These are statistical models used to evaluate dichotomous data, and were considered appropriate given the supralinear nature of the observed relationship between Libby Amphibole exposure and prevalence of discrete pleural thickening. All of the candidate models had adequate fit as assessed by the Hosmer-Lemeshow test (a form of the Pearson chi-squared goodness of fit statistic) (Hosmer and Lameshow, 2000). BMDs and corresponding BMDLs were estimated for each of the candidate models. For the BMD estimates, a 10% BMR was used (see Section 5.2.2). Models were compared using the AIC--values were quite similar among the candidate models, ranging from 75.7 to 78.1. The model with the lowest AIC was the 3-parameter log-logistic model (AIC=75.7). Since BMD and BMDL estimates were similar from the set of candidate models, the 3-parameter log-logistic model was selected. See Table E-2.

Different exposure lags (0, 5, 10, 15 and 20 years) were then investigated for this model. The AIC values did not vary much for lags of 0 to 15 years (AIC ranging from 75.1 to 75.7); the 10-year lagged exposure provided the lowest AIC, and was selected as the preferred exposure metric. There was a notable decrease in model fit when using the 20-year lagged exposure (AIC of 77.0). In addition, there were cases of discrete pleural thickening in the full cohort with fewer than 20 years since first exposure; therefore, using such a long lag (which necessitates the assumption that these are background cases) was not judged to be appropriate.

The various model forms were compared using Akaike's Information Criterion (AIC), and general model fit was evaluated with the Hosmer-Lemeshow test. This is a goodness-of-fit test which compares observed and expected events. Observations are sorted in increasing order of estimated probability of the event occurring and then divided into ~10 groups. The GOF statistic is calculated as the Pearson chi-square statistic of observed and expected frequencies in these groups. The BMD was estimated for each candidate model using a BMR of 10% and assuming a

background rate of 1%. BMDLs were obtained by the profile likelihood method as recommended by Crump and Howe (Crump and Howe, 1985), using the NLMIXED procedure in SAS (Wheeler, 2005).

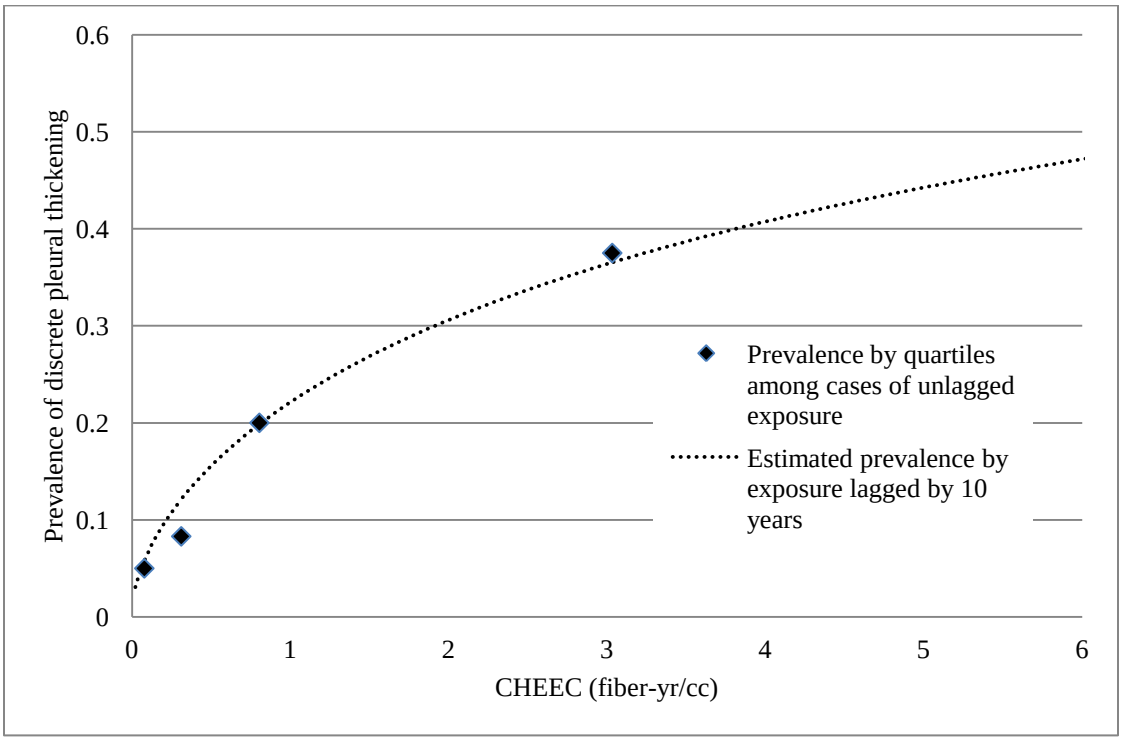
The 3-parameter log-logistic model using the 10-year lagged exposure had a p-value for fit of 0.74, an AIC value of 75.1, and the exposure variable was statistically significantly associated with odds of discrete pleural thickening (beta [SE]=0.6524 [0.2741], p-value=0.0189). This model yielded a BMD of 0.2543 fibers-yr/cc, and corresponding BMDL of 0.0757 fibers-yr/cc for a 10% increase in prevalence of discrete pleural thickening. See Table E-2 and Figure E-1.

TABLE E-2 Evaluation of different model forms for the 2004 post 1972 set

Model	Exposure Metric	Form	AIC	Hosmer-Lemeshow GOF p-value	BMD	BMDL
Logistic	CHEEC	P(CE)=1/[1+exp(-a-b*CE)]	78.3	0.7442	0.5715	0.2547
Logistic	ln(CHEEC)	P(CE)=1/[1+exp(-a-b*ln(CE))]	76.2	0.7073	0.2490	0.0558
Probit model	CHEEC	P(CE)=Φ(a+b*CE)	77.9	0.7726	1.5267	0.9185
Probit model	ln(CHEEC)	P(CE)=Φ(a+b*ln(CE))	76.6	0.6650	0.2276	0.0472
3-parameter log-logistic	ln(CHEEC	P(CE)=bkg+(1 – bkg) / [1 + exp(-a – b*ln(CE))]	75.7	0.7339	0.3447	0.0956
CE, lag 5			75.3	0.5519	0.2980	0.0887
CE, lag 10*			**75.1**	**0.6833**	**0.2543**	**0.0757**
CE, lag 15			75.4	0.4226	0.1993	0.0536
CE, lag 20			77.0	0.6363	0.1258	0.0196
Dichotomous Hill†	ln(CHEEC)	P(CE) = bkg + (Plateau – bkg)*CE^b / [exp(-a)+CE^b]	77.7	0.6724	0.3295	0.0961
Michaelis-Menten±	ln(CHEEC)	P(CE) = bkg + (Plateau – bkg)*CE / [exp(-a)+CE]	75.8	0.5413	0.3330	0.1342

*Parameter estimates for the best fitting model are as follows: intercept = -1.3040 (SE=0.4378), b=0.6524 (SE=0.2741, p-value=0.0189).
†For statistical modeling, the equivalent model form was used: P(CHEEC) = bkg + (Plateau – bkg) / [1 + exp(-a – b*ln(CE))]
± For statistical modeling, the equivalent model form was used: P(CE) = bkg + (Plateau – bkg) / [1 + exp(-a – ln(CHEEC))]

Figure E-1. Observed prevalence of discrete pleural thickening and estimated probability of discrete pleural thickening



DERIVATION OF THE CANDIDATE POD AND RFC FOR DISCRETE PLEURAL THICKENING USING THE 3-PARAMETER LOG-LOGISTIC MODEL

The candidate POD is 0.0757 fibers-yr/cc, the $BMDL_{10}$ for this data set. RfC is derived from the POD using the duration of exposure of 70 years, lagged by 10 years, and a total uncertainty factor of 100. See Section 5.1.3.2. This is the first approach referred to in Section 5.2.3.1.

> RfC = 0.0757 fibers-yr/cc x 1/ (70 – 10) years x 1/100 = 1E-05 fibers/cc (rounded to 1 significant digit)

2. STATISTICAL ANALYSIS OF THE FULL DATA SET

Identification of Key Explanatory Variables

In order to begin modeling the data, key explanatory variables were identified using logistic regression to analyze the data of Rohs et al. (2008). Logistic regression was performed using the R statistical software version 2.11.1. All fitting was performed using individual data, without any grouping. The dependent variable was discrete pleural thickening (n = 59) noted on chest x-rays of former workers in the Marysville facility (n = 252) and no reported history of exposure to commercial asbestos at other locations. The available potential explanatory variables included CE (cumulative exposure at the time of x-ray, f-yrs/cc; equivalent to CHEEC used in the University of Cincinnati report), T (time between first exposure and date of x-ray, yrs), age at

time of x-ray, gender, smoking status (ever, never), and body mass index (BMI). The BMI variable was missing for 34 individuals.

Initial analysis showed that CE was a significant explanatory variable using both CE and log(CE). The strategy used to determine what other explanatory variables were influential consisted of including CE and then adding one additional explanatory variable at a time. Explanatory variables having $p > 0.2$ were dropped from further consideration. Explanatory variables having $p < 0.2$ were given further consideration.

Body mass index (BMI) was investigated as a potential explanatory variable because fat pads can sometimes be misdiagnosed as pleural thickening. Thus, there might be a positive relation between BMI and pleural thickening. Analysis of a model with CE or log (CE) plus BMI ($n = 218$) showed that BMI was not a significant explanatory variable. Two subsequent models using BMI cutoffs of 25 and 30 also showed that BMI was not a significant explanatory variable. Analysis of a model with CE or log (CE) plus smoking indicated smoking was not a significant explanatory variable.

Analysis of a model of CE plus gender indicated gender was a potential contributing explanatory variable ($p = 0.18$). However, it should be noted that the worker cohort was highly imbalanced with 236 males and 16 females. Only 3 females have a cumulative human equivalent exposure greater than 0.15 f-yr/cc. These considerations indicated that the potential relevance of gender as an explanatory variable should be viewed with caution. Analysis of log (CE) plus gender showed that gender was not a significant explanatory variable. Accordingly, gender was eliminated as an explanatory variable.

The importance of T (the time from first exposure until the time of examination) is clearly illustrated by comparing the results of Lockey et al. (1984) with the results of Rohs et al. (2008). These two studies were conducted in the same occupational cohort 24 years apart. In the initial study (Lockey et al., 1984), only 2% of the individuals showed pleural changes; in the follow-up study (Rohs et al., 2008), 28% of the individuals showed pleural changes. Logistic fitting of a model including CE or log (CE) plus T showed that T was a highly significant explanatory variable with $p < 0.0005$. This result is consistent with findings in other occupational cohorts exposed to various forms of asbestos fibers that the time from first exposure is a significant explanatory variable, even in the absence of continued exposure (Ehrlich et al., 1992; Järvholm, 1992). T was retained as an explanatory variable. However, an important point of clarification is that the T variable is not the same as time of event. The discrete pleural thickening could have formed at any time before the x-ray was taken (for example, discrete pleural thickening detected in 2004 could have been present in 1990).

Analysis of a model of CE plus age at x-ray indicated that age was a significant explanatory variable with $p = 0.032$. Analysis of a model of log (CE) plus age at x-ray showed that age at x-ray was a potentially significant explanatory variable with $p = 0.14$. It should be noted that this

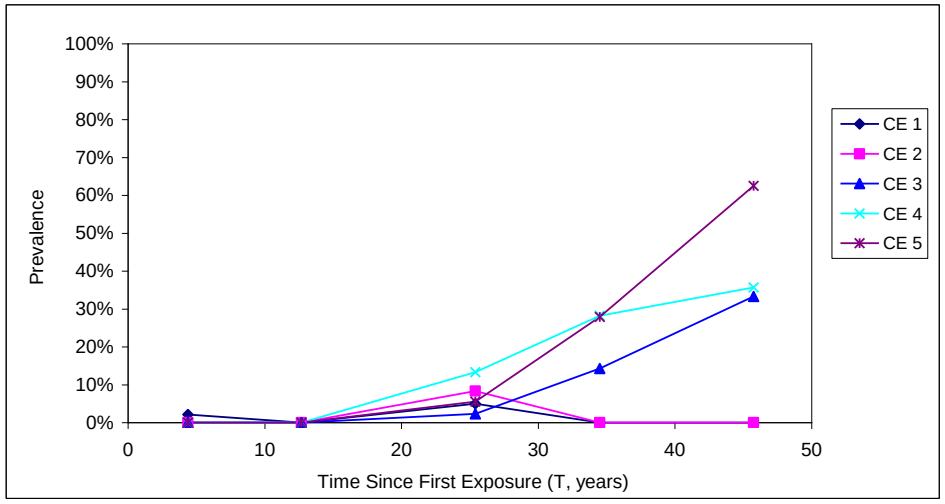
result does not mean that age is an independent risk factor for the development of discrete pleural thickening. In fact there is no biological evidence that age is an independent predictor of the development of discrete pleural thickening without a history of previous exposure to durable mineral fibers such as amphibole fibers. Rather, it is likely that the association between age and prevalence is because age at x-ray is related to time from first exposure (T), which is clearly one of the key explanatory variables. Therefore, age at x-ray was not included as an explanatory variable.

Selection of Model Form

Figure E-1 (Panel A) presents a plot of prevalence of discrete pleural thickening as a function of time from first exposure (T), stratified by cumulative exposure (CE). As seen, the prevalence appears to be low (close to zero) until about 15-20 years after first exposure and then appears to rise in a non-linear fashion. Figure E-1 (Panel B) presents a plot of prevalence as a function of cumulative exposure, stratified according to time from first exposure. As seen, prevalence appears to rise rapidly with increasing cumulative exposure, but then tends to flatten out (plateau).

FIGURE E-1 Raw data plots

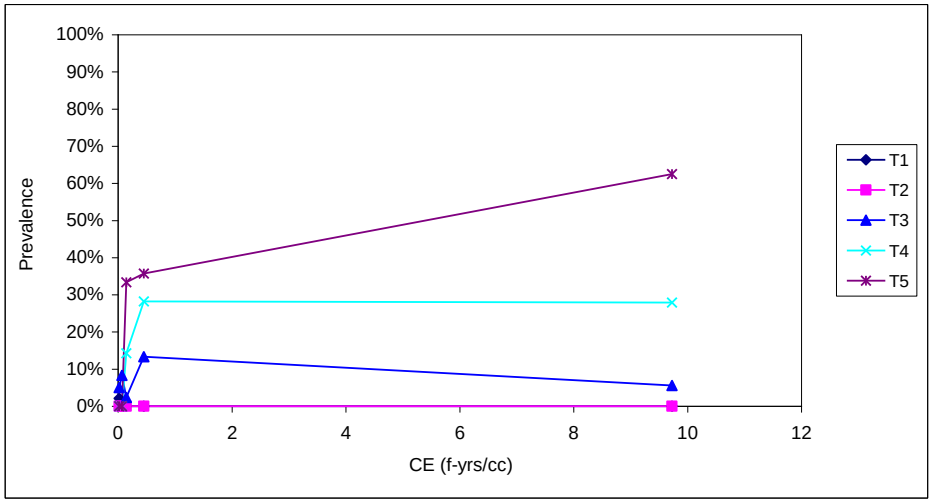
Panel A. Prevalence vs Time Since First Exposure (Grouped by CE)



CE Bins

Bin No.	Min	Max	Mean	N	Cases	Prev
CE1	0	0.05	0.021	67	2	3.0%
CE2	0.05	0.1	0.071	44	1	2.3%
CE3	0.1	0.2	0.145	108	10	9.3%
CE4	0.2	1	0.452	101	20	19.8%
CE5	1	35	9.728	114	28	24.6%

Panel B. Prevalence vs CE (Grouped by Time Since First Exposure)



T Bins

Index	Min	Max	Mean	N	Cases	Prev
T1	0	10	4.39	87	1	1.1%
T2	10	20	12.69	53	0	0.0%
T3	20	30	25.41	123	8	6.5%
T4	30	40	34.50	118	27	22.9%
T5	40	50	45.76	53	25	47.2%

Based on these attributes of the base data set, the objective was to select a model that included a plateau term whose value depended on T. Several alternative model forms were investigated, using the Dichotomous Hill model as the starting point:

$$p(CE) = bkg + (Plateau - bkg) / [1 + \exp\{-a - b*\ln(CE)\}]$$

In the Dichotomous Hill model, the plateau term is a constant, with a value bounded between background and 1.0. In order to be consistent with the data, this model was modified so that the plateau term was a function of T. Several different non-linear equations for the plateau function were tested, including the following:

- $Plateau = MIN[1, bkg + (1-bkg)*k1*T]$
- $Plateau = MIN[1, bkg + (1-bkg)*k1*T^2]$
- $Plateau = MIN[1, bkg + (1-bkg)*k1*T^3]$
- $Plateau = bkg + (1-bkg)* \Phi(T|m,s)$, where $\Phi(T|m,s)$ = cumulative normal probability function
- $Plateau = bkg + (1-bkg)* G(T|\alpha,\beta)$, where $G(T|\alpha,\beta)$, = cumulative gamma probability function
- $Plateau = bkg + (1-bkg)* W(T|\alpha,\beta)$, where $W(T|\alpha,\beta)$ = cumulative Weibull probability function

Based on Akaike's Information Criterion (AIC), the cumulative normal equation was found to fit the data best. Combining this equation for the plateau term with the basic probability model yields:

$$p(CE,T) = bkg + (1 - bkg) * \Phi(T|m,s) / [1 + \exp\{-a - b*\ln(CE)\}]$$

Further testing indicated that the lowest AIC was achieved when the b term was set to 1.0, resulting in a modified version of the discrete Michaelis-Menten equation:

$$p(CE,T) = bkg + (1 - bkg) * \Phi(T|m,s) / [1 + \exp\{-a - \ln(CE)\}]$$

This equation can also be written as:

$$p(CE,T) = bkg + (1 - bkg) * \Phi(T|m,s) * \{CE/[CE + \exp(-a)]\}$$

This equation was selected as the preferred model for fitting to the data. In this model, T (years) and CE (f-yrs/cc) are explanatory variables. Fitting parameters are m, s, and a. Background is a constant (0.01).

Parameterization

Fitting of the model to selected data sets was performed using the method of maximum likelihood (MLE), using individual data without binning. The BMD for any specified value of T is calculated from the MLE parameters and the specified value of T as follows:

$$BMD_T = \exp [-a - \ln\{Q*\Phi(T|m,s)-1\}]$$

Where:

$$Q = (1-bkg) / (BMR - bkg)$$

For a BMR of 10% extra risk, the value Q is 0.10.

Model Fitting Results

Table E-3 provides the model fitting results for each of the three data sets evaluated for each of 5 lags of CE and for each of 5 values of T. In all cases, the Benchmark Response (BMR) is 10% extra risk. Based on a background rate of 0.01, this BMR corresponds to a probability of 0.109.

TABLE E-3. MODEL FITTING RESULTS FOR THE FULL DATA SET

Study	Year of Hire	N	Cases	CE Lag	MLE Parameters				T = 30		T = 35		T = 40		T = 50		T = 70	
					m	s	a	AIC	BMD	BMDL	BMD	BMDL	BMD	BMDL	BMD	BMDL	BMD	BMDL
1980+ 2004	All	434	61	0	42.38	13.30	1.977	278.02	0.1822	0.0709	0.0731	0.0260	0.0421	0.0138	0.0224	0.0067	0.0157	0.0042
				5	42.44	13.54	2.000	277.87	0.1711	0.0666	0.0707	0.0253	0.0412	0.0136	0.0221	0.0066	0.0154	0.0042
				10	42.58	14.10	2.061	277.61	0.1477	0.0580	0.0651	0.0235	0.0389	0.0129	0.0212	0.0064	0.0146	0.0040
				15	42.86	15.16	2.167	277.67	0.1166	0.0486	0.0567	0.0219	0.0352	0.0124	0.0197	0.0062	0.0133	0.0038
				20	43.28	16.06	2.395	279.11	0.0876	0.0349	0.0449	0.0159	0.0286	0.0091	0.0162	0.0045	0.0107	0.0028
1980+ 2004	≥ 1972	198	13	0	31.41	10.47	-0.015	88.85	0.2930	0.1023	0.1900	0.0399	0.1462	0.0227	0.1177	0.0136	0.1128	0.0109
				5	31.58	11.81	0.095	88.43	0.2623	0.0956	0.1770	0.0399	0.1374	0.0232	0.1082	0.0142	0.1011	0.0112
				10	3.5E+05	3.0E+06	0.162	87.81	0.2402	0.0905	0.2402	0.0432	0.2402	0.0262	0.2402	0.0162	0.2402	0.0123
				15	1.4E+06	5.4E+06	6.5E-01	88.29	0.1766	0.0643	0.1766	0.0315	0.1766	0.0185	0.1766	0.0107	0.1766	0.0075
				20	2.1E+06	4.2E+06	1.5E+00	91.23	0.1036	0.0220	0.1036	0.0059	0.1036	0.0029	0.1036	0.0013	0.1036	0.0007
1980+ 2004	< 1972	236	48	0	43.15	13.33	2.259	192.77	0.1689	0.0227	0.0613	0.0071	0.0341	0.0037	0.0175	0.0017	0.0119	0.0010
				5	43.22	13.46	2.331	192.86	0.1540	0.0190	0.0569	0.0059	0.0318	0.0031	0.0164	0.0014	0.0111	0.0008
				10	43.44	13.88	2.472	193.04	0.1270	0.0092	0.0492	0.0028	0.0279	0.0015	0.0145	0.0007	0.0097	0.0004
				15	43.71	14.83	2.625	193.34	0.0934	--	0.0406	--	0.0241	--	0.0128	--	0.0084	--
				20	44.18	15.84	2.903	194.27	0.0642	--	0.0303	--	0.0185	--	0.0101	--	0.0065	--

The BMD for any specified value of T is calculated from the model parameter estimates and the specified value of T as follows:

$$BMD = \exp[-a - \ln\{(1-bkg) / (BMR - bkg)*\Phi(T|m,s)-1\}]$$

The BMDL is estimated by re-writing the model so that BMD appears as an explicit term in the model, for a specified T of interest:

$$BMR = bkg + (1-bkg)*\Phi(T|m,s) / (1 + \exp(-a - \ln(BMD))]$$

Solving for a yields: $-a = \ln[Q*\Phi(70|m,s)-1] + \ln(BMD70)$

Substituting yields: $p(CE,T) = bkg + (1-bkg)*\Phi(T|m,s) / [1+ \exp(z')]$

Where: $z' = \ln(Q*\Phi(70|m,s)-1) + \ln(BMD70) - \ln(CE)$

Simplifying yields: $p(CE,T) = bkg + (1-bkg)*\Phi(T|m,s) / [1+ Q*\Phi(70|m,s)-1)* BMD70/ CE]$

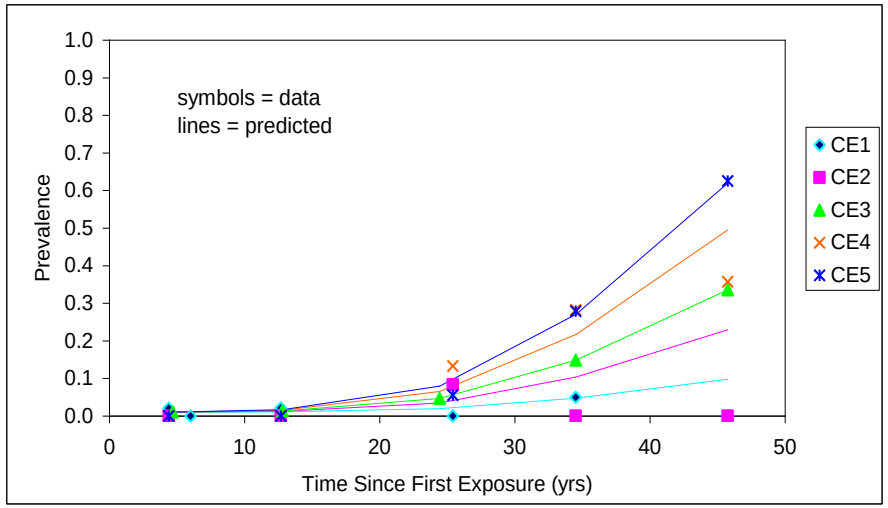
Using this equation, a trial value of the BMD is selected and treated as a constant, and the equation is re-fit to the data to find the MLE values of the remaining parameters (m, s). After optimization, the value of the log-likelihood is recorded for the specified trial value of the BMD, and the process is repeated for other trial values of the BMD. The BMDL is the trial value of the BMD where the log-likelihood decreases from the MLE log-likelihood value by an amount equal to CHIDIST (2α, 1)/2. For $\alpha = 0.05$, the decrease is 1.3528.

Inspection of this table reveals that, for each of the three data sets evaluated, there is relatively little effect of CE lag over the interval 0-15 years. For the full data set and the post-1972 data set, the lowest AIC is achieved for a lag of 10 years. However, the difference in AIC values between lags of zero, 5, and 10 years is sufficiently small that the difference is not considered to be significant.

Figure E-2 presents a graph comparing the observed data to the predicted values from the model (no lag) for the full data set. As above, this requires grouping the observed data into bins, even though fitting was performed using the individual data. Because the choice of bins is arbitrary, the appearance of the graphs would likely be changed somewhat if different bins were chosen. Nevertheless, it seems apparent that the model predictions are in good accord with the data.

FIGURE E-2 Observed versus predicted for base-case data set

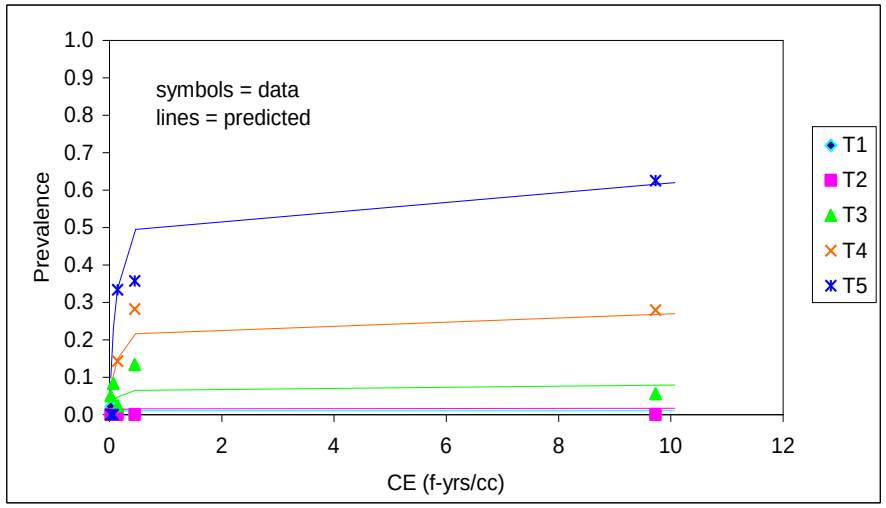
Panel A. Observed vs Predicted Prevalence as a Function of Time Since First Exposure (Grouped by CE)



CE Bins

Index	Min	Max	Mean	N	Cases	Prev
CE1	0	0.05	0.021	67	2	3.0%
CE2	0.05	0.1	0.071	44	1	2.3%
CE3	0.1	0.2	0.145	108	10	9.3%
CE4	0.2	1	0.452	101	20	19.8%
CE5	1	35	9.728	114	28	24.6%

Panel B. Observed vs Predicted Prevalence as a Function of CE (Grouped by Time Since First Exposure)



T Bins

Index	Min	Max	Mean	N	Cases	Prev
T1	0	10	4.39	87	1	1.1%
T2	10	20	12.69	53	0	0.0%
T3	20	30	25.41	123	8	6.5%
T4	30	40	34.50	118	27	22.9%
T5	40	50	45.76	53	25	47.2%

Derivation of the POD and RfC for Discrete Pleural Thickening Using the Cumulative Normal Michaelis-Menten Model

A candidate POD and RfC is derived for discrete pleural thickening from the combined 1980 + 2004 data set as this data set provides the widest distribution of T values. A lag period of five years is used because Larson et al. (2010b) showed that discrete pleural thickening could be observed much earlier than previously thought.

Because the RfC is intended to provide protection for a lifetime of exposure (exposure begins at birth and continues to age 70), the point of departure is the $BMDL_{10}$ with T = 70 years of 0.0041 fibers-yr/cc calculated with the CumNorm Michaelis-Menten model. The POD is divided by duration of exposure of 70 years, lagged by 5 years, and then divided by an uncertainty factor. In this case as the model accounts for the full lifetime of exposure of 70 years, the uncertainty factor of 100 is reduced to 30.

RfC = 0.0041 fibers-yr/cc x 1/ (70 -5 years) x 1/30 = 2E-06 fibers/cc (rounded to one significant digit)

To provide a frame of reference, the calculation above was repeated with the data set restricted to those hired in 1972 or later when industrial hygiene data were collected in the facility.
RfC = 0.0141 fibers-yr/cc x 1/ (70 – 5) years x 1/30 = 7E-06 fibers/cc (rounded to one significant digit)

The reasonably good correlation in the calculated RfCs with the two different data sets provides some confidence in the exposure reconstruction pre 1972.

An alternative candidate POD is the $BMDL_{10}$ with T = 40 years of 0.0134 fibers-yr/cc calculated with the Cumulative Normal Michaelis-Menten model. The $BMDL_{10}$ with T = 40 years is used because it is near the upper end of the range of T values available in the data set (Tmax = 47.375 years). A lag time of 5 years and a total uncertainty factor of 100 are used. See Section 5.1.3.3. This is the third approach referred to in Section 5.2.3.1.

RfC = 0.0134 fibers-yr/cc x 1/ (40 – 5) years x 1/100 = 4E-06 fibers/cc (rounded to one significant digit).

Sensitivity Analysis
For purposes of comparison, RfC values were calculated using alternative modeled values of T for the full data set (all workers) and those hired in 1972 or later. These results are summarized in Table E-4. The calculations for the RfC based on T = 30, T = 35, T = 40, and T = 50 used a lag of 5 years and a total uncertainty factor of 100. The calculations for the RfC based on T = 70 used a lag of 5 years and a total uncertainty factor of 30, as the model accounts for the full exposure of 70 years.

TABLE E-4 Sensitivity analysis of RfC based on alternative modeled values of T

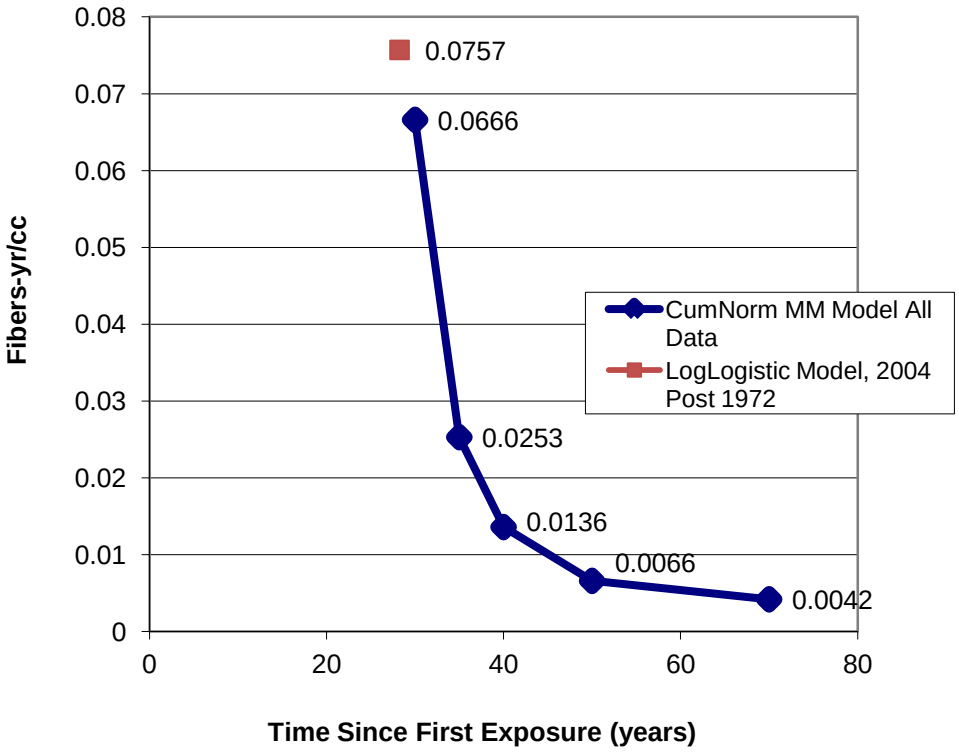
Basis	All Workers	Hired in 1972 or Later
T = 30	2.6E-05	3.8E-05
T = 35	8.3E-06	1.3E-05
T = 40	3.8E-06	6.8E-06
T = 50	1.4E-06	3.6E-06
T = 70	2.1E-06	7.2E-06

The University of Cincinnati increased the exposure metric by a factor of 2 between 1972 and 1967 to account for conditions in the facility before engineering controls were added. For the purposes of comparison, the cumulative exposure was also calculated without this doubling. Plots of prevalence of discrete pleural thickening with these two different exposure metrics are virtually identical (not shown).

One worker in the 1980 study was exposed only 5 months before x-ray and showed discrete pleural thickening. Excluding this worker from the analysis did not change the result.

Figure E-4 shows a plot of the PODs (fibers-yr/cc) versus time from first exposure (years) calculated from each of the models. Because the 3-parameter loglogistic model is independent of time from first exposure, the mean value of T for the data set is used. As there are few individuals with long T and low cumulative exposure, it is not clear whether the apparent plateau with the Cumulative Normal Michaelis-Menten model is a reflection of the limitation of the data or an expression of the underlying biology.

Figure E-3 PODs (fibers-yr/cc) versus time from first exposure (years)



Appendix F: Marysville Worker Occupational Exposure Reconstruction

The Development of a Cumulative Human Equivalent Exposure Concentration

BY:

James E. Lockey, MD, MS

Carol Rice, Ph.D.

Eric Borton, BS

Timothy Hilbert, MS

Grace LeMasters, Ph.D.

University of Cincinnati
Department of Environmental Health
3223 Eden Ave., ML 0056
Cincinnati, OH 45267

Introduction

This project builds on the previous work of Dr. James Lockey et al. investigating possible effects of exposures to dust containing Libby amphiboles at a plant in Marysville, Ohio[1,2]. The data used in the original exposure reconstruction and as reported in the published manuscripts, was based on the exposures measurements available at that time[1]. This exposure reconstruction is based on approximately five times additional occupational fiber exposure data than was previously utilized in 1980. These exposure measurements were recently obtained by the US Environmental Protection Agency (EPA) from the company and through trial transcripts from the United States of America vs. WR Grace, et al., as well as the archived data used in the 1980 exposure reconstruction. Four steps were undertaken to construct an exposure matrix describing exposure over each year from 1957 to 2000. In a final fifth step, this matrix was used to calculate an exposure metric for workers.

1. Data searches, requests, and document selection
2. Document evaluation, data entry, cleaning, editing and standardization
3. Completeness and trends in measurements
4. Decisions relevant to the exposure matrix
5. Development of a cumulative human equivalent exposure concentration

1. Data searches, requests, and document selection

Three sources of paper records were identified. First, sampling reports from OM Scott that included measurements at the facility pre- and post-1980 were received via the EPA. These reports contained both measurement results and information about the plant. OM Scott was also contacted with a request for available maps of the plant layout prior to 1980. Secondly, archived files from the Lockey et al, (1984) study were identified. Lastly, as a result of the recent WR Grace trial, there was additional discovery of material relevant to the OM Scott plant. The Department of Justice (DOJ) was contacted for the release of these data. There were seven 4" binders available for review and every page (approximately 3,150 pages) was scanned visually to identify pages relevant to the current project. Aspects of particular interest included the manufacturing process, usage and source of raw materials, engineering and design changes in the plant, work practices and exposure assessment methodology. Approval was received from the DOJ to utilize the relevant data for this project.

2. Document evaluation, data entry (qualitative and quantitative), cleaning, editing and standardization

All of the records--both the qualitative and quantitative--were reviewed in this second phase.

2.1. Qualitative information:

Written reports, letters, memos and notes contained background information on plant operations. A total of 1,489 pages were read for potentially useful and pertinent information regarding OM Scott and abstracted into a data file. From these records, we obtained:

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

- Process descriptions were derived including workers per shift, workers per department, sources of raw materials, and raw material volume in number of railroad cars received, tonnage of railroad cars from Libby and South Carolina, and tonnage of unexpanded vermiculite received.

- For each department a list of job titles and tasks

Gaps in understanding were filled-in with information gathered from the focus groups, specifically regarding:

- Plant lay-out and changes over time, including engineering controls
- Historical pattern of job rotations within department from 1957 to 1980
- Time spent in work locations at the plant site
- Overtime associated with departments and season
- Use/non-use of respirators.

2.2 Quantitative data:

Air sampling reports include quantitative measurement of airborne dust and fiber concentration associated with a department job. These records were computerized following the data entry scheme provided on June 1, 2009 and approved. Records were double entered and verified.

Two identical Microsoft Access databases were created for initial and duplicate entry of the quantitative data. Each individual performing data entry had a unique and separate database to avoid possible data entry confusion. Variables to be entered have been previously provided. A random 10% check of entered data was conducted throughout the data entry process to maintain quality of data, to address data entry questions and to resolve potential database issues. Data entry differences were below 5% throughout the entry process.

Each record was assigned a document and record identification (ID) number. The document ID variable was based on data source. For example, if the data were provided by the EPA from OM Scott then the EPA document ID was used. Data hardcopies from the EPA, Department of Justice and 1980 UC data were each numbered starting from 1. The document ID variable states EPA, DOJ or UC followed by the document number. Record IDs were generated

by using a unique identifier like a sample number for each document. If a unique identifier was unable to be discerned then the entry personnel was instructed to consecutively number each sample per document starting from 1.

A final verification of data entry used SAS version 9.2 PROC COMPARE to import the initial and duplicate Access tables. Discrepancies were below 5% as a result of the 10% random checks throughout the entry process. All discrepancies were addressed by reviewing the original document. The initial and duplicate Access databases were archived. A copy of the initial database was converted to Microsoft Excel format for ease of standardization and analyses.

2.3 Process of standardization

The standardization process included categorizing entered data into appropriate variable fields, spell checking, identifying duplicate record entry from duplicate documents, merging records for the same sample or measurement, evaluating data for completeness and categorizing groups of data based on type of sample or measurement.

Data were reviewed and edited to ensure the information was entered into the appropriate data field. A frequency of the data fields using SAS 9.2 PROC FREQ identified spelling differences and patterns to ensure correct labeling of the data. Additional data variables were created depending on recognized need to distinguish important pieces of data. A new variable called group ID was created to identify, track and consolidate partial and/or complete duplicate data into one unique sample. Partial data were identified on a combination of sample date, sample record ID, sample result, volume, sampling time and/or document patterns. A document pattern would include instances where only a group of sample results were available in one document and another document(s) would match the exact sequence of sample results.

Data were further categorized based on the type of sample. Categories include dust samples, bulk samples, personal and area fiber samples, limit of detection (LOD) or quantification (LOQ) samples, off-site locations, and time weighted average samples. Some samples were collected with a direct reading fibrous aerosol monitor, but these were not used as there was no calibration information included in the records. Thus, only the fiber count data collected with a sampling pump were used. In addition, group IDs lacking a sample result, sample year or department were excluded.

Personal and area samples were plotted by year and department and found to be visually similar. In addition the range, means, and standard deviations were approximately equal. Therefore, personal and area sample datasets were merged and both utilized for the development of the Exposure Matrix. Group IDs with only LOD or LOQ values were grouped by year and categorized as trionize or background. In order to assign an estimate for the LOD or LOQ the median value of each group was divided by two and assigned to all samples in that group. Given the small number of LOD and LOQ samples (n=35), it is unlikely any detectable bias was

introduced using this method. Time weighted average (TWA) values were not utilized when the individual measurements that comprised the TWA were already available.

Sample analysis did not specify the type of fibers identified in the fiber counts. Counting rules used included any fiber with the proper dimensions and not specifically Libby amphibole fibers. Attempts in other studies to convert from total dust to fiber count have relied on similarities in equipment or process where side-by-side samples were collected. We did not identify any 'pairs' of dust/fiber data from this plant. Moreover, fibers are a minor component of the dust exposure, limiting an ability to find a relationship over time. Therefore, total dust measurements were not converted to fiber counts and were not used as part of the fiber exposure estimation.

3. Completeness and trends in measurements

From the paper records, we concluded that additional information would be helpful from workers in order to obtain descriptions of work organization and practices. Focus groups discussions were conducted with long-term OM Scott workers (n=15) in 2010. These focus groups provided valuable qualitative data in order to fill gaps regarding work plant operations, especially during the earlier years.

As described earlier, the data used for exposure reconstruction was obtained from three sources: UC archived records (reported previously by Lockey et al.), information obtained by the EPA from the company, and from the DOJ documents. Table 1 shows that a total of 914 IH fiber measurements were available for this analysis. Of this total, only 180 (19.6%) of the IH fiber measurements were available from the UC archived records. The yearly number of samples collected was not uniform. As shown in table 2, the first fiber count measurements were available in 1972 and the last in 1994. About 26% of the samples were collected in 1978. Focus group participants reported working in the summer. Summer activities, however, involved fewer work hours and included clean-up and repair activities in addition to production. Since less than 6% of the fiber samples were collected during the summer months, no seasonal trend analysis was possible.

4. Decisions relevant to the exposure matrix:

4.1 General issues:

A graphical display of fiber count results indicated that all samples in various trionizing jobs generally followed the same pattern: higher in the early years of IH sampling, and declining *gradually* over time. Further, from the focus groups, we learned that no one, single engineering change resulted in a dramatic reduction in the perception of dustiness in the plant. Thus, the

workers' recollections supported the findings from the IH data demonstrating a gradual decline in levels of exposure rather than a dramatic step-wise drop due to any one engineering change.

Changes in work practices such as the use of compressed air and brooms for clean-up versus the use of wet vacuuming may result in a marked decreases in exposure We discussed work practices in the focus groups, and no remarkable changes were documented. Participants did note that during some years, sampling practices included leaving pumps in control rooms during high-dust activities. High-dust activities included the use of compressed air to remove particulate from surface areas. We did not find any documentation that high exposure work was excluded from the sampling effort in the IH reports. In fact, in the early years, some activities recorded in the sampling record included reference to compressed air "blow down", one of the activities associated with potentially high exposures. Consequently, no adjustment was made for any potentially un-sampled periods from 1972 through 1994 when IH measurements were available.

Per the focus groups, workers reported very sporadic usage of respirators due to heat and discomfort. Because of the heat, the workers preferred paper masks, and reported reusing them from day to day. There was no documentation of fit-testing of the paper masks. Paper masks may provide some protection against the larger particles, but likely provided little reduction in respirable particles, particularly when reused. Therefore, no adjustment was made to lower the exposure estimates due to respirator use.

4.2 Vermiculite raw material sources:

Libby vermiculite usage ended in 1980 per shipping records obtained from B. Benson and an Agency for Toxic Substances and Disease Registry (ATSDR) report[3,4]. Post 1980 usage included African/Virginia/South Carolina vermiculite until 2000. In 2000, corn cobs were introduced as an inert carrier of lawn care chemicals, and vermiculite usage ended. There were two primary sources of information regarding vermiculite sources:

An internal UC document from the 1980 study with estimates of railroad car loads delivered to the plant per year. Documents indicate railroad cars from Libby were 100 ton cars and from South Carolina 70 ton cars.

The Chamberlain memo provides information regarding vermiculite sources for 1964-1972 in railroad car loads per year.

Per the UC document, 100% South Carolina vermiculite was estimated to be used from 1957-1960. Per the Chamberlain memo, Libby vermiculite began arriving in 1960. Focus groups placed it earlier, in 1958 or 1959. We believe there is sufficient evidence to support a 1959 start date for Libby vermiculite with 1957 and 1958 assumed to be 100% South Carolina vermiculite.

Documentation was found from the original 1980 UC documents indicating an estimated Libby tonnage contribution of 32% from 1959-1963. These percentages for 1959-1963 were adopted for use in this project. After adjusting for the difference in rail car sizes, the Chamberlain memo indicates that Libby tonnage usage increased from 57% in 1964 to 73% in 1965 to 92% in 1966. Table 3 illustrates the distribution of unexpanded vermiculite sources received at the plant between 1957 and 1971. From 1959 until 1971 fiber level adjustments were made based on the percent Libby versus South Carolina vermiculite tonnage received at the plant. The estimates were derived from 1972 when the earliest IH samples were available and 93% of the vermiculite was Libby.

To develop the relationship of fiber levels between South Carolina and Libby vermiculite, samples that recorded a 100% of either source for vermiculite were identified. Two jobs with a higher number of samples from the same year from each source were used to establish the relationship: track-unload for 1977 and expander for 1978. The samples used included 22 Libby track-unload, 8 Libby expander, 17 South Carolina track-unload, and 7 South Carolina expander. A weighted average of these samples generated a 10:1 fiber count ratio for Libby:South Carolina vermiculite. This ratio was used for estimating the proportion of Libby versus South Carolina fiber exposure levels from 1959 to 1971. From 1972 and beyond, IH measurements were available and no adjustment in the IH data was made based on vermiculite source. Tonnage records demonstrate that Libby was the primary source of vermiculite from 1972 until 1979, supplemented by African vermiculite, and that Libby vermiculite usage ended in 1980.

The 100% Libby samples were compared to samples labeled as 50% Libby. The resultant measurements were accordingly lower, demonstrating internal consistency within the data.

Assessment of exposure in 1977 during application of the final, expanded product that included a mix of South African and Libby vermiculite showed no fibers. Therefore, fiber exposure estimation was restricted to jobs in the plant areas where expanding was conducted.

4.3 Exposure estimates by time period for the trionizing department:

For this project, exposures of interest were from 1957 through 2000. Exposure measurements in the plant where vermiculite was used were initiated in 1972. For prior years, it was necessary to estimate exposure from the measurements collected in 1972 and later and with supporting qualitative information. Important changes occurred in production due to increasing use of engineering controls to reduce airborne particulate. In addition, the source of vermiculite changed over the years. Therefore, the exposure estimation process was divided into two efforts: 1972 and later when IH measurements were available; 1957 to 1971, when no IH measurements were available. The exposure estimation process is described below, first for Trionizing where

vermiculite was expanded and then for other departments where either no or expanded vermiculite was used.

Trionizing department exposure estimation ≥ 1972- 2000:

For the years with exposure measurements, fiber exposure level was estimated from the measurement data. This was done by department.

Trionizing Department – The trionizing department included jobs from the entry of vermiculite into the plant, through final product. These were: track at raw material entry and production jobs of screen/mill, dryer, expander, blender, resin, and clean-up, Workers rotated through the various jobs within the department. Overall rotation among jobs reported in the 1980 Lockey et al. study was verified by the focus groups.

Plots of the measurements over time were made for individual trionizing jobs. Based on these plots, it was determined that all IH sample results from the various trionizing production jobs (screen/mill through clean-up) followed the same general distribution and should be combined. The track job included two very different work activities: unloading rail cars containing vermiculite (*track unload*) and general track work such as bringing in the rail cars, and monitoring discharge (*track other*). The two track job activities (*unload* and *other*) had a substantially larger range of sampling results and were treated separately.

The following steps were followed:

1. The data were log-transformed.

2. For all exposure values for the combined trionizing jobs from 1972-1979, a curve was drawn connecting the mean values of years having at least 40 exposure measurements (1973, 1976, and 1978). This criteria was chosen to assure that stable means were used to define the curve over this time period. For each year, the annual exposure estimate was determined by exponentiation of the value from the curve. The sharp decline seen in exposures throughout this time period parallels the addition of engineering controls including dust collection, enclosing vibrating conveyors, adding ventilators, erecting a wall between track and trionizing, and sealing leaks in the system. As values for 1980-1994 were similar and near the level of detection, the mean value for all the samples was used and then extended until 2000.

3. The measurement results for track unload and track other were plotted and a straight line produced to best fit the data points. An estimate of exposure at each year was determined by exponentiation of the value on the line for that year.

4. For the trionizing department, it was estimated that 11% of work time was spent in track and 89% in all other jobs. This is consistent with the previous weights used in the 1980 Lockey study and confirmed by the focus group.

5. The Focus groups reported that when working track, track unload required about 25% of the time and track other comprised about 75% of the track job time. Therefore, a weighted average for exposure at track within the trionizing department was derived. This 25% time estimate for track unload is higher than that previously published.[1]

Figure 1 illustrates on a log scale a fitted line of all usable IH measurements across all jobs (except track) within the trionizing department.

Trionizing department exposure estimation 1957-1971:

There are no IH measurements available prior to 1972. Engineering changes did not result in "step-function" decreases in exposures based on focus group reports. Rather a more gradual decline in exposure occurred beginning with improvements in 1968, when two dust collectors were added. Focus group workers report that dust exposures in trionizing were at least two times higher in the 1960's. Track jobs, however, were outdoors and likely unaffected by plant engineering controls. Hence, estimates for fiber exposure levels for track duties were adjusted by type of vermiculite only.

For trionizing employees, excluding outdoor track duties, the estimate from the focus group of 'twice as high' was generated beginning from 1972 and increasing until 1967. The year 1972 was used as the start of the "gradual" retrospective increase in exposure back to 1967 as 1972 was the first year when IH measurements were available, and the percent Libby vermiculite utilized was 93%. The year 1967 was selected as this was the year preceding engineering controls. A line was drawn to connect these two points and then the adjustment was made for the percent yearly Libby and South Carolina vermiculite utilized from 1967 through 1971. Prior to 1967, exposure was extended backward in time, assuming no change from the 1967 value except for a yearly adjustment for percent Libby and South Carolina usage. As described above and shown in figure 1, after 1980 when Libby vermiculite was no longer used and major environmental controls had been implemented, fiber exposure levels remained near the level of detection (0.01) through the last available IH information in 1994. The levels were estimated to be the same from 1994 forward until 2000 when vermiculite was no longer used.

4.4 Exposure estimates for non-trionizing departments:

Departments using only expanded vermiculite or no vermiculite were defined as having "plant background" exposure. These included the departments of polyform, plant maintenance, office, research, pilot plant, warehouse, central maintenance, and packaging. This decision was based on plots of available sampling data showing similar levels, and qualitative reports documenting that there were not fibers in the finished product. Plant background prior to 1972 was calculated using similar methodology as for trionizing. Although the background level was not affected by engineering control as in trionizing, exposures would be affected by the percent of Libby vermiculite used. Therefore, for the years prior to 1972, the measured plant background rate in 1972 of 0.02 was adjusted by the yearly percent Libby vermiculite utilized.

The two years prior to Libby vermiculite usage, 1956 and 1957, were assigned level of detection (0.01). This is in line with IH measurements post Libby vermiculite usage through 1994.

Polyform began in 1969, and no unexpanded vermiculite was used there. The background exposure level was used for any time in Polyform.

Plant Maintenance – Although there were some differences of opinion in the focus group regarding where plant maintenance spent their time, the consensus reached was to assign approximately 50% of time in trionizing and 50% in areas defined as plant background for their work in shop and other departments.

Office – Assigned plant background.

Research – Assigned plant background.

Pilot plant – Per the focus group participants, the pilot plant did not have its own expander, and used only expanded vermiculite in test and run simulations. Plant background levels were thus assigned to the pilot plant.

Warehouse – Only expanded vermiculite was in this area. Although bags did break, the exposure was to final product, not unexpanded vermiculite.

Central Maintenance – According to the focus group, these employees worked outside of trionizing for about 90% time (background) and 10% (trionizing) for installation of new equipment/parts. Around 1982 central maintenance department was discontinued, and the work was contracted to outside personnel.

Packaging – Assigned plant background.

Table 4 illustrates the fiber exposure matrix from 1957 to 2000 using this methodology.

4.5. Decisions related to break periods and hours worked:

Cumulative exposure is the product over time of the level of exposure and duration. Level of exposure is derived from the exposure matrix and duration from the work history. However, in this workforce, work time is complicated by breaks where exposure is at a lower level and seasonal changes resulting in extra hours worked beyond the usual 40 hour week. Each of these factors is described below:

According to the focus group data there was approximately a 30 minute break for lunch and two fifteen minute breaks during the day. Therefore, every worker was considered to have at least one hour of background exposure daily. There was no documentation that a 3rd fifteen minute break was provided when working longer than eight hours in a day.

Employees in some departments frequently worked extra hours each day, and weekends as well, depending on the production needs and season. Decisions regarding this work organization are summarized below:

1) Extra hours – Were defined as hours worked in excess of 8 hours per day,

2) Four departments worked no extra hours – office, pilot plant, research, central maintenance

3) According to focus group data, the only departments that worked extra hours outside of their own department were trionizing and polyform. Thus, a decision was needed as to how to appropriate the amount of overtime spent outside trionizing and polyform.

Extra hours for polyform workers - According to the focus groups, polyform workers first worked in their own department, and went to trionizing to work extra hours. According to workers, about 75 percent of the daily overtime was in their own department. Therefore, for each four hours worked beyond the normal eight hour day, it is estimated that they spent three hours in polyform and one in trionizing. This rule was not applied to 8-hour weekend days worked.

Extra hours for trionizing workers – As for polyform workers, above, it is estimated that trionizing workers spent three hours in trionizing and one hour in polyform as a daily average.

4) Schedules by season differed due to production rate:

For trionizing, plant maintenance, polyform, warehouse, and packaging the spring schedule was from January through May – 7 days @ 12 hrs

For trionizing, plant maintenance, polyform, warehouse, and packaging the summer schedule was from June – August – 5 days @ 8 hrs. Due to the difficulty that heat and humidity brought to the process, polyform was shut down during summer. During the summer, polyform workers did outside jobs. As these jobs have the same exposure level as polyform (background rate), no adjustment was made for the summer polyform shutdowns. The trionizing department more typically slowed down production in the summer, and this is reflected in the number of hours worked from June through August.

For trionizing, plant maintenance, polyform, warehouse, and packaging the fall schedule was from September through December – 5 days @12 hrs and 2 weekend days @ 8 hrs.

In light of these extra hours, exposure values by department and season were modified for use in the cumulative equivalent human equivalent exposure concentration estimations.

5. Development of a cumulative human equivalent exposure concentration

An EPA adjustment of cumulative occupational exposure to fibers to continuous human exposure to fibers (24 hrs/day; 7 days/week) was provided by B. Benson. This adjustment was

accepted as provided for the development of a cumulative human equivalent exposure concentration (CHEEC) for the Marysville occupational cohort.

5.1 Seasonal schedule correction factor:

For this project the Correction Factor was adjusted for the specific information on work schedules related to the seasonal changes to meet production demands as described above in section 4.4. UC applied these correction factors supplied by the EPA (B. Benson) to the work history data obtained by UC during 1980 and updated in 2004.

5.2 Decision rules to address department changes occurring within seasons:

Decision rules were implemented to systematically standardize each worker's occupational history to a format that corresponded directly with the seasonal changes that occurred at the plant. Previous decisions related to department exposure levels and seasonal work resulted in six unique exposure categories: trionizing, plant maintenance, central maintenance, polyform, background (office, research, pilot plant), and background with extra time (warehouse, packaging). The date of any job change by a worker between these six categories was adjusted so the change occurred at the starting month for the nearest season.

5.3 Development of CHEEC

In preparation for creating the CHEEC, the exposure matrix was converted to a seasonal (spring, summer, fall) exposure value. This value is the estimate of the amount of exposure occurring by department for each season of each year. With the worker's occupational histories standardized to the same seasons, the CHEEC for each worker was then calculated as the sum of exposure values for all seasons worked between1957-2000. The correction factors used in derivation of the CHEEC are outlined below.

General Procedure

$(\text{Cumulative Fibers})_{OCCUP} \times \text{Correction Factor} = (\text{Cumulative Fibers})_{HEC}$

OCCUP = Occupational Exposure

HEC = Human Equivalent Concentration for exposure of 24 hrs/day, 7 days/week

The Correction Factor usually used with an occupational study is 5 days/7 days x 10 m^3/20 m^3

UC Procedure

$\text{CHEEC} = (\text{Exposure Est}_{\text{year-dept-season 1}} \times \text{Correction Factor}_{\text{season 1}} \times \text{Seasonal Duration Factor}) + (\text{Exposure Est}_{\text{year-dept-season 2}} \times \text{Correction Factor}_{\text{season 2}} \times \text{Seasonal Duration Factor}) + \ldots (\text{Exposure Est}_{\text{year-dept-season x}} \times \text{Correction Factor}_{\text{season}} \times \text{Seasonal Duration Factor})$

Where the Seasonal Duration Factor for the Spring is 5/12 year; the Summer is 3/12 year; the Fall is 4/12 year.

Detailed calculations follow.

Work schedule for trionizing, plant maintenance, polyform, warehouse, and packaging

Spring

January 1 to May 31: 7 days/week, 12 hrs/day, with New Years' Day off, and accounting for leap years

151.25 -1 = 150.25 days

Breathing rate, working = 1.25 m^3/hr x 12 hrs = 15 m^3

Breathing rate, not working = 0.625 m^3/hr x 12 hrs = 7.5 m^3

Total breathing rate = 15 + 7.5 = 22.5 m^3/day

Correction Factor Spring = 150.25/151.25 x 15/22.5 = 0.662259

Summer

June 1 to August 31: 5 days/week, 8 hrs/day, 2 week summer vacation

(92 – 14) x 5/7 = 55.714286 days

Breathing rate, working = 1.25 m^3/hr x 8 hrs = 10 m^3

Breathing rate, not working = 0.625 m^3/hr x 16 hrs = 10 m^3

Total breathing rate = 10 + 10 = 20 m^3/day

Correction Factor Summer = 55.714286/92 x 10/20 = 0.302795

Fall

September 1 to December 31: 5 days/week, 12 hrs/day and 2 days/week, 8 hrs/day, with Christmas Day off

122 – 1 = 121 days

Breathing rate, working, 12 hr day = 1.25 m^3/hr x 12 hrs = 15 m^3

Breathing rate, working, 8 hr day = 1.25 m^3/hr x 8 hrs = 10 m^3

Breathing rate, not working = 0.625 m^3/hr x 16 hrs = 10 m^3

Total breathing rate, 12 hour work day = 15 + 7.5 = 22.5 m^3/day

Total breathing rate, 8 hr work day = 10 + 10 = 20 m^3/day

Correction Factor Fall = 121/122 x (86.42857 x 15/22.5 + 34.57143 x 10/20)/121 = 0.613973

Work schedule for office, pilot plant, research, and central maintenance

No extra days or extra hours

Spring

January 1 to May 31: 5 days/week, 8 hrs/day, with New Years' Day off, and accounting for leap years

(151.25 -1) x 5 days/7 days = 107.321429

Breathing rate, working = 1.25 m^3/hr x 8 hrs = 10 m^3

Breathing rate, not working = 0.625 m^3/hr x 16 hrs = 10 m^3

Total breathing rate = 10 + 10 = 20 m^3/day

Correction Factor Spring = 107.321429/151.25 x 10/20 = 0.354782

Summer

June 1 to August 31: 5 days/week, 8 hrs/day, 2 week summer vacation

(92 – 14) x 5/7 = 55.714286 days

Breathing rate, working = 1.25 m^3/hr x 8 hrs = 10 m^3

Breathing rate, not working = 0.625 m^3/hr x 16 hrs = 10 m^3

Total breathing rate = 10 + 10 = 20 m^3/day

Correction Factor Summer = 55.714286/92 x 10/20 = 0.302795

Fall

September 1 to December 31: 5 days/week, 8 hrs/day, with Christmas Day off

(122 – 1) x 5/7 = 86.428571 days

Breathing rate, working, 8 hr day = 1.25 m^3/hr x 8 hrs = 10 m^3

Breathing rate, not working = 0.625 m^3/hr x 16 hrs = 10 m^3

Total breathing rate = 10 + 10 = 20 m^3/day

Correction Factor Fall = 86.428571/122 x 10/20 = 0.354215

5.4 Results of the Cumulative human equivalent exposure concentration (CHEEC)

To verify the accuracy of the CHEEC calculations, several quality control checks were conducted. The distribution was evaluated by reviewing the mean, median, standard deviation, highest 10 values, and lowest 10 values. Several workers were also randomly selected and their values hand-calculated to ensure all programming was correct. Tables 5-7 provide a list of all 280 subjects participating in the 2004 Marysville health update. [2] These tables describe each subject's identification number, job start and stop date, date of radiograph, age, gender, body mass index, smoking history, asbestos exposures, health outcomes, and the cumulative human equivalent exposure concentration (CHEEC) for all departmental exposures they reported while employed at the OM Scott Marysville, Ohio plant.

6.0 Strengths and Limitations:

There are major strengths in this exposure reconstruction project.

1. Data were gathered from court records, federal sources and archived files, totaling over 3000 pages. These data were reviewed and both qualitative and quantitative data were abstracted to aid in this reconstruction.

2. Approximately five times more fiber measurements became available than had been used in the original studies.

3. Two focus groups were conducted in 2010 with long term workers who provided input regarding exposure and production process changes.

4. There were sufficient data available to examine exposure intensity over time for jobs within the trionizing department as well as for other departments. These data enhanced exposure estimates for all departments from 1972 to 1994.

5. IH data were available allowing for comparisons of fiber counts when 100% Libby or 100% South Carolina vermiculite was used in order to calculate a ratio of fibers in each.

6. There were data available from archived records, Scott memos, and worker information that allowed for exposure estimates to be adjusted for type of vermiculite used from 1957 until 1971 when no IH data were available.

7. Worker report data were available that provided documentation for increased dustiness before IH data were available, compared with years when measurements were available.

8. Based on past and current data gathered in the focus group, exposures were adjusted to account for seasonal work schedules by departments.

9. All decisions based on level of exposure by year were data driven.

The limitations for this project are also recognized.

1. The exposure metric used (fibers/cc) results from an analytical method that is a count of fibers (defined as any viewed elongated particle in excess of 5 um in length and with a length to width ratio of 3:1) collected on a filter and viewed at 400x with light microscopy. The composition of the fiber is not known. Also, a fiber with diameter less than a limit of resolution of 0.2 um cannot be viewed with this method.

2. It is unknown if other sampling results exist. If any are found in the future, these can be incorporated into a future exposure assessment.

3. Some dusty activities may not have been sampled or rarely sampled e.g., summer cleanup. We have no way of estimating the effect of these activities on overall exposure estimates.

4. We did not reduce exposure estimates due to possible use of respiratory protection. Substantially more documentation regarding enforced usage, fit testing and cleaning/storage protocols would be needed for meaningful reduction in exposure estimates.

5. By combining all individual trionizing job duties into one department exposure, the non-expander trionizing exposure estimates may have been overestimated as there were more expander measurements, and these were somewhat higher than for other job duties.

6. From 1980 forward, Libby vermiculite was not used. Thus for any individual year during this period, exposure from a qualitative and quantitative perspective does not reflect Libby amphibole exposure.

7. Seasonal work schedule adjustments were based on recall of focus group participants and may over or under estimate true durations and location of additional work hours.

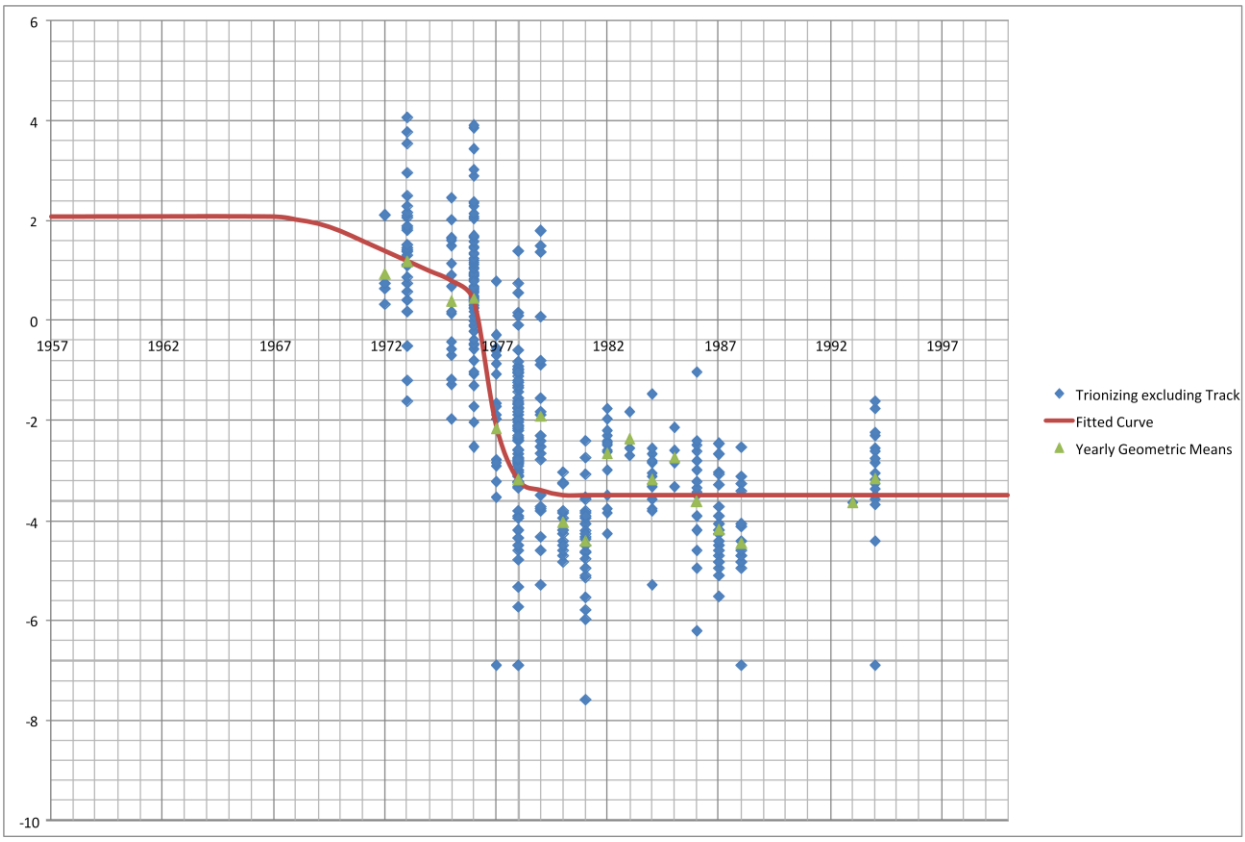
Literature cited.

1. 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.

2. Rohs AM, Lockey JE, Dunning JE, Shukla R, Fan H, Hilbert T, Borton E, Wiot J, Meyer C, Shipley RT, LeMasters GK, 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.

3. Benson R. Use of Libby amphibole in Marysville, Ohio. Ref 8P-W, US EPA Region 8,December 7, 2009:1-2.

4. U.S. Department of Health and Human Services, Agency for Toxic Substances and Disease Registry (ATSDR). Health consultation: The Scotts Company, LLC. EPA Facility ID: OHD990834483. September 22, 2005.



Log of fiber count (fiber/cc)

Figure F-1. Illustrates on a log scale a fitted line of all usable IH measurements across all jobs (except track) within the trionizing department.

Table 1. Industrial Hygiene Fiber Measurements by Document Source

Document Source	Trionize	Background	Total (%)
DOJ	38	0	38 (4.16)
EPA	398	122	520 (56.89)
UC	135	45	180(19.69)
COMBINED	172	4	176(19.26)
Total (%)	743 (81.29)	171 (18.71)	914

Table 2. Industrial Hygiene Fiber Measurements by Department and Year

Dept	1972	1973	1975	1976	1977	1978	1979	1980	1981	1982	1983	1984	1985	1986	1987	1988	1993	1994	Total (Dept %)
BACKGROUND	3	0	2	0	10	54	2	0	12	7	3	11	5	23	13	16	0	10	**171** (18.71)
TRIONIZE	9	40	20	115	68	183	26	23	38	24	8	27	14	52	33	31	3	29	**743** (81.29)
Total (Year %)	**12** (1.31)	**40** (4.38)	**22** (2.41)	**115** (12.58)	**78** (8.53)	**237** (25.93)	**28** (3.06)	**23** (2.52)	**50** (5.47)	**31** (3.39)	**11** (1.20)	**38** (4.16)	**19** (2.08)	**75** (8.21)	**46** (5.03)	**47** (5.14)	**3** (0.33)	**39** (4.27)	**914** (100.00)

Table 3. Tonnage by year and vermiculite source

Year	% Tonnage Libby	% Tonnage SC	Comment
1957		100	No confirmation of Libby usage
1958		100	No confirmation of Libby usage
1959	32	68	Libby usage began per focus groups; Chamberlain says 1960
1960	32	68	Chamberlain memo and 1980 chart
1961	32	68	Chamberlain memo and 1980 chart
1962	32	68	Chamberlain memo and 1980 chart
1963	32	68	Chamberlain memo and 1980 chart
1964	57	43	Chamberlain memo
1965	73	27	Chamberlain memo
1966	92	8	Chamberlain memo
1967	87	13	Chamberlain memo
1968	79	21	Chamberlain memo
1969	82	18	Chamberlain memo
1970	90	10	Chamberlain memo
1971	95	5	Chamberlain memo

Table 4. Exposure Matrix Assuming Doubling of Fiber Levels from 1972 to 1967 but with Adjustment for Vermiculite Source from 1957-1971

Department	1957	1958	1959	1960	1961	1962	1963	1964	1965	1966	1967	1968	1969	1970	1971
Trionizing	0.729	0.729	2.825	2.825	2.825	2.825	2.825	4.462	5.510	6.755	6.427	5.542	5.279	4.923	4.316
Plant maint (50/50)	0.369	0.369	1.416	1.416	1.416	1.416	1.416	2.237	2.763	3.387	3.222	2.779	2.648	2.470	2.168
Central maint (90/10)	0.082	0.082	0.289	0.289	0.289	0.289	0.289	0.457	0.565	0.692	0.659	0.569	0.543	0.509	0.449
Background*	0.010	0.010	0.008	0.008	0.008	0.008	0.008	0.012	0.015	0.019	0.018	0.016	0.017	0.018	0.019
	1972	**1973**	**1974**	**1975**	**1976**	**1977**	**1978**	**1979**	**1980**	**1981**	**1982**	**1983**	**1984**	**1985**	**1986-2000**
Trionizing	3.674	3.007	2.464	2.019	1.391	0.150	0.086	0.077	0.063	0.063	0.060	0.060	0.055	0.055	0.052
Plant maint (50/50)	1.847	1.513	1.242	1.020	0.705	0.090	0.053	0.044	0.036	0.036	0.035	0.035	0.032	0.032	0.031
Central maint (90/10)	0.385	0.319	0.264	0.220	0.157	0.030	0.027	0.017	0.015	0.015	0.015	0.015			
Background*	0.020	0.020	0.020	0.020	0.020	0.020	0.020	0.010	0.010	0.010	0.010	0.010	0.010	0.010	0.010

*Background applies to Pilot Plant, Research, Polyform, Office, Packaging, Warehouse

APPENDIX G. EXTRA RISK AND UNIT RISK CALCULATION

The following tables illustrate the computational details of the unit risks for mesothelioma mortality (Tables G-1 and G-2) and for lung cancer mortality (Tables G-3 and G-4). Section 5.4.5.1 details the application of the life-table methodology for mesothelioma. The results of Tables G-1 and G-2 are shown in Table 5-17 and are not adjusted for the underascertainment of mesothelioma described in the Section 5.4.5.1.1. The unit risks adjusted for underascertainment are shown in Table 5-18.

Column Definitions for Tables G-1 and G-2

Column A: Age interval up to age 85.

Column B: All-cause mortality rate for interval i ($\times 10^5$/year) (2007 data NVSR 58(19) 2010).

Column C: All-cause hazard rate for interval i (h^*_i) (= all-cause mortality rate × number of years in age interval).

Column D: Probability of surviving interval i (q_i) (= $\exp(-h^*_i)$).

Column E: Probability of surviving up to interval i (S_i) ($S_1 = 1$; $S_i = S_{i-1} \times q_{i-1}$, for i>1).

Column F: Lagged exposure at mid-interval (x dose).

Column G: Mesothelioma mortality hazard rate in exposed people for interval. To estimate the LEC_{01}, i.e., the 95% lower bound on the continuous exposure giving an extra risk of 1%, the 95% upper bound on the regression coefficient is used.

Column H: All-cause hazard rate in exposed people for interval i (h^*x_i) (= $h^*_i + (hx_i - h_i)$).

Column I: Probability of surviving interval i without dying from mesothelioma for exposed people (qx_i) (= $\exp(-h^*x_i)$).

Column J: Probability of surviving up to interval i without dying from mesothelioma for exposed people (Sx_i) ($Sx_1 = 1$; $Sx_i = Sx_{i-1} \times qx_{i-1}$, for i>1).

Column K: Conditional probability of dying from mesothelioma in interval i for exposed people (= $(hx_i/h^*x_i) \times Sx_i \times (1-qx_i)$) (Rx, the lifetime probability of dying from mesothelioma for exposed people = the sum of the conditional probabilities across the intervals).

Note that the life tables for mesothelioma mortality estimate the extra risk as the absolute risk since there is no assumption of a background risk in the absence of exposure. In each of the life tables, inhalation exposure commences at age 16 years and continues at the same exposure concentration for the duration of the life table. This allows for the computation of an "adult-only" occupational lifetime unit risk, which is then scaled by a ratio of 70:54 to account

for risk over the standard 70-year lifetime. While exposure is initiated in the life table at age 16 years, this exposure is lagged to match the corresponding exposure-response models, which provide the hazard rates per unit of exposure. For example, in Table G-1, Column F shows exposure lagged by 10 years so that no lagged exposure appears in the table until age 26 years. In Table G-2, Column F shows exposure lagged by 15 years so that no lagged exposure appears in the table until age 31 years.

Table G-1. Mesothelioma extra risk calculation for environmental exposure to 0.1479 fibers/cc Libby Amphibole asbestos using the metric of cumulative exposure with a 10-year exposure lag and a 5-year half-life of exposure, as described in Section 5.4.5.3 as the reasonable upper bound

A	B	C	D	E	F	G	H	I	J	K
Age int.	All cause mortality (xE5/yr)	All cause hazard rate (h*)	Prob. of surviving interval (q)	Prob. of surviving up to interval (S)	Lagged exp. mid. int. (Xdose)	Exposed meso. hazard rate (hx)	Exposed all cause haz. rate (h*x)	Exposed prob. of surviving interval (qx)	Exposed prob. of surviving up to int. (Sx)	Exposed cond. prob. of meso. in interval (Rx)
<1	684.5	0.0068	0.9932	1.0000	0.000	0.0000	0.0068	0.9932	1.0000	0.0000
1-2	28.6	0.0003	0.9997	0.9932	0.000	0.0000	0.0003	0.9997	0.9932	0.0000
2-3	28.6	0.0003	0.9997	0.9929	0.000	0.0000	0.0003	0.9997	0.9929	0.0000
3-4	28.6	0.0003	0.9997	0.9926	0.000	0.0000	0.0003	0.9997	0.9926	0.0000
4-5	29.9	0.0003	0.9997	0.9923	0.000	0.0000	0.0003	0.9997	0.9923	0.0000
5-6	13.7	0.0001	0.9999	0.9920	0.000	0.0000	0.0001	0.9999	0.9920	0.0000
6-7	13.7	0.0001	0.9999	0.9919	0.000	0.0000	0.0001	0.9999	0.9919	0.0000
7-8	13.7	0.0001	0.9999	0.9918	0.000	0.0000	0.0001	0.9999	0.9918	0.0000
8-9	13.7	0.0001	0.9999	0.9916	0.000	0.0000	0.0001	0.9999	0.9916	0.0000
9-10	13.7	0.0001	0.9999	0.9915	0.000	0.0000	0.0001	0.9999	0.9915	0.0000
10-11	18.7	0.0002	0.9998	0.9914	0.000	0.0000	0.0002	0.9998	0.9914	0.0000
11-12	18.7	0.0002	0.9998	0.9912	0.000	0.0000	0.0002	0.9998	0.9912	0.0000
12-13	18.7	0.0002	0.9998	0.9910	0.000	0.0000	0.0002	0.9998	0.9910	0.0000
13-14	18.7	0.0002	0.9998	0.9908	0.000	0.0000	0.0002	0.9998	0.9908	0.0000
14-15	18.7	0.0002	0.9998	0.9906	0.000	0.0000	0.0002	0.9998	0.9906	0.0000
15-16	61.9	0.0006	0.9994	0.9904	0.000	0.0000	0.0006	0.9994	0.9904	0.0000
16-17	61.9	0.0006	0.9994	0.9898	0.000	0.0000	0.0006	0.9994	0.9898	0.0000
17-18	61.9	0.0006	0.9994	0.9892	0.000	0.0000	0.0006	0.9994	0.9892	0.0000
18-19	61.9	0.0006	0.9994	0.9886	0.000	0.0000	0.0006	0.9994	0.9886	0.0000
19-20	61.9	0.0006	0.9994	0.9880	0.000	0.0000	0.0006	0.9994	0.9880	0.0000
20-21	98.3	0.0010	0.9990	0.9874	0.000	0.0000	0.0010	0.9990	0.9874	0.0000
21-22	98.3	0.0010	0.9990	0.9864	0.000	0.0000	0.0010	0.9990	0.9864	0.0000
22-23	98.3	0.0010	0.9990	0.9854	0.000	0.0000	0.0010	0.9990	0.9854	0.0000
23-24	98.3	0.0010	0.9990	0.9845	0.000	0.0000	0.0010	0.9990	0.9845	0.0000
24-25	98.3	0.0010	0.9990	0.9835	0.000	0.0000	0.0010	0.9990	0.9835	0.0000

Table G-1. Mesothelioma extra risk calculation for environmental exposure to 0.1479 fibers/cc Libby Amphibole asbestos using the metric of cumulative exposure with a 10-year exposure lag and a 5-year half-life of exposure, as described in Section 5.4.5.3 as the reasonable upper bound (continued)

A	B	C	D	E	F	G	H	I	J	K
Age int.	All cause mortality (xE5/yr)	All cause hazard rate (h*)	Prob. of surviving interval (q)	Prob. of surviving up to interval (S)	Lagged exp. mid. int. (Xdose)	Exposed meso. hazard rate (hx)	Exposed all cause haz. rate (h*x)	Exposed prob. of surviving interval (qx)	Exposed prob. of surviving up to int. (Sx)	Exposed cond. prob. of meso. in interval (Rx)
25-26	99.4	0.0010	0.9990	0.9825	0.000	0.0000	0.0010	0.9990	0.9825	0.0000
26-27	99.4	0.0010	0.9990	0.9815	0.144	0.0001	0.0011	0.9989	0.9815	0.0001
27-28	99.4	0.0010	0.9990	0.9806	0.401	0.0002	0.0012	0.9988	0.9805	0.0002
28-29	99.4	0.0010	0.9990	0.9796	0.626	0.0003	0.0013	0.9987	0.9793	0.0003
29-30	99.4	0.0010	0.9990	0.9786	0.821	0.0004	0.0014	0.9986	0.9780	0.0004
30-34	110.8	0.0055	0.9945	0.9777	1.268	0.0006	0.0062	0.9938	0.9767	0.0006
35-39	145.8	0.0073	0.9927	0.9723	1.701	0.0009	0.0082	0.9919	0.9706	0.0008
40-44	221.6	0.0111	0.9890	0.9652	1.918	0.0010	0.0121	0.9880	0.9628	0.0009
45-49	340.0	0.0170	0.9831	0.9546	2.026	0.0010	0.0180	0.9821	0.9512	0.0010
50-54	509.0	0.0255	0.9749	0.9385	2.080	0.0011	0.0265	0.9738	0.9342	0.0010
55-59	726.3	0.0363	0.9643	0.9149	2.107	0.0011	0.0374	0.9633	0.9098	0.0010
60-64	1,068.3	0.0534	0.9480	0.8823	2.121	0.0011	0.0545	0.9470	0.8764	0.0009
65-69	1,627.5	0.0814	0.9218	0.8364	2.127	0.0011	0.0825	0.9209	0.8299	0.0009
70-74	2,491.3	0.1246	0.8829	0.7710	2.131	0.0011	0.1256	0.8819	0.7642	0.0008
75-79	3,945.9	0.1973	0.8209	0.6807	2.132	0.0011	0.1984	0.8201	0.6740	0.0007
80-84	6,381.4	0.3191	0.7268	0.5588	2.133	0.0011	0.3202	0.7260	0.5527	0.0005
										Absolute R_x = 0.0100

Absolute risk = 0.01000, exp. level = 0.1479; Occupational lifetime unit risk = 0.0676 (Based on occupational exposures beginning at age 16 years); Scaled occupational lifetime unit risk = 0.0876 (Scaled by ratio of 70:54 to account for risk over 70 year lifetime).

Table G-2. Mesothelioma extra risk calculation for environmental exposure to 0.2446 fibers/cc Libby Amphibole asbestos using the metric of cumulative exposure with a 15-year exposure lag and a 5-year half-life of exposure, as described in Section 5.4.5.3 as the lowest information criterion

A	B	C	D	E	F	G	H	I	J	K
Age int.	All cause mortality (xE5/yr)	All cause hazard rate (h*)	Prob. of surviving interval (q)	Prob. of surviving up to interval (S)	Lagged exp. mid. int. (Xdose)	Exposed meso. hazard rate (hx)	Exposed all cause haz. rate (h*x)	Exposed prob. of surviving interval (qx)	Exposed prob. of surviving up to int. (Sx)	Exposed cond. prob. of meso in interval (Rx)
<1	684.5	0.0068	0.9932	1.0000	0.000	0.0000	0.0068	0.9932	1.0000	0.0000
1-2	28.6	0.0003	0.9997	0.9932	0.000	0.0000	0.0003	0.9997	0.9932	0.0000
2-3	28.6	0.0003	0.9997	0.9929	0.000	0.0000	0.0003	0.9997	0.9929	0.0000
3-4	28.6	0.0003	0.9997	0.9926	0.000	0.0000	0.0003	0.9997	0.9926	0.0000
4-5	29.9	0.0003	0.9997	0.9923	0.000	0.0000	0.0003	0.9997	0.9923	0.0000
5-6	13.7	0.0001	0.9999	0.9920	0.000	0.0000	0.0001	0.9999	0.9920	0.0000
6-7	13.7	0.0001	0.9999	0.9919	0.000	0.0000	0.0001	0.9999	0.9919	0.0000
7-8	13.7	0.0001	0.9999	0.9918	0.000	0.0000	0.0001	0.9999	0.9918	0.0000
8-9	13.7	0.0001	0.9999	0.9916	0.000	0.0000	0.0001	0.9999	0.9916	0.0000
9-10	13.7	0.0001	0.9999	0.9915	0.000	0.0000	0.0001	0.9999	0.9915	0.0000
10-11	18.7	0.0002	0.9998	0.9914	0.000	0.0000	0.0002	0.9998	0.9914	0.0000
11-12	18.7	0.0002	0.9998	0.9912	0.000	0.0000	0.0002	0.9998	0.9912	0.0000
12-13	18.7	0.0002	0.9998	0.9910	0.000	0.0000	0.0002	0.9998	0.9910	0.0000
13-14	18.7	0.0002	0.9998	0.9908	0.000	0.0000	0.0002	0.9998	0.9908	0.0000
14-15	18.7	0.0002	0.9998	0.9906	0.000	0.0000	0.0002	0.9998	0.9906	0.0000
15-16	61.9	0.0006	0.9994	0.9904	0.000	0.0000	0.0006	0.9994	0.9904	0.0000
16-17	61.9	0.0006	0.9994	0.9898	0.000	0.0000	0.0006	0.9994	0.9898	0.0000
17-18	61.9	0.0006	0.9994	0.9892	0.000	0.0000	0.0006	0.9994	0.9892	0.0000
18-19	61.9	0.0006	0.9994	0.9886	0.000	0.0000	0.0006	0.9994	0.9886	0.0000
19-20	61.9	0.0006	0.9994	0.9880	0.000	0.0000	0.0006	0.9994	0.9880	0.0000
20-21	98.3	0.0010	0.9990	0.9874	0.000	0.0000	0.0010	0.9990	0.9874	0.0000
21-22	98.3	0.0010	0.9990	0.9864	0.000	0.0000	0.0010	0.9990	0.9864	0.0000
22-23	98.3	0.0010	0.9990	0.9854	0.000	0.0000	0.0010	0.9990	0.9854	0.0000
23-24	98.3	0.0010	0.9990	0.9845	0.000	0.0000	0.0010	0.9990	0.9845	0.0000
24-25	98.3	0.0010	0.9990	0.9835	0.000	0.0000	0.0010	0.9990	0.9835	0.0000

Table G-2. Mesothelioma extra risk calculation for environmental exposure to 0.2446 fibers/cc Libby Amphibole asbestos using the metric of cumulative exposure with a 15-year exposure lag and a 5-year half-life of exposure, as described in Section 5.4.5.3 as the lowest information criterion (continued)

A	B	C	D	E	F	G	H	I	J	K
Age int.	All cause mortality (xE5/yr)	All cause hazard rate (h*)	Prob. of surviving interval (q)	Prob. of surviving up to interval (S)	Lagged exp. mid. int. (Xdose)	Exposed meso. hazard rate (hx)	Exposed all cause haz. rate (h*x)	Exposed prob. of surviving interval (qx)	Exposed prob. of surviving up to int. (Sx)	Exposed cond. prob. of meso in interval (Rx)
25-26	99.4	0.0010	0.9990	0.9825	0.000	0.0000	0.0010	0.9990	0.9825	0.0000
26-27	99.4	0.0010	0.9990	0.9815	0.000	0.0000	0.0010	0.9990	0.9815	0.0000
27-28	99.4	0.0010	0.9990	0.9806	0.000	0.0000	0.0010	0.9990	0.9806	0.0000
28-29	99.4	0.0010	0.9990	0.9796	0.000	0.0000	0.0010	0.9990	0.9796	0.0000
29-30	99.4	0.0010	0.9990	0.9786	0.000	0.0000	0.0010	0.9990	0.9786	0.0000
30-31	110.8	0.0055	0.9945	0.9777	0.000	0.0000	0.0011	0.9989	0.9777	0.0000
31-32	110.8	0.0055	0.9945	0.9777	0.238	0.0001	0.0012	0.9988	0.9766	0.0001
32-33	110.8	0.0055	0.9945	0.9777	0.664	0.0002	0.0013	0.9987	0.9754	0.0002
33-34	110.8	0.0055	0.9945	0.9777	1.035	0.0004	0.0015	0.9985	0.9741	0.0003
34-35	110.8	0.0055	0.9945	0.9777	1.357	0.0005	0.0016	0.9984	0.9727	0.0005
35-39	145.8	0.0073	0.9927	0.9723	2.097	0.0007	0.0080	0.9920	0.9712	0.0007
40-44	221.6	0.0111	0.9890	0.9652	2.813	0.0010	0.0120	0.9880	0.9634	0.0009
45-49	340.0	0.0170	0.9831	0.9546	3.171	0.0011	0.0181	0.9821	0.9519	0.0010
50-54	509.0	0.0255	0.9749	0.9385	3.350	0.0011	0.0266	0.9738	0.9348	0.0011
55-59	726.3	0.0363	0.9643	0.9149	3.440	0.0012	0.0375	0.9632	0.9103	0.0011
60-64	1,068.3	0.0534	0.9480	0.8823	3.485	0.0012	0.0546	0.9469	0.8768	0.0010
65-69	1,627.5	0.0814	0.9218	0.8364	3.507	0.0012	0.0826	0.9207	0.8302	0.0010
70-74	2,491.3	0.1246	0.8829	0.7710	3.518	0.0012	0.1258	0.8818	0.7644	0.0009
75-79	3,945.9	0.1973	0.8209	0.6807	3.524	0.0012	0.1985	0.8200	0.6740	0.0007
80-84	6,381.4	0.3191	0.7268	0.5588	3.527	0.0012	0.3203	0.7259	0.5527	0.0006
										Absolute R_x = 0.0100

Absolute risk = 0.01000; exp level = 0.2446; Occupational lifetime unit risk = 0.0409 (Based on occupational exposures beginning at age 16 years); Scaled occupational lifetime unit risk = 0.0530 (Scaled by ratio of 70:54 to account for risk over 70 year lifetime).

The following tables show details of the computations of the unit risks for lung cancer mortality (Tables G-3 and G-4). Section 5.4.5.2 details the application of the life-table methodology for lung cancer. The results of Tables G-3 and G-4 are shown in Table 5-19.

Column Definitions for Tables G-3 and G-4

Column A: Age interval up to age 85.

Column B: All-cause mortality rate for interval i ($\times 10^5$/year) (2007 data NVSR 58(19) 2010).

Column C: Lung cancer mortality rate for interval i ($\times 10^5$/year) (2003-2007 SEER Table 15.10, age-specific U.S. death rates).

Column D: All-cause hazard rate for interval i (h^*_i) (= all-cause mortality rate × number of years in age interval).

Column E: Probability of surviving interval i (q_i) (= $\exp(-h^*_i)$).

Column F: Probability of surviving up to interval i (S_i) ($S_1 = 1$; $S_i = S_{i-1} \times q_{i-1}$, for i>1).

Column G: Lung cancer mortality hazard rate for interval i (h_i) (= lung cancer mortality rate × number of years in interval).

Column H: Conditional probability of dying from lung cancer in interval i (= $(h_i/h^*_i) \times S_i \times (1-q_i)$), i.e., conditional upon surviving up to interval i (Ro, the background lifetime probability of dying from lung cancer = the sum of the conditional probabilities across the intervals).

Column I: Lagged exposure at mid-interval (x dose).

Column J: Lung cancer mortality hazard rate in exposed people for interval. To estimate the LEC_{01}, i.e., the 95% lower bound on the continuous exposure giving an extra risk of 1%, the 95% upper bound on the regression coefficient is used, i.e., MLE + 1.645 × SE.

Column K: All-cause hazard rate in exposed people for interval i (h^*x_i) (= $h^*_i + (hx_i - h_i)$).

Column L: Probability of surviving interval i without dying from lung cancer for exposed people (qx_i) (= $\exp(-h^*x_i)$).

Column M: Probability of surviving up to interval i without dying from lung cancer for exposed people (Sx_i) ($Sx_1 = 1$; $Sx_i = Sx_{i-1} \times qx_{i-1}$, for i>1).

Column N: Conditional probability of dying from lung cancer in interval i for exposed people (= $(hx_i/h^*x_i) \times Sx_i \times (1-qx_i)$) (Rx, the lifetime probability of dying from lung cancer for exposed people = the sum of the conditional probabilities across the intervals).

Note that the life tables for lung cancer mortality estimate the extra risk as $(R_x - R_o) / (1 - R_o)$, where R_x is the lifetime cancer mortality risk in the exposed population and R_o is the

lifetime lung cancer mortality risk in an unexposed population (i.e., the background risk). In each of the life tables, inhalation exposure commences at age 16 years and continues at the same exposure concentration for the duration of the life table. This allows for the computation of an "adult-only" occupational lifetime unit risk, which is then scaled by a ratio of 70:54 to account for risk over the standard 70-year lifetime. While exposure is initiated at age 16 years, this exposure is lagged to match the corresponding exposure-response models, which provide the hazard rates per unit of exposure. For example, in Tables G-3 and G-4, Column I shows exposure lagged by 10 years so that no lagged exposure appears until age 26 years.

Table G-3. Lung cancer extra risk calculation for environmental exposure to 0.191 fibers/cc Libby Amphibole asbestos using a linear exposure-response model based on the metric of cumulative exposure with a 10-year exposure lag, as described in Section 5.4.5.3 as the reasonable upper bound

A	B	C	D	E	F	G	H	I	J	K	L	M	N
Age Int.	All cause mortality (xE5/yr)	Lung CA mortality (xE5/yr)	All cause hazard rate (h*)	Prob. of surviving interval (q)	Prob. of surviving up to interval (S)	Lung CA hazard rate (h)	Cond. prob. of lung CA mortality in interval (Ro)	Lagged exp. mid. int. (Xdose)	Exposed lung CA hazard rate (hx)	Exposed all cause haz. rate (h*x)	Exposed prob. of surviving interval (qx)	Exposed prob. of surviving up to int. (Sx)	Exposed Cond. prob. of lung CA in interval (Rx)
<1	684.5	0	0.0068	0.9932	1.0000	0.0000	0.0000	0.00	0.0000	0.0068	0.9932	1.0000	0.0000
1-2	28.6	0	0.0003	0.9997	0.9932	0.0000	0.0000	0.00	0.0000	0.0003	0.9997	0.9932	0.0000
2-3	28.6	0	0.0003	0.9997	0.9929	0.0000	0.0000	0.00	0.0000	0.0003	0.9997	0.9929	0.0000
3-4	28.6	0	0.0003	0.9997	0.9926	0.0000	0.0000	0.00	0.0000	0.0003	0.9997	0.9926	0.0000
4-5	29.9	0	0.0003	0.9997	0.9923	0.0000	0.0000	0.00	0.0000	0.0003	0.9997	0.9923	0.0000
5-6	13.7	0	0.0001	0.9999	0.9920	0.0000	0.0000	0.00	0.0000	0.0001	0.9999	0.9920	0.0000
6-7	13.7	0	0.0001	0.9999	0.9919	0.0000	0.0000	0.00	0.0000	0.0001	0.9999	0.9919	0.0000
7-8	13.7	0	0.0001	0.9999	0.9918	0.0000	0.0000	0.00	0.0000	0.0001	0.9999	0.9918	0.0000
8-9	13.7	0	0.0001	0.9999	0.9916	0.0000	0.0000	0.00	0.0000	0.0001	0.9999	0.9916	0.0000
9-10	13.7	0	0.0001	0.9999	0.9915	0.0000	0.0000	0.00	0.0000	0.0001	0.9999	0.9915	0.0000
10-11	18.7	0	0.0002	0.9998	0.9914	0.0000	0.0000	0.00	0.0000	0.0002	0.9998	0.9914	0.0000
11-12	18.7	0	0.0002	0.9998	0.9912	0.0000	0.0000	0.00	0.0000	0.0002	0.9998	0.9912	0.0000
12-13	18.7	0	0.0002	0.9998	0.9910	0.0000	0.0000	0.00	0.0000	0.0002	0.9998	0.9910	0.0000
13-14	18.7	0	0.0002	0.9998	0.9908	0.0000	0.0000	0.00	0.0000	0.0002	0.9998	0.9908	0.0000
14-15	18.7	0	0.0002	0.9998	0.9906	0.0000	0.0000	0.00	0.0000	0.0002	0.9998	0.9906	0.0000
15-16	61.9	0	0.0006	0.9994	0.9904	0.0000	0.0000	0.00	0.0000	0.0006	0.9994	0.9904	0.0000

Table G-3. Lung cancer extra risk calculation for environmental exposure to 0.191 fibers/cc Libby Amphibole asbestos using a linear exposure-response model based on the metric of cumulative exposure with a 10-year exposure lag, as described in Section 5.4.5.3 as the reasonable upper bound (continued)

A	B	C	D	E	F	G	H	I	J	K	L	M	N
Age Int.	All cause mortality (xE5/yr)	Lung CA mortality (xE5/yr)	All cause hazard rate (h*)	Prob. of surviving interval (q)	Prob. of surviving up to interval (S)	Lung CA hazard rate (h)	Cond. prob. of lung CA mortality in interval (Ro)	Lagged exp. mid. int. (Xdose)	Exposed lung CA hazard rate (hx)	Exposed all cause haz. rate (h*x)	Exposed prob. of surviving interval (qx)	Exposed prob. of surviving up to int. (Sx)	Exposed Cond. prob. of lung CA in interval (Rx)
16-17	61.9	0	0.0006	0.9994	0.9898	0.0000	0.0000	0.00	0.0000	0.0006	0.9994	0.9898	0.0000
17-18	61.9	0	0.0006	0.9994	0.9892	0.0000	0.0000	0.00	0.0000	0.0006	0.9994	0.9892	0.0000
18-19	61.9	0	0.0006	0.9994	0.9886	0.0000	0.0000	0.00	0.0000	0.0006	0.9994	0.9886	0.0000
19-20	61.9	0	0.0006	0.9994	0.9880	0.0000	0.0000	0.00	0.0000	0.0006	0.9994	0.9880	0.0000
20-21	98.3	0.1	0.0010	0.9990	0.9874	0.0000	0.0000	0.00	0.0000	0.0010	0.9990	0.9874	0.0000
21-22	98.3	0.1	0.0010	0.9990	0.9864	0.0000	0.0000	0.00	0.0000	0.0010	0.9990	0.9864	0.0000
22-23	98.3	0.1	0.0010	0.9990	0.9854	0.0000	0.0000	0.00	0.0000	0.0010	0.9990	0.9854	0.0000
23-24	98.3	0.1	0.0010	0.9990	0.9845	0.0000	0.0000	0.00	0.0000	0.0010	0.9990	0.9845	0.0000
24-25	98.3	0.1	0.0010	0.9990	0.9835	0.0000	0.0000	0.00	0.0000	0.0010	0.9990	0.9835	0.0000
25-26	99.4	0.2	0.0010	0.9990	0.9825	0.0000	0.0000	0.00	0.0000	0.0010	0.9990	0.9825	0.0000
26-27	99.4	0.2	0.0010	0.9990	0.9815	0.0000	0.0000	0.10	0.0000	0.0010	0.9990	0.9815	0.0000
27-28	99.4	0.2	0.0010	0.9990	0.9806	0.0000	0.0000	0.29	0.0000	0.0010	0.9990	0.9806	0.0000
28-29	99.4	0.2	0.0010	0.9990	0.9796	0.0000	0.0000	0.48	0.0000	0.0010	0.9990	0.9796	0.0000
29-30	99.4	0.2	0.0010	0.9990	0.9786	0.0000	0.0000	0.67	0.0000	0.0010	0.9990	0.9786	0.0000
30-34	110.8	0.5	0.0055	0.9945	0.9777	0.0000	0.0000	1.24	0.0000	0.0055	0.9945	0.9777	0.0000
35-39	145.8	2.1	0.0073	0.9927	0.9723	0.0001	0.0001	2.20	0.0001	0.0073	0.9927	0.9722	0.0001
40-44	221.6	7.9	0.0111	0.9890	0.9652	0.0004	0.0004	3.15	0.0004	0.0111	0.9890	0.9652	0.0004
45-49	340.0	20.2	0.0170	0.9831	0.9546	0.0010	0.0010	4.11	0.0011	0.0171	0.9831	0.9545	0.0010

Table G-3. Lung cancer extra risk calculation for environmental exposure to 0.191 fibers/cc Libby Amphibole asbestos using a linear exposure-response model based on the metric of cumulative exposure with a 10-year exposure lag, as described in Section 5.4.5.3 as the reasonable upper bound (continued)

A	B	C	D	E	F	G	H	I	J	K	L	M	N
Age Int.	All cause mortality (xE5/yr)	Lung CA mortality (xE5/yr)	All cause hazard rate (h*)	Prob. of surviving interval (q)	Prob. of surviving up to interval (S)	Lung CA hazard rate (h)	Cond. prob. of lung CA mortality in interval (Ro)	Lagged exp. mid. int. (Xdose)	Exposed lung CA hazard rate (hx)	Exposed all cause haz. rate (h*x)	Exposed prob. of surviving interval (qx)	Exposed prob. of surviving up to int. (Sx)	Exposed Cond. prob. of lung CA in interval (Rx)
50-54	509.0	39.8	0.0255	0.9749	0.9385	0.0020	0.0018	5.06	0.0022	0.0257	0.9747	0.9384	0.0020
55-59	726.3	74.7	0.0363	0.9643	0.9149	0.0037	0.0034	6.02	0.0042	0.0368	0.9639	0.9146	0.0038
60-64	1,068.3	139.8	0.0534	0.9480	0.8823	0.0070	0.0060	6.97	0.0080	0.0544	0.9470	0.8815	0.0069
65-69	1,627.5	220.9	0.0814	0.9218	0.8364	0.0110	0.0089	7.93	0.0129	0.0832	0.9201	0.8348	0.0103
70-74	2,491.3	304.3	0.1246	0.8829	0.7710	0.0152	0.0110	8.88	0.0181	0.1275	0.8803	0.7682	0.0131
75-79	3,945.9	369.5	0.1973	0.8209	0.6807	0.0185	0.0114	9.84	0.0224	0.2013	0.8177	0.6762	0.0137
80-84	6,381.4	379.4	0.3191	0.7268	0.5588	0.0190	0.0091	10.79	0.0235	0.3236	0.7236	0.5529	0.0111
							R_o = 0.0531						R_x = 0.0625

Extra risk = 0.01001; exp level = 0.191; Occupational lifetime unit = 0.0524 (Based on occupational exposures beginning at age 16 years); Scaled occupational lifetime unit = 0.0679 (Scaled by ratio of 70:54 to account for risk over 70-year lifetime).

Table G-4. Lung cancer extra risk calculation for environmental exposure to 0.333 fibers/cc Libby Amphibole asbestos using the metric of cumulative exposure with a 10-year exposure lag and a 10-year half-life of exposure, as described in Section 5.4.5.3 as the lowest information criterion

A	B	C	D	E	F	G	H	I	J	K	L	M	N
Age int.	All cause mortality (xE5/yr)	Lung CA mortality (xE5/yr)	All cause hazard rate (h*)	Prob. of surviving interval (q)	Prob. of surviving up to interval (S)	Lung CA hazard rate (h)	Cond. prob. of lung CA mortality in interval (Ro)	Lagged exp. mid. int. (Xdose)	Exposed lung CA hazard rate (hx)	Exposed all cause hazard rate (h*x)	Exposed prob. of surviving interval (qx)	Exposed prob. of surviving up to int. (Sx)	Exposed cond. prob. of lung CA in interval (Rx)
<1	684.5	0	0.0068	0.9932	1.0000	0.0000	0.0000	0.00	0.0000	0.0068	0.9932	1.0000	0.0000
1-2	28.6	0	0.0003	0.9997	0.9932	0.0000	0.0000	0.00	0.0000	0.0003	0.9997	0.9932	0.0000
2-3	28.6	0	0.0003	0.9997	0.9929	0.0000	0.0000	0.00	0.0000	0.0003	0.9997	0.9929	0.0000
3-4	28.6	0	0.0003	0.9997	0.9926	0.0000	0.0000	0.00	0.0000	0.0003	0.9997	0.9926	0.0000
4-5	29.9	0	0.0003	0.9997	0.9923	0.0000	0.0000	0.00	0.0000	0.0003	0.9997	0.9923	0.0000
5-6	13.7	0	0.0001	0.9999	0.9920	0.0000	0.0000	0.00	0.0000	0.0001	0.9999	0.9920	0.0000
6-7	13.7	0	0.0001	0.9999	0.9919	0.0000	0.0000	0.00	0.0000	0.0001	0.9999	0.9919	0.0000
7-8	13.7	0	0.0001	0.9999	0.9918	0.0000	0.0000	0.00	0.0000	0.0001	0.9999	0.9918	0.0000
8-9	13.7	0	0.0001	0.9999	0.9916	0.0000	0.0000	0.00	0.0000	0.0001	0.9999	0.9916	0.0000
9-10	13.7	0	0.0001	0.9999	0.9915	0.0000	0.0000	0.00	0.0000	0.0001	0.9999	0.9915	0.0000
10-11	18.7	0	0.0002	0.9998	0.9914	0.0000	0.0000	0.00	0.0000	0.0002	0.9998	0.9914	0.0000
11-12	18.7	0	0.0002	0.9998	0.9912	0.0000	0.0000	0.00	0.0000	0.0002	0.9998	0.9912	0.0000
12-13	18.7	0	0.0002	0.9998	0.9910	0.0000	0.0000	0.00	0.0000	0.0002	0.9998	0.9910	0.0000
13-14	18.7	0	0.0002	0.9998	0.9908	0.0000	0.0000	0.00	0.0000	0.0002	0.9998	0.9908	0.0000
14-15	18.7	0	0.0002	0.9998	0.9906	0.0000	0.0000	0.00	0.0000	0.0002	0.9998	0.9906	0.0000
15-16	61.9	0	0.0006	0.9994	0.9904	0.0000	0.0000	0.00	0.0000	0.0006	0.9994	0.9904	0.0000

Table G-4. Lung cancer extra risk calculation for environmental exposure to 0.333 fibers/cc Libby Amphibole asbestos using the metric of cumulative exposure with a 10-year exposure lag and a 10-year half-life of exposure, as described in Section 5.4.5.3 as the lowest information criterion (continued)

A	B	C	D	E	F	G	H	I	J	K	L	M	N
Age int.	All cause mortality (xE5/yr)	Lung CA mortality (xE5/yr)	All cause hazard rate (h*)	Prob. of surviving interval (q)	Prob. of surviving up to interval (S)	Lung CA hazard rate (h)	Cond. prob. of lung CA mortality in interval (Ro)	Lagged exp. mid. int. (Xdose)	Exposed lung CA hazard rate (hx)	Exposed all cause hazard rate (h*x)	Exposed prob. of surviving interval (qx)	Exposed prob. of surviving up to int. (Sx)	Exposed cond. prob. of lung CA in interval (Rx)
16-17	61.9	0	0.0006	0.9994	0.9898	0.0000	0.0000	0.00	0.0000	0.0006	0.9994	0.9898	0.0000
17-18	61.9	0	0.0006	0.9994	0.9892	0.0000	0.0000	0.00	0.0000	0.0006	0.9994	0.9892	0.0000
18-19	61.9	0	0.0006	0.9994	0.9886	0.0000	0.0000	0.00	0.0000	0.0006	0.9994	0.9886	0.0000
19-20	61.9	0	0.0006	0.9994	0.9880	0.0000	0.0000	0.00	0.0000	0.0006	0.9994	0.9880	0.0000
20-21	98.3	0.1	0.0010	0.9990	0.9874	0.0000	0.0000	0.00	0.0000	0.0010	0.9990	0.9874	0.0000
21-22	98.3	0.1	0.0010	0.9990	0.9864	0.0000	0.0000	0.00	0.0000	0.0010	0.9990	0.9864	0.0000
22-23	98.3	0.1	0.0010	0.9990	0.9854	0.0000	0.0000	0.00	0.0000	0.0010	0.9990	0.9854	0.0000
23-24	98.3	0.1	0.0010	0.9990	0.9845	0.0000	0.0000	0.00	0.0000	0.0010	0.9990	0.9845	0.0000
24-25	98.3	0.1	0.0010	0.9990	0.9835	0.0000	0.0000	0.00	0.0000	0.0010	0.9990	0.9835	0.0000
25-26	99.4	0.2	0.0010	0.9990	0.9825	0.0000	0.0000	0.00	0.0000	0.0010	0.9990	0.9825	0.0000
26-27	99.4	0.2	0.0010	0.9990	0.9815	0.0000	0.0000	0.16	0.0000	0.0010	0.9990	0.9815	0.0000
27-28	99.4	0.2	0.0010	0.9990	0.9806	0.0000	0.0000	0.48	0.0000	0.0010	0.9990	0.9806	0.0000
28-29	99.4	0.2	0.0010	0.9990	0.9796	0.0000	0.0000	0.77	0.0000	0.0010	0.9990	0.9796	0.0000
29-30	99.4	0.2	0.0010	0.9990	0.9786	0.0000	0.0000	1.04	0.0000	0.0010	0.9990	0.9786	0.0000
30-34	110.8	0.5	0.0055	0.9945	0.9777	0.0000	0.0000	1.74	0.0000	0.0055	0.9945	0.9777	0.0000
35-39	145.8	2.1	0.0073	0.9927	0.9723	0.0001	0.0001	2.64	0.0001	0.0073	0.9927	0.9722	0.0001
40-44	221.6	7.9	0.0111	0.9890	0.9652	0.0004	0.0004	3.27	0.0004	0.0111	0.9889	0.9652	0.0004

Table G-4. Lung cancer extra risk calculation for environmental exposure to 0.333 fibers/cc Libby Amphibole asbestos using the metric of cumulative exposure with a 10-year exposure lag and a 10-year half-life of exposure, as described in Section 5.4.5.3 as the lowest information criterion (continued)

A	B	C	D	E	F	G	H	I	J	K	L	M	N
Age int.	All cause mortality (xE5/yr)	Lung CA mortality (xE5/yr)	All cause hazard rate (h*)	Prob. of surviving interval (q)	Prob. of surviving up to interval (S)	Lung CA hazard rate (h)	Cond. prob. of lung CA mortality in interval (Ro)	Lagged exp. mid. int. (Xdose)	Exposed lung CA hazard rate (hx)	Exposed all cause hazard rate (h*x)	Exposed prob. of surviving interval (qx)	Exposed prob. of surviving up to int. (Sx)	Exposed cond. prob. of lung CA in interval (Rx)
45-49	340.0	20.2	0.0170	0.9831	0.9546	0.0010	0.0010	3.72	0.0012	0.0172	0.9830	0.9545	0.0011
50-54	509.0	39.8	0.0255	0.9749	0.9385	0.0020	0.0018	4.04	0.0023	0.0258	0.9746	0.9383	0.0021
55-59	726.3	74.7	0.0363	0.9643	0.9149	0.0037	0.0034	4.26	0.0044	0.0370	0.9637	0.9144	0.0039
60-64	1,068.3	139.8	0.0534	0.9480	0.8823	0.0070	0.0060	4.42	0.0083	0.0547	0.9468	0.8812	0.0071
65-69	1,627.5	220.9	0.0814	0.9218	0.8364	0.0110	0.0089	4.53	0.0131	0.0834	0.9200	0.8343	0.0105
70-74	2,491.3	304.3	0.1246	0.8829	0.7710	0.0152	0.0110	4.61	0.0181	0.1274	0.8803	0.7675	0.0130
75-79	3,945.9	369.5	0.1973	0.8209	0.6807	0.0185	0.0114	4.67	0.0220	0.2008	0.8180	0.6757	0.0135
80-84	6,381.4	379.4	0.3191	0.7268	0.5588	0.0190	0.0091	4.71	0.0226	0.3227	0.7242	0.5527	0.0107
							R_o = 0.0531						R_x = 0.0626

Extra risk = 0.01001; exp level = 0.333; Occupational lifetime unit risk = 0.0300 (Based on occupational exposures beginning at age 16 years); Scaled occupational lifetime unit = 0.0389 (Scaled by ratio of 70:54 to account for risk over 70-year lifetime).