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Draft
NIOSH CURRENT INTELLIGENCE BULLETIN

**Asbestos Fibers and Other Elongate Mineral Particles:
State of the Science and Roadmap for Research
Version 4**

January 2010

**Department of Health and Human Services
Centers for Disease Control and Prevention
*National Institute for Occupational Safety and Health***

Foreword

Asbestos has been a highly visible issue in public health for over three decades. During the mid- to late-20th century, many advances were made in the scientific understanding of worker health effects from exposure to asbestos fibers and other elongate mineral particles (EMPs). It is now well documented that fibers of asbestos minerals, when inhaled, can cause serious diseases in exposed workers. However, many questions and areas of confusion and scientific uncertainty remain. For instance, due to the mineralogical complexity of the asbestos minerals, the scientific literature contains various inconsistencies in the definition and application of the term asbestos for health protection guidance and regulatory purposes.

As the federal agency responsible for conducting research and making recommendations for the prevention of worker injury and illness, the National Institute for Occupational Safety and Health (NIOSH) is undertaking a reappraisal of how to ensure optimal protection of workers from exposure to asbestos fibers and other EMPs. As a first step in this effort, NIOSH convened an internal work group to develop a framework for future scientific research and policy development. The NIOSH Mineral Fibers Work Group prepared a first draft of this *State of the Science and Roadmap for Scientific Research (Roadmap)*, summarizing NIOSH's understanding of occupational exposure and toxicity issues concerning asbestos fibers and other EMPs.

NIOSH invited comments on the occupational health issues identified and the framework for research suggested in the first draft *Roadmap*. NIOSH sought other views about additional key issues that should be identified, additional research that should be conducted, and methods for conducting the research. In particular, NIOSH sought input from stakeholders concerning study designs, techniques for generating size-selected fibers, analytic approaches, sources of particular types of EMPs suitable for experimental studies, and worker populations suitable for epidemiological study. Based on comments received during the public and expert peer review process, NIOSH revised the *Roadmap* and invited public review of the revised version by stakeholders. After further revision and public comment, a revised draft *Roadmap* was submitted for review by the National Academies of Science in early 2009. Based on the National Academies assessment of the draft *Roadmap*, revisions were made and NIOSH is now disseminating this fourth version of the document for final public comment.

The purpose of the *Roadmap* is to outline a research agenda that will guide the development of specific research programs and projects that will provide a broader and clearer understanding of the important determinants of toxicity for asbestos and other EMPs. NIOSH recognizes that results from such research may impact environmental as well as occupational health policies and practices. Many of the issues that are important in the workplace are also important to communities and to the general population.

Therefore, NIOSH envisions that the planning and conduct of the research will be a collaborative effort involving active participation of multiple federal agencies, including the Agency for Toxic Substances and Disease Registry (ATSDR), the Consumer Product Safety Commission (CPSC), the Environmental Protection Agency (EPA), the Mine Safety and Health Administration (MSHA), the National Institute of Environmental Health Sciences (NIEHS), the National Institute of Standards and Technology (NIST), the National Toxicology Program (NTP), the Occupational Safety and Health Administration (OSHA), and the United States Geological Survey (USGS), as well as labor, industry, academia, health and safety practitioners, and other interested parties, including international groups. This collaboration will help to focus the scope of the research, to fund and conduct research, and to develop and disseminate informational materials describing research results and their implications for establishing new occupational and public health policies.

The *Roadmap* also includes a clarified rewording of the NIOSH recommended exposure limit (REL) for airborne asbestos fibers. This clarification is not intended to establish a new NIOSH occupational health policy for asbestos, and no regulatory response by OSHA or MSHA is requested or expected.

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Director

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Executive Summary

In the 1970s, federal enforcement agencies in the United States developed occupational regulatory definitions and standards for exposure to airborne asbestos fibers based on human evidence of respiratory disease observed in exposed workers. Since the promulgation of these standards, which apply to the six commercially used asbestos minerals—chrysotile, and the amphibole minerals cummingtonite-grunerite asbestos (amosite), riebeckite asbestos (crocidolite), actinolite asbestos, anthophyllite asbestos, and tremolite asbestos—the use of asbestos in the United States has declined substantially and mining of asbestos in the United States ceased in 2002. Nevertheless, many asbestos products remain in use and new asbestos-containing products continue to be manufactured in or imported into the United States.

As more information became available on the relationship between the dimensions of asbestos fibers and their ability to cause respiratory disease and cancer, interest increased in exposure to other “mineral fibers.” The term “mineral fiber” has been frequently used by non-mineralogists to encompass thoracic-size elongate mineral particles (EMPs) that grow either in an asbestiform habit (e.g., asbestos fibers) or in a nonasbestiform habit (e.g., as needle-like [acicular] or prismatic crystals), as well as EMPs that result from the crushing or fracturing of non-fibrous minerals (e.g., cleavage fragments). EMPs that grow in asbestiform habits are clearly of substantial health concern. It remains uncertain whether other thoracic-size EMPs with mineralogical compositions similar to the asbestiform minerals also warrant substantial health concern.

In 1990, NIOSH revised its recommendation concerning occupational exposure to airborne asbestos fibers. At issue were concerns about potential health risks associated with worker exposures to EMPs with mineralogical compositions similar to those of the asbestos minerals and the inability of the analytical method routinely used for airborne fibers (i.e., phase contrast microscopy [PCM]) to differentiate between individual particles of these other EMPs and fibers from the asbestos minerals. This problem was further compounded by the lack of more sensitive analytical methods that could distinguish asbestos fibers from other EMPs having the same elemental composition. To address these concerns and ensure that workers are protected, NIOSH defined “airborne asbestos fibers” to encompass not only fibers from the six previously listed asbestos minerals (chrysotile, crocidolite, amosite, anthophyllite asbestos, tremolite asbestos, and actinolite asbestos), but also EMPs from their nonasbestiform analogs. NIOSH retained the use of PCM for measuring airborne fiber concentrations and counting those EMPs having: (1) an aspect ratio of 3:1 or greater; and (2) a length greater than 5 μm . NIOSH also retained its recommended exposure limit (REL) of 0.1 “airborne asbestos fibers” per cubic centimeter (f/cm^3).

Since 1990, several persistent concerns have been raised about the revised NIOSH recommendation. These concerns include:

- NIOSH's explicit inclusion of EMPs from nonasbestiform amphiboles in its 1990 revised definition of "airborne asbestos fibers" is based on inconclusive science and contrasts with the regulatory approach subsequently taken by OSHA and by MSHA.
- The revised "airborne asbestos fibers" definition does not explicitly encompass EMPs from other asbestiform amphiboles (e.g., winchite and richterite) or other fibrous minerals (e.g., erionite) that have been associated with health effects similar to those caused by asbestos.
- The specified dimensional criteria (length and aspect ratio) for EMPs covered by the revised "airborne asbestos fibers" definition may not be optimal for protecting the health of exposed workers because they are not based solely on health concerns.
- Other physicochemical parameters, such as durability and surface activity, may be important toxicological parameters but are not reflected in the revised definition of "airborne asbestos fibers."
- NIOSH's use of the term "airborne asbestos fibers" to describe all airborne EMPs covered by the REL differs from the way mineralogists use the term and this inconsistency leads to confusion about the toxicity of EMPs.

NIOSH recognizes that its 1990 description of the particles included in the REL for airborne asbestos fibers has created confusion, causing many to infer that the nonasbestiform minerals included in the NIOSH definition are "asbestos." In this document, NIOSH makes clear that such nonasbestiform minerals are not "asbestos" or "asbestos minerals," and clarifies which particles are included in the REL. This clarification also provides a basis for a better understanding of the need for the proposed research. Clarification of this REL does not change the existing NIOSH occupational health policy for asbestos, and no regulatory response by OSHA or MSHA is requested or expected.

PCM, the primary method specified by NIOSH, OSHA, and MSHA for analysis of air samples for asbestos fibers, has several limitations, including limited ability to resolve very thin fibers and to differentiate various types of EMPs. Occupational exposure limits derived from human risk assessments have been based on airborne asbestos fiber concentrations determined directly using PCM or indirectly using conversions to estimated PCM-based fiber concentrations from older impinger-based particle count

concentrations. Current lung cancer risk estimates for airborne asbestos fiber exposure are based on only a subset of airborne fibers ascertained using PCM. The standard PCM method counts only fibers longer than 5 μm . Moreover some fibers longer than 5 μm are too thin to be detected by PCM. Thus, this analytical method leaves an undetermined number of fibers collected on each sample uncounted. More sensitive analytical methods are currently available, but standardization and validation of these methods will be required before they can be recommended for routine analysis. In addition, any substantive change in analytical techniques used to evaluate exposures to asbestos and/or the criteria for determining exposure concentrations will necessitate a reassessment of current risk estimates, which are based on PCM-derived fiber concentrations.

While epidemiological evidence clearly indicates a causal relationship between exposure to fibers from the asbestos minerals and various adverse health outcomes, including asbestosis, lung cancer, and mesothelioma, results from epidemiological studies of workers exposed to EMPs from the nonasbestiform analogs of the asbestos minerals are equivocal. Due to various study limitations, NIOSH has viewed findings from these studies as providing inconclusive, as opposed to either positive or negative, evidence. Populations of interest for possible epidemiological studies include workers at talc mines in upstate New York and workers at taconite mines in northeastern Minnesota, whose exposures are to predominantly nonasbestiform EMPs. Studies may also be warranted for worker populations exposed to other EMPs, such as winchite and richterite fibers (i.e., asbestiform EMPs identified in vermiculite from a former mine near Libby, Montana), zeolites, amphiboles, and other minerals.

Although additional opportunities for informative observational epidemiological studies may be somewhat limited, there is considerable potential for experimental animal and *in vitro* studies to address specific scientific questions relating to the toxicity of EMPs. Short-term *in vivo* animal studies and *in vitro* studies have been conducted to variously examine cellular and tissue responses to EMPs, identify pathogenic mechanisms involved in those responses, and understand morphological and/or physicochemical EMP properties controlling those mechanisms. Long-term studies of animals exposed to EMPs have been conducted to assess the risk for adverse health outcomes (primarily lung cancer, mesothelioma, and lung fibrosis) associated with various types and dimensions of EMPs. Such studies have produced evidence demonstrating the importance of dimensional characteristics of mineral particles for determining carcinogenic potential of durable EMPs. In fact, NIOSH's policy decision in 1990 to include the nonasbestiform analogs of the asbestos minerals as covered minerals under its definition of "airborne asbestos fibers" was largely based on evidence from these long-term animal studies. Although *in vitro* studies and animal studies are subject to uncertainties with respect to how their findings apply to humans, such studies are warranted to systematically study and better understand the impacts of dimension, morphology, chemistry, and biopersistence of EMPs on malignant and nonmalignant respiratory disease outcomes.

To reduce existing scientific uncertainties and to help resolve current policy controversies, a strategic research program is needed that encompasses endeavors in toxicology, exposure assessment, epidemiology, mineralogy, and analytical methods. The findings of such research can contribute to the development of new policies for exposures to airborne asbestos fibers and other EMPs with recommendations for exposure indices that are not only more effective in protecting workers' health, but are firmly based on quantitative estimates of health risk. To bridge existing scientific uncertainties, this *Roadmap* proposes that interdisciplinary research address the following three strategic goals: (1) develop a broader and clearer understanding of the important determinants of toxicity for EMPs; (2) develop information on occupational exposures to various EMPs and health risks associated with such exposures; and (3) develop improved sampling and analytical methods for asbestos fibers and other EMPs.

Developing a broader and clearer understanding of the important determinants of toxicity for EMPs will involve systematically conducting *in vitro* studies and *in vivo* animal studies to ascertain which physical and chemical properties of EMPs influence their toxicity and their underlying mechanisms of action. The *in vitro* studies could help inform on membranolytic, cytotoxic, and genotoxic activities as well as signaling mechanisms. The *in vivo* animal studies will involve a multi-species testing approach for short-term assays to develop information for designing chronic inhalation studies and to develop information on biomarkers and mechanisms of disease. Chronic animal inhalation studies are required to address the impacts of dimension, morphology, chemistry, and biopersistence on critical disease endpoints of cancer induction and nonmalignant respiratory disease. Chronic inhalation studies will be designed to provide solid scientific evidence on which to base human risk assessments for a variety of EMPs.

Developing information and knowledge on occupational exposures to various EMPs and potential health outcomes will involve: (1) collecting and analyzing available occupational exposure information to ascertain the characteristics and extent of exposure to various types of EMPs; (2) collecting and analyzing available information on health outcomes associated with exposures to various types of EMPs; (3) conducting epidemiological studies of workers exposed to various types of EMPs to better define the association between exposure and health effects; and (4) developing and validating methods for screening, diagnosis, and secondary prevention for diseases caused by exposure to asbestos fibers and other EMPs.

Developing improved sampling and analytical methods for EMPs will involve: (1) reducing inter-operator and inter-laboratory variability of currently used analytical methods; (2) developing a practical analytical method that will permit the counting, sizing, and identification of all EMPs deemed biologically relevant; (3) developing a practical analytical method that can assess the potential durability of EMPs as one determinant of biopersistence in the lung; and (4) developing and validating size-

selective sampling methods for collecting and quantifying airborne thoracic-size asbestos fibers and other EMPs.

A primary anticipated outcome of the research that is broadly outlined above would be the identification of the physicochemical parameters such as chemical composition, dimensional attributes (e.g., ranges of length, width, and aspect ratio), and durability as predictors of biopersistence, as well as of particle surface characteristics or activities (e.g., generation reactive oxygen species [ROS]) as determinants of toxicity of asbestos fibers and other EMPs. The results of the research would also help define the sampling and analytical methods that closely measure the important toxic characteristics. These results can then inform development of appropriate recommendations for worker protection.

Another outcome of the research might be the development of criteria that could be used to reliably predict the relative potential risk associated with exposure to any particular type of EMP based on results of *in vitro* testing and/or short-term *in vivo* testing. Such criteria might include specific chemical compositions, dimensional attributes (e.g., ranges of length, width, and aspect ratio), and durability as predictors of biopersistence, as well as particle surface characteristics or activities. This could reduce the need for comprehensive toxicity testing with long-term *in vivo* animal studies and/or epidemiological evaluation of each type of EMP. The results from such studies could be used to fill in knowledge gaps beyond EMPs to encompass predictions of relative toxicities and adverse health outcomes associated with exposure to other elongate particles (EPs), including inorganic and organic manufactured particles. A coherent risk management approach that fully incorporates an understanding of the toxicity of particles could then be developed to minimize the potential for disease in exposed individuals and populations. Whether criteria can be developed to evaluate the potential toxicity of EMPs based exclusively on *in vitro* or short-term *in vivo* testing is currently unclear, but the challenge to work toward such an outcome could stimulate beneficial research and debate.

Asbestos Fibers and Other Elongate Mineral Particles: State of the Science and Roadmap for Scientific Research is intended to define the scientific and technical research issues that need to be addressed to ensure that workers are optimally protected from health risks posed by exposures to asbestos fibers and other EMPs. Achievement of the research goals framed in the *Roadmap* will require a significant investment of time, scientific talent, and resources by NIOSH and others. This investment, however, can result in a sound scientific basis for better occupational health protection policies for asbestos fibers and other EMPs.

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Document History

Throughout its development, this *Roadmap* has undergone substantial public comment and scientific peer review with subsequent revision. A listing of the various draft versions disseminated for public comment and/or scientific peer review is presented here.

February 2007 –Draft entitled *Asbestos and Other Mineral Fibers: A Roadmap for Scientific Research* was disseminated for public comment and scientific peer review.

June 2008 –Draft entitled *Revised Draft NIOSH CURRENT INTELLIGENCE BULLETIN - Asbestos Fibers and Other Elongate Mineral Particles: State of the Science and Roadmap for Research* was disseminated for public comment.

January 2009 –Draft entitled *Revised Draft NIOSH CURRENT INTELLIGENCE BULLETIN - Asbestos Fibers and Other Elongated Mineral Particles: State of the Science and Roadmap for Research* was submitted to the Institute of Medicine and the National Research Council of the National Academies of Science for scientific review.

January 2010 –Draft entitled *Draft NIOSH CURRENT INTELLIGENCE BULLETIN - Asbestos Fibers and Other Elongate Mineral Particles: State of the Science and Roadmap for Research – Version 4* is being disseminated for public comment.

Abbreviations

8-OHdG	8-hydroxydeoxyguanosine
AED	aerodynamic equivalent diameter
AIHA	American Industrial Hygiene Association
AP-1	activator protein-1
ASTM	ASTM International
ATSDR	Agency for Toxic Substances Disease Registry
BAL	bronchoalveolar lavage
BrdU	bromodeoxyuridine
CI	confidence interval
COX-2	cyclooxygenase-2
CPSC	Consumer Product Safety Commission
DM	dark-medium microscopy
DNA	deoxyribonucleic acid
DPPC	dipalmitoyl phosphatidylcholine
ED	electron diffraction
EDS	energy dispersive X-ray spectroscopy
EGFR	epidermal growth factor receptor
EM	electron microscopy
EMP	elongate mineral particle
EP	elongate particle
EPA	U.S. Environmental Protection Agency
ERK	extracellular signal-regulated kinase
ESR	electron spin resonance
f/cm ³	fibers per cubic centimeter
f/mL-yr	fibers per milliliter-year
HSL/ULO	Health and Safety Laboratory/UL Optics
ICD	International Classification of Diseases
IgG	immunoglobulin G
IL	interleukin
IMA	International Mineralogical Association
IMIS	Integrated Management Information System
IP	intrapertoneal
ISO	International Organization for Standardization
L	liter
LDH	lactate dehydrogenase
LOQ	limit of quantification
MDH	Minnesota Department of Health
mg/m ³ -d	milligrams per cubic meter-days
MAPK	mitogen-activated protein kinase
MMAD	mass median aerodynamic diameter
MMMf	man-made mineral fiber

Abbreviations (continued)

MMVF	man-made vitreous fiber
mppcf	million particles per cubic foot
MSHA	Mine Safety and Health Administration
mRNA	messenger ribonucleic acid
NADPH	nicotinamide adenine dinucleotide phosphate
NFκB	nuclear factor kappa beta
NIEHS	National Institute of Environmental Health Sciences
NMRD	nonmalignant respiratory disease
NIOSH	National Institute for Occupational Safety and Health
NIST	National Institute of Standards and Technology
NORA	National Occupational Research Agenda
NORMS	National Occupational Respiratory Mortality System
NTP	National Toxicology Program
OSHA	Occupational Safety and Health Administration
PCM	phase contrast microscopy
PEL	permissible exposure limit
RCF	refractory ceramic fiber
REL	recommended exposure limit
ROS	reactive oxygen species
RTV	RT Vanderbilt Company, Inc.
SAED	selected area X-ray diffraction
SEM	scanning electron microscopy
SMR	standardized mortality ratio
SO	superoxide anion
SOD	superoxide dismutase
SV40	simian virus 40
SVF	synthetic vitreous fiber
SWCNT	single-walled carbon nanotubes
TEM	transmission electron microscopy
TF	tissue factor
TGF	transforming growth factor
TNF-α	tumor necrosis factor-alpha
TWA	time-weighted average
USGS	United States Geological Survey
XPS	X-ray photoelectron spectroscopy

1 INTRODUCTION

1
2
3 Many workers are exposed to a broad spectrum of inhalable particles in their places of
4 work. These particles vary in origin, size, shape, chemistry, and surface properties.
5 Considerable research over many years has been undertaken to understand the potential
6 health effects of these particles and the particle characteristics that are most important in
7 conferring their toxicity. Elongate particles (EPs) have been the subject of much
8 research, and the major focus of research on EPs has related to asbestos particles, a group
9 of elongate mineral particles (EMP) that have long been known to cause serious disease
10 when inhaled. Because of the demonstrated health effects of asbestos, research attention
11 has also been extended not only to other EMPs, but also to synthetic vitreous fibers which
12 have dimensions similar to asbestos fibers and, more recently, to engineered carbon
13 nanotubes and carbon nanofibers. While non-mineral EPs are of interest, they are not the
14 subject of this *Roadmap*, which focuses on EMPs.

15
16 Occupational health policies and associated federal regulations controlling occupational
17 exposure to airborne asbestos fibers have been in existence for decades. Nevertheless,
18 important uncertainties remain to be resolved to fully inform possible revision of existing
19 federal policies and/or development of new federal policies to protect workers from
20 health effects caused by occupational exposure to airborne asbestos fibers. Further
21 research is warranted to develop the science-based knowledge needed to inform the
22 development of new or revised occupational health policies and regulations concerning
23 asbestos fibers.

24
25 In addition, health effects caused by exposures to other (non-asbestos) EMPs have not
26 been studied as thoroughly as the health effects caused by exposures to asbestos fibers.
27 Miners and others exposed to amphibole fibers associated with vermiculite from a mine
28 near Libby, Montana, may not have been exposed to commercial asbestos fibers, but the
29 adverse health outcomes they experienced as a result of their exposure indicated that
30 those EMPs were every bit as toxic. Some hardrock miner populations are exposed to
31 EMPs, including elongate "cleavage fragments" of nonasbestiform amphiboles, which
32 some laboratory studies have found to demonstrate asbestos-like toxicity, while
33 epidemiological studies to date remain inconclusive. Also, studies of human populations
34 exposed to airborne fibers of erionite, a fibrous mineral that is neither asbestos nor
35 amphibole, have documented high rates of malignant mesothelioma (a cancer most
36 commonly associated with exposure to asbestos fibers). Further research is warranted to
37 understand how properties of EMPs determine toxicity so that the nature and magnitude
38 of any potential toxicity associated with an EMP to which workers are exposed in any
39 place of work can be readily predicted and controlled, even when exhaustive long-term
40 studies of that particular EMP have not been carried out.

41
42 This document, *Asbestos Fibers and Other Elongate Mineral Particles: State of the*
43 *Science and Roadmap for Research*, has been prepared and is being disseminated with

1 the intent of motivating eventual development and implementation of a coordinated,
2 interdisciplinary research program that can effectively address key remaining issues
3 relating to health hazards associated with exposure asbestos fibers and other EMPs.
4

5 Section 2 (*Overview of Current Issues*) of the *Roadmap* provides an overview of
6 available scientific information and identifies important issues which need to be resolved
7 before recommendations for occupational exposure to airborne asbestos fibers and related
8 EMPs can be improved and before recommendations for occupational exposure to other
9 EMPs can be developed. The nature of occupational exposures to asbestos has changed
10 over the last several decades. Once dominated by chronic exposures in asbestos textile
11 mills, friction product manufacturing, cement pipe fabrication, and insulation
12 manufacture and installation, current occupational exposures to asbestos in the United
13 States primarily occur during maintenance activities or remediation of buildings
14 containing asbestos. OSHA has estimated that 1.3 million workers in general industry
15 continue to be exposed to asbestos; NIOSH has estimated that nearly 45,000 mine
16 workers may be exposed. These current occupational exposure scenarios frequently
17 involve short-term, intermittent exposures, and proportionately fewer long fibers than
18 workers were exposed to in the past. The generally lower current exposures give added
19 significance to the question of whether or not there is an asbestos exposure threshold
20 below which workers would incur no risk of adverse health outcomes. The large number
21 of potentially exposed workers and these changed exposure scenarios also give rise to the
22 need to better understand whether appropriate protection is provided by the current
23 occupational exposure recommendations and regulations. In addition, limited
24 information is currently available on exposures to, and health effects of, other EMPs.
25

26 Section 3 (*Framework for Research*) of this *Roadmap* provides a general framework for
27 research needed to address the key issues. NIOSH envisions that this general framework
28 will serve as a basis for a future interdisciplinary research program carried out a variety
29 of organizations to elucidate exposures to EMPs, any adverse health effects caused by
30 these exposures, and the influence of size, shape, and other physical and chemical
31 characteristics of EMPs on human health. Findings from this research would provide a
32 basis for determining which EMPs should be included in recommendations to protect
33 workers from hazardous occupational exposures along with appropriate exposure limits.
34 A fully informed strategy for prioritizing research on EMPs will be based on a systematic
35 collection and evaluation of available information on occupational exposures to EMPs.
36

37 Section 4 (*The Path Forward*) of this *Roadmap* broadly outlines a proposed structure for
38 development and oversight of a comprehensive, interdisciplinary research program. Key
39 to this approach will be the active involvement of stakeholders representing parties with
40 differing views, expert study groups specifying and guiding various components of the
41 research program, and a multidisciplinary group providing careful ongoing review and
42 oversight to ensure relevance, coordination, and impact of the overall research program.
43 NIOSH does not intend this (or any other) section of the *Roadmap* to be prescriptive, so
44 detailed research aims, specific research priorities, and funding considerations have

1 intentionally not been specified. Rather, it is expected that these more detailed aspects of
2 the program will be most effectively developed with collaborative input from scientists,
3 policy experts, and managers from various agencies, as well as from other interested
4 stakeholders.
5
6

2 OVERVIEW OF CURRENT ISSUES

2.1 Background

Prior to the 1970s, concern about the health effects of occupational exposure to airborne fibers was focused on six commercially exploited minerals termed "asbestos:" the serpentine mineral chrysotile and the amphibole minerals cummingtonite-grunerite asbestos (amosite), riebeckite asbestos (crocidolite), actinolite asbestos, anthophyllite asbestos, and tremolite asbestos. The realization that dimensional characteristics of asbestos fibers were important physical parameters in the initiation of respiratory disease led to studies of other elongate mineral particles (EMPs) of similar dimensions [Stanton et al. 1981].

To date, interest in EMPs other than asbestos fibers has been focused primarily on fibrous minerals exploited commercially (e.g., wollastonite, sepiolite, and attapulgite). Exposure to airborne thoracic-size EMPs generated from the crushing and fracturing of nonasbestiform amphibole minerals has also garnered substantial interest. The asbestos minerals, as well as other types of fibrous minerals, are typically associated with other minerals in geologic formations at various locations in the United States [Van Gosen 2007]. The biological significance of occupational exposure to airborne particles remains unknown for many of these minerals and will be difficult to ascertain given the mixed and sporadic nature of exposure in many work environments and the general lack of well-characterized exposure information.

The complex and evolving terminology used to name and describe the various minerals from which airborne EMPs are generated has led to much confusion and uncertainty in scientific and lay discourse related to asbestos fibers and other EMPs. To help reduce such confusion and uncertainty about the content of this *Roadmap*, several new terms are used in the Roadmap and defined in the Glossary (Section 6). However, the lack of uniformity in the use of terms and the lack of precision in the definitions for many of the scientific terms remain issues which cannot be resolved in this *Roadmap*. Definitions for mineralogical and other scientific terms used in the Roadmap are provided from a variety of sources.

To address current controversies and uncertainties concerning exposure assessment and health effects relating to asbestos fibers and other EMPs, strategic research endeavors are needed in toxicology, exposure assessment, epidemiology, and analytical methods. The results of such research can inform the potential development of new policies for asbestos fibers and other EMPs with recommendations for exposure limits that are firmly based on well-established risk estimates and that effectively protect workers' health. What follows in the remainder of Section 2 is an overview of: (1) definitions and terms relevant to asbestos fibers and other EMPs; (2) trends in production and use of asbestos; (3)

1 occupational exposures to asbestos and asbestos-related diseases; (4) sampling and
2 analytical issues; and (5) physicochemical properties associated with EMP toxicity.

3 4 **2.2 Minerals and Mineral Morphology**

5
6 Minerals are naturally occurring inorganic compounds with a specific crystalline
7 structure and elemental composition. Asbestos is a term applied to several silicate
8 minerals from the serpentine and amphibole groups that grow in a fibrous habit and have
9 properties that have made them commercially valuable. The fibers of all varieties of
10 asbestos are long, thin, and usually flexible when separated. One variety of asbestos,
11 chrysotile, is a mineral in the serpentine group of sheet silicates. Five varieties of
12 asbestos are minerals in the amphibole group of double-chain silicates—riebeckite
13 asbestos (crocidolite), cummingtonite-grunerite asbestos (amosite), anthophyllite
14 asbestos, tremolite asbestos, and actinolite asbestos [Virta 2002].
15

16 Although a large amount of health information has been generated on workers
17 occupationally exposed to asbestos, limited mineral characterization information and the
18 use of non-mineralogical names for asbestos have resulted in uncertainty and confusion
19 about the specific nature of exposures described in many published studies. Trade names
20 for mined asbestos minerals predated the development of rigorous scientific
21 nomenclature. For example, amosite is the trade name for asbestiform cummingtonite-
22 grunerite and crocidolite is the trade name for asbestiform riebeckite. A changing
23 mineralogical nomenclature for amphiboles has also contributed to frequent uncertainty
24 in the specific identification of minerals reported in the literature. Over the past 50 years,
25 several systems for naming amphibole minerals have been used. The current
26 mineralogical nomenclature was unified by the International Mineralogical Association
27 (IMA) under a single system in 1978 [Leake 1978] and later modified in 1997 [Leake et
28 al. 1997]. For some amphibole minerals, the name assigned under the 1997 IMA system
29 is different than the name used prior to 1978.
30

31 Adding to the complexity of the nomenclature, serpentine and amphibole minerals
32 typically develop through the alteration of other minerals. Consequently, they may exist
33 as partially altered minerals having variations in elemental compositions. For example,
34 the microscopic analysis of an elongate amphibole particle using energy dispersive X-ray
35 spectroscopy (EDS) can reveal variations in elemental composition along the particle's
36 length, making it difficult to identify the particle as a single specific amphibole mineral.
37 In addition, a mineral may occur in different growth forms, or "habits," both sharing the
38 same name, elemental composition, and chemical structure.
39

40 Mineral habit results from the environmental conditions present during a mineral's
41 formation. The mineralogical terms applied to habits are generally descriptive (e.g.,
42 fibrous, massive, prismatic, acicular, asbestiform, tabular, and platy). Both asbestiform
43 (fibrous) and nonasbestiform (massive) versions (i.e., analogs) of the same mineral can

1 occur in juxtaposition or matrixed together, so that both analogs of the same mineral can
2 occur within a narrow geological formation.

3
4 The habits of amphibole minerals vary from stubby prismatic crystals of hornblende,
5 through prismatic or acicular crystals of riebeckite, actinolite, tremolite and others, to
6 fibrous forms of grunerite (amosite), anthophyllite, tremolite-actinolite, and riebeckite
7 (crocidolite). The prismatic and acicular crystal habits occur more commonly, and
8 asbestiform habit is relatively rare. Some of the amphiboles, such as hornblendes, are not
9 known to occur in an asbestiform habit. The asbestiform varieties range from finer
10 (flexible) to coarser (more brittle) and often are found in a mixture of fine and coarse
11 fibrils. In addition, properties vary (e.g., density of (010) defects) even within an
12 apparently homogeneous specimen [Dorling and Zussman 1987].

13
14 In the scientific literature, the term “mineral fibers” has often been used to refer not only
15 to particles that have grown in a fibrous or asbestiform habit, but also to particles that
16 have grown as needle-like (acicular) single crystals. The term “mineral fibers” has
17 sometimes also encompassed other prismatic crystals and cleavage fragments that meet
18 specified dimensional criteria. Cleavage fragments are generated by crushing and
19 fracturing minerals, including the nonasbestiform analogs of the asbestos minerals.
20 While the substantial hazards of inhalational exposure to airborne asbestos fibers have
21 been well documented, there is ongoing controversy about whether exposure to thoracic-
22 size EMPs from nonasbestiform analogs of the asbestos minerals is also substantially
23 hazardous.

24 25 **2.3 Terminology**

26
27 The use of non-standard terminology or terms with imprecise definitions when reporting
28 studies makes it difficult to fully understand the implications of these studies or to
29 compare the results to other studies. For the health community, this ultimately hampers
30 research efforts, leads to ambiguity in exposure-response relationships, and could also
31 lead to imprecise recommendations to protect human health. Terms are often interpreted
32 differently between disciplines. The situation is complicated by further different usage of
33 the same terms by stakeholders outside of the scientific community. NIOSH has
34 carefully reviewed numerous resources and has not found current references for standard
35 terminology and definitions in several disciplines that are complete and unambiguous.
36 An earlier tabulation of asbestos-related terminology by the USGS demonstrated similar
37 issues [Lowers and Meeker 2002].

38
39 NIOSH supports the development of standard terminology and definitions which are
40 acceptable to the majority of scientists relevant to the issues of asbestos and other EMPs.
41 NIOSH also supports the dissemination of standard terminology and definitions to the
42 community of non-scientists and encourages adoption and usage by this community. The
43 need for the development and standardization of unambiguous terminology and

1 definitions warrants a priority effort of the greater scientific community that should
2 precede, or at least be concurrent with, further research efforts.

3 4 **2.3.1 Geological Definitions**

5
6 The minerals of primary concern are the minerals which have been regulated as asbestos
7 (chrysotile, amosite, crocidolite, tremolite asbestos, actinolite asbestos and anthophyllite
8 asbestos). However, some of these mineral names (crocidolite and amosite) are not
9 recognized as proper mineral names. In addition, there is also interest in related minerals
10 that may resemble asbestos (e.g. fibrous antigorite, richterite, and winchite), unrelated
11 fibrous minerals (e.g. the zeolites erionite and mordenite, the clay minerals sepiolite and
12 palygorskite, etc.), and individual particles or fragments of the nonasbestiform asbestos
13 minerals. Individual minerals are precisely defined by their chemical composition and
14 crystallography. Ionic substitutions occur in minerals, especially for metal cations of
15 similar ionic charge or size. Such substitution can result in an *isomorphous series* (also
16 referred to as *solid-solution* or *mixed crystal*) consisting of minerals of varying
17 composition between end-members with a specific chemical composition. The
18 differences in chemical composition within an isomorphous series can result in different
19 properties such as color and hardness, as well as differences in crystal properties by
20 alteration of unit-cell dimensions. It is sometimes possible to differentiate mineral
21 species based on distinctive changes through an isomorphous series. However, in
22 general, classification occurs by an arbitrary division based on chemistry, and this can be
23 complicated by having multiple sites of possible substitution (e.g., in a specific mineral,
24 calcium may exchange for magnesium in one position while sodium and potassium may
25 be exchanged in another position). These allocations are open to re-evaluation and re-
26 classification over time (e.g., the mineral richterite was once known as soda-tremolite).

27
28 When certain minerals were marketed or regulated as asbestos, the mineral names had
29 definitions that may have been imprecise at the time and may have changed over time. In
30 particular, the mineral name amosite was a commercial term for a mineral that was not
31 well defined at first. The definition of amosite in the *Dictionary of Mining, Mineral, and*
32 *Related Terms* [USBOM 1996] and in the *Glossary of Geology* [American Geological
33 Institute 2005] allow for the possibility that amosite may be anthophyllite asbestos,
34 although it is now known to be a mineral in the cummingtonite-grunerite series. This is
35 one source of confusion in the literature.

36
37 A further source of confusion comes from the use of the geological terms for a mineral
38 habit. Minerals of the same chemistry differing only in the expression of their
39 crystallinity (e.g., massive, fibrous, asbestiform, prismatic) are not differentiated in
40 geology as independent species. Thus, tremolite in a fibrous crystal habit is not given a
41 separate name (either chemical or common) from tremolite in a more massive habit.
42 However, the asbestiform habit is somewhat unique in mineralogy, and crystals grown in
43 this habit can be distinguished by certain characteristics, such as parallel or radiating
44 growth of very thin and elongate crystals that are to some degree flexible, and, for

1 amphiboles, a particular combination of twinning, stacking faults and defects [Chisholm,
2 1973]. Nevertheless, asbestiform and nonasbestiform habits are commonly found
3 together, and an asbestos deposit or product derived from it may not include wholly
4 asbestiform material in the same way in which minerals not considered as asbestos may
5 contain asbestiform material. The mineralogical community uses many terms, including
6 fibril, fiber, fibrous, acicular, needlelike, prismatic, and columnar, to denote crystals that
7 are elongate. In contrast, in sedimentology, similar terms have been defined with specific
8 axial ratios.

9
10 Thus it is not clear, even from a single source, exactly what range of morphologies are
11 described by these terms and the degree of overlap, if any. For example, the *Dictionary*
12 *of Mining, Mineral, and Related Terms* defines fibril as “a single fiber, which cannot be
13 separated into smaller components without losing its fibrous properties or appearance,”
14 but also defines a fiber as “the smallest single strand of asbestos or other fibrous
15 material.”

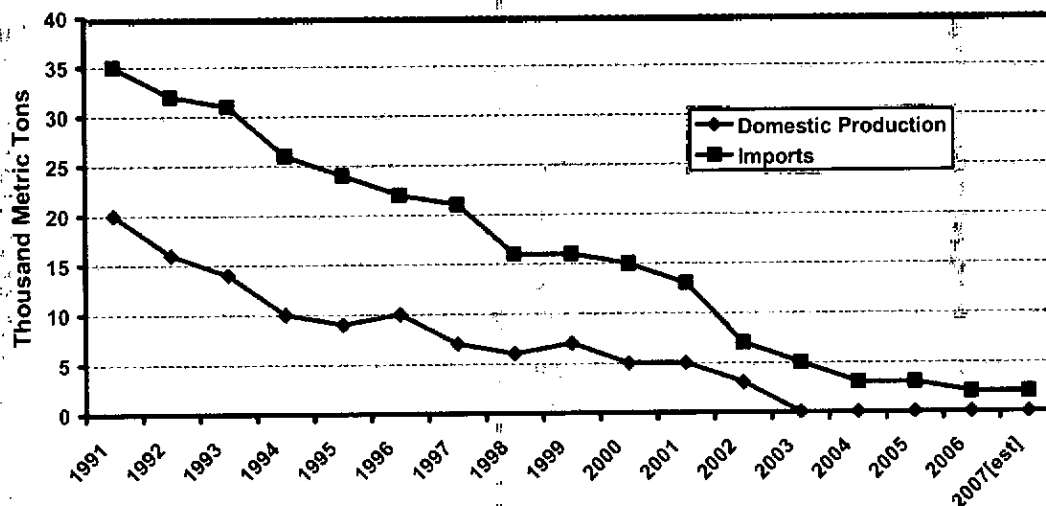
16 17 **2.3.2 Other Terms and Definitions.**

18
19 Health-related professions also employ terminology that can be used imprecisely. For
20 example, the terms “inhalable” and “respirable” have different meanings, but are
21 sometimes used interchangeably. Particles can enter the human airways, but the
22 aspiration efficiency, the degree of penetration to different parts of the airways, and the
23 extent of deposition depend on particle aerodynamics, as well as on the geometry and
24 flow dynamics within the airways. In addition to obvious differences between species
25 (e.g. mouse, rat, dog, primate, human), there is a significant range of variation within a
26 species based on, for example, age, sex, body mass, and work-rate. Thus, these terms
27 may mean different things to a toxicologist engaging in animal inhalation experiments, an
28 environmental specialist concerned with childhood exposure, and an industrial hygienist
29 concerned with adult, mostly male, workers.

30 31 **2.4 Trends in Asbestos Use, Occupational Exposures, and Disease**

32 33 **2.4.1 Trends in Asbestos Use**

34
35 Over recent decades, mining and use of asbestos have declined in the United States. The
36 mining of asbestos in the United States ceased in 2002. Consumption of raw asbestos
37 continues to decline from a peak of 803,000 metric tons in 1973 [USGS 2006]. In 2006,
38 2000 metric tons of raw asbestos were imported, down from an estimated 35,000 metric
39 tons in 1991 (see Figure 1) and a peak of 718,000 metric tons in 1973. Unlike
40 information on the importation of raw asbestos, information is not readily available on
41 the importation of asbestos-containing products. The primary recent uses for asbestos
42 materials in the United States are estimated as 55% for roofing products, 26% for
43 coatings and compounds, and 19% for other applications [USGS 2007], and more
44 recently as 84% for roofing products and 16% for other applications [USGS 2008].



1
2 **Figure 1.** U.S. asbestos production and imports, 1991–2007. Source of data: USGS [2008].
3

4 Worldwide, the use of asbestos has declined. Using the amount of asbestos mined as a
5 surrogate for the amount used, worldwide annual use has declined from about 5 million
6 metric tons in 1975 to about 2 million metric tons since 1999 [Taylor et al. 2006]. The
7 European Union has banned imports and the use of asbestos with limited exceptions. In
8 other regions of the world, there is a continued demand for inexpensive, durable
9 construction materials. Consequently, markets remain strong in some countries for
10 asbestos-cement products, such as asbestos-cement panels for construction of buildings
11 and asbestos-cement pipe for water-supply lines. Currently over 70% of all mined
12 asbestos is used in Eastern Europe and Asia [Tossavainen 2005].
13

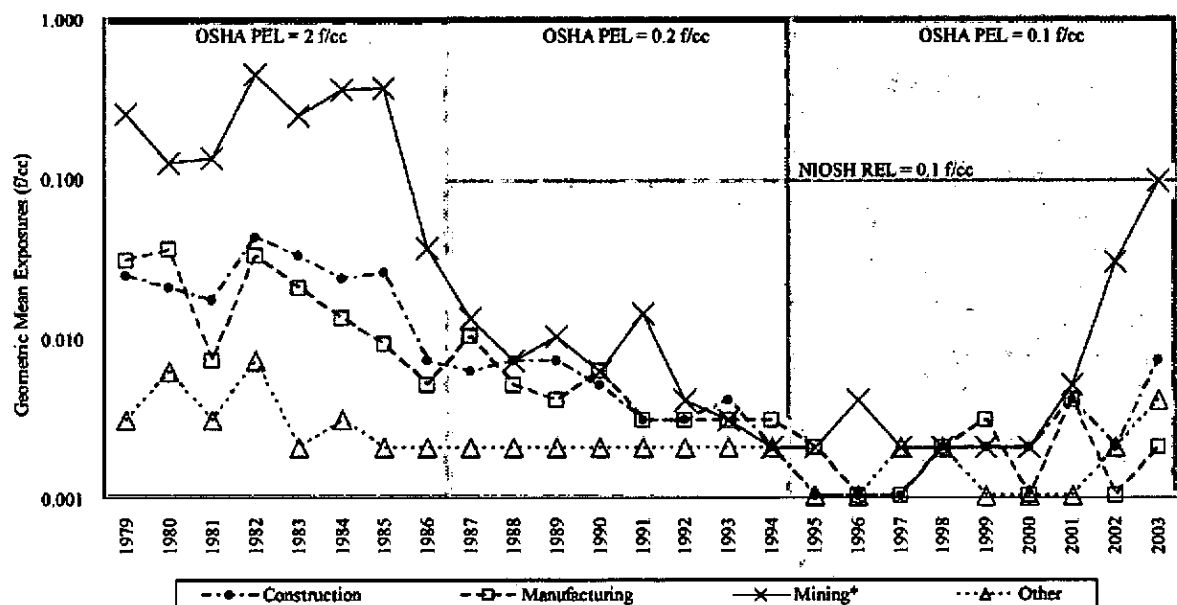
14 Historically, chrysotile accounted for more than 90% of the world's mined asbestos; it
15 presently accounts for over 99% [Ross and Virta 2001; USGS 2008]. Mining of
16 crocidolite (asbestiform riebeckite) and amosite (asbestiform cummingtonite-grunerite)
17 deposits have accounted for most of the remaining asbestos, although mining of amosite
18 ceased in 1992 and mining of crocidolite ended in 1997. Small amounts of anthophyllite
19 asbestos have been mined in Finland [Ross and Virta 2001] and are currently being
20 mined in India [Ansari et al. 2007].
21

22 **2.4.2 Trends in Occupational Exposure** 23

24 Since 1986, the annual geometric mean concentrations of occupational exposures to
25 asbestos in the United States, as reported in the Occupational Safety and Health
26 Administration's (OSHA) Integrated Management Information System (IMIS) and the
27 Mine Safety and Health Administration's (MSHA) database, have been consistently
28 below the NIOSH recommended exposure limit (REL) of 0.1 fibers per cubic centimeter
29 of air (f/cm³) for all major industry divisions (Figure 2). The number of occupational

1 asbestos exposures that were measured and reported in IMIS decreased from an average
 2 of 890 per year during the 8-year period of 1987–1994 to 241 per year during the 5-year
 3 period of 1995–1999 and 135 for the 4 year period of 2000–2003. The percentage
 4 exceeding the NIOSH REL decreased from 6.3% in 1987–1994 to 0.9% in 1995–1999,
 5 but increased to 4.3% in 2000–2003. During the same three periods, the number of
 6 exposures measured and reported in MSHA’s database decreased from an average of 47
 7 per year during 1987–1994 to an average of 23 per year during 1995–1999, but increased
 8 to 84 during 2000–2003, most of which were collected in 2000. The percentage
 9 exceeding the NIOSH REL decreased from 11.1% in 1987–1994 to 2.6% in 1995–1999,
 10 but increased to 9.8% in 2000–2003 [NIOSH 2007a].

11
 12 The preceding summary of occupational exposures to asbestos is based on the OSHA and
 13 MSHA regulatory definitions relating to asbestos. Because of analytical limitations of
 14 the phase contrast microscopy (PCM) method and the variety of workplaces from which
 15 the data were obtained, it is unclear what portions of these exposures were to EMPs from
 16 nonasbestiform analogs of the asbestos minerals, which have been explicitly
 17 encompassed by the NIOSH REL for airborne asbestos fibers since 1990.
 18



19
 20 **Figure 2.** Asbestos: Annual geometric mean exposure concentrations by major industry division,
 21 MSHA and OSHA samples, 1979–2003. Source of data: NIOSH [2007a]. Note: the MSHA PEL
 22 for this time period was 2 f/cm³.
 23

24 Very limited information is available on the number of workers still exposed to asbestos.
 25 Based on MSHA [2002] mine employment data, an estimated 44,000 miners and other
 26 mine workers may be exposed to asbestos or amphibole cleavage fragments during the
 27 mining of some mineral commodities [NIOSH 2002]. OSHA estimated in 1990 that
 28 about 568,000 workers in production and services industries and 114,000 in construction
 29 industries may be exposed to asbestos in the workplace [OSHA 1990]. More recently,

1 OSHA has estimated that 1.3 million employees in construction and general industry face
2 significant asbestos exposure on the job [OSHA 2008].

3
4 In addition to evidence from OSHA and MSHA that indicates a reduction in occupational
5 exposures in the United States over the last several decades of the 1900s, other
6 information compiled on workplace exposures to asbestos indicates that the nature of
7 occupational exposures to asbestos has changed [Rice and Heineman 2003]. Once
8 dominated by chronic exposures in manufacturing processes such as those used in textile
9 mills, friction product manufacturing, and cement pipe fabrication, current occupational
10 exposures to asbestos in the United States primarily occur during maintenance activities
11 or remediation of buildings containing asbestos. These current occupational exposure
12 scenarios frequently involve short-term, intermittent exposures.

13 14 **2.4.3 Trends in Asbestos-related Disease**

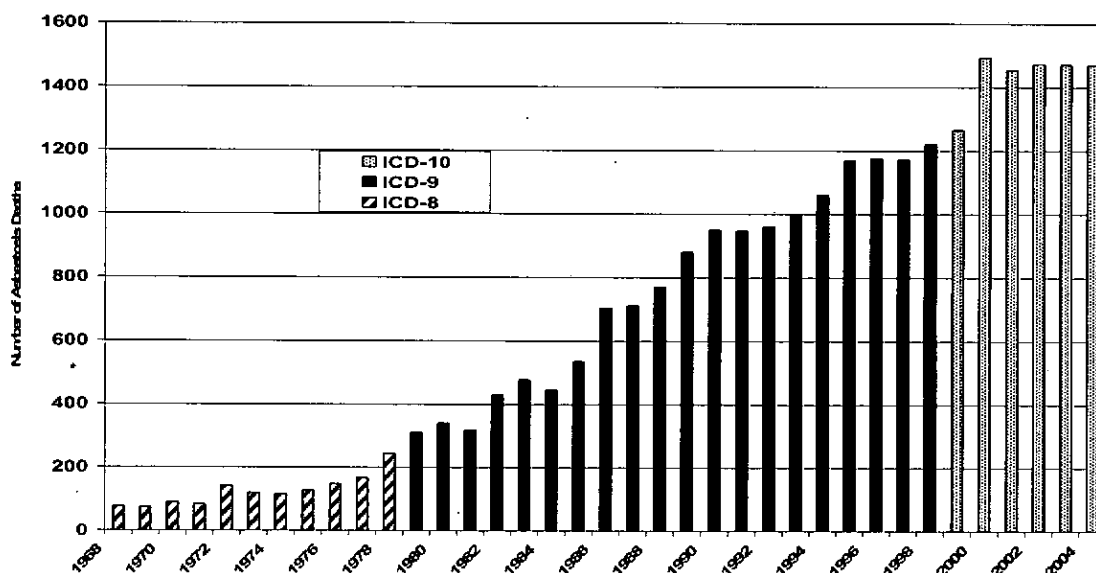
15
16 Epidemiological studies of workers occupationally exposed to asbestos have clearly
17 documented their substantially increased risk of several respiratory diseases, including
18 lung cancer, mesothelioma, diffuse fibrosis of the lung, and non-malignant pleural
19 abnormalities including acute pleuritis and chronic diffuse and localized thickening of the
20 pleura. In addition, it has been determined that laryngeal cancer [IOM 2006] and ovarian
21 cancer [Straif et al. 2009] can be caused by exposure to asbestos, and evidence suggests
22 that asbestos may also cause other diseases (e.g., pharyngeal, stomach, and colorectal
23 cancers [IOM 2006] and immune disorders [ATSDR 2001]).

24
25 National surveillance data, showing trends over time, are available for two diseases with
26 rather specific mineral fiber etiologies—asbestosis and malignant mesothelioma (see
27 following sub-sections). Lung cancer is known to be caused in part by asbestos fiber
28 exposure, but has multiple etiologies. Ongoing national surveillance for lung cancer
29 caused by asbestos exposure has not been done. However, using various assumptions
30 and methods, several researchers have projected the number of U.S. lung cancer deaths
31 caused by asbestos. Examples of the projected number of asbestos-caused lung cancer
32 deaths in the United States include 55,100 [Walker et al. 1983] and 76,700 [Lilienfeld et
33 al. 1988], each of these projections representing the 30-year period from 1980 through
34 2009. However, in the absence of specific diagnostic criteria and a specific disease code
35 for the subset of lung cancers caused by asbestos, ongoing surveillance cannot be done
36 for lung cancer caused by asbestos.

37 38 **2.4.3.1 Asbestosis**

39
40 NIOSH has annually tracked U.S. asbestosis deaths since 1968 and malignant
41 mesothelioma deaths since 1999 using death certificate data in the National Occupational
42 Respiratory Mortality System (NORMS). NORMS data, representing all deaths among
43 U.S. residents, show that asbestosis deaths increased almost 20-fold from the late 1960s
44 to the late 1990s (Figure 6) [NIOSH 2007b]. Asbestosis mortality trends are expected to

1 substantially trail trends in asbestos exposures (see Section 2.4.2) for two primary
2 reasons: (1) the latency period between asbestos exposure and asbestosis onset is
3 typically long, commonly one or two decades or more; and (2) asbestosis is a chronic
4 disease, so affected individuals can live for many years with the disease before
5 succumbing. In fact, asbestosis deaths have apparently plateaued (at nearly 1,500 per
6 year) since 2000 (Figure 3) [NIOSH 2007b]. Ultimately, it is anticipated that the annual
7 number of asbestosis deaths in the United States will decrease substantially as a result of
8 documented reductions in exposure. However, asbestos usage has not been completely
9 eliminated, and asbestos-containing materials remain in place in structural materials and
10 machinery, so the potential for exposure remains. Thus, asbestosis deaths in the United
11 States are anticipated to continue to occur for several decades.
12

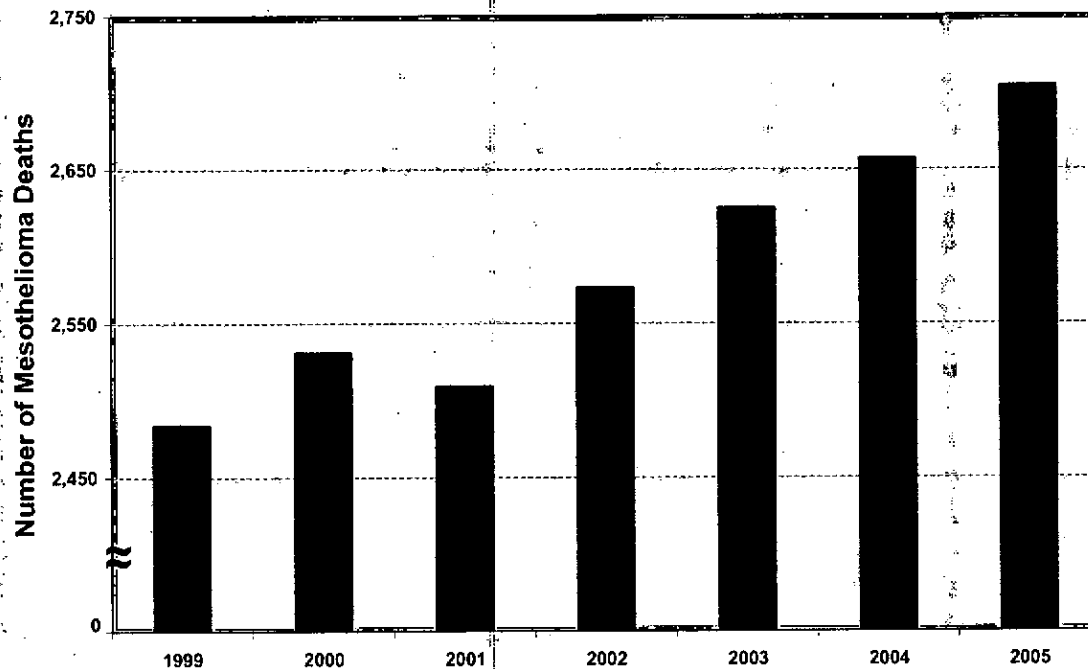


13 **Figure 3.** Number of asbestosis deaths, U.S. residents age 15 and over, 1968–2004. Source of
14 data: NIOSH [2007b].
15
16

17 2.4.3.2 Malignant Mesothelioma

18
19 Malignant mesothelioma, an aggressive disease that is nearly always fatal, is known to be
20 caused by exposure to asbestos and some other mineral fibers [IOM 2006]. The
21 occurrence of mesothelioma has been strongly linked with occupational exposures to
22 asbestos [Bang et al. 2006]. There had been no discrete International Classification of
23 Disease (ICD) code for mesothelioma until its most recent 10th revision. Thus, only
24 seven years of NORMS data are available with a specific ICD code for mesothelioma
25 (Figure 4); during this period, there was a 9% increase in annual mesothelioma deaths,
26 from 2,484 in 1999 to 2,704 in 2005 [NIOSH 2007b]. A later peak for mesothelioma
27 deaths than for asbestosis deaths would be entirely expected, given the longer latency for
28 mesothelioma [Järholm et al. 1999]. One analysis of malignant mesothelioma incidence
29 based on the National Cancer Institute's Surveillance, Epidemiology, and End Results

1 (SEER) Program data found that an earlier steep increase in incidence had moderated and
2 that mesothelioma incidence may have actually peaked sometime in the 1990s in SEER-
3 covered areas [Weill et al. 2004]. In contrast to NORMS data, which represents a census
4 of all deaths in the entire United States, the analyzed SEER data were from areas in
5 which a total of only about 15% of the U.S. population resides.



6
7 **Figure 4.** Number of malignant mesothelioma deaths, U.S. residents age 15 and over, 1999–
8 2005. Source of data: NIOSH [2007b].
9

10 **2.5 Clinical Issues**

11
12 A thorough review of how asbestos-related diseases are diagnosed is beyond the scope of
13 this document, and authoritative guidance on the diagnosis and attribution of asbestos-
14 caused diseases has been published elsewhere [Anonymous 1997; British Thoracic
15 Society Standards of Care Committee 2001; Henderson et al. 2004; ATS 2004].
16

17 The diagnosis of asbestos-caused malignancies (e.g., lung cancer and malignant
18 mesothelioma) is almost always based on characteristic histology (or abnormal cytology
19 in some cases). Despite research on other possible etiologies, genetic susceptibilities, and
20 hypothesized co-factors such as simian virus 40, it is generally accepted that most cases
21 of malignant mesothelioma are caused by exposure to asbestos or other mineral (e.g.,
22 erionite) fibers [Robinson and Lake 2005; Carbone and Bedrossian 2006]. Of particular
23 concern to patients diagnosed with malignant mesothelioma, as well as to individuals

1 who remain at-risk due to past exposures, the disease currently is essentially incurable
2 [British Thoracic Society Standards of Care Committee 2001]. Diagnosis may be
3 relatively straightforward, but can be difficult due to a challenging differential diagnosis
4 [Lee et al. 2002]. Advances have been made to improve diagnostic testing for malignant
5 mesothelioma using immunochemical markers and other more sophisticated
6 histopathological analyses, and additional research is aimed at improving treatment of the
7 disease [Robinson and Lake 2005]. Notable recent research efforts have been directed
8 towards the development of biomarkers for mesothelioma that can be assessed by
9 noninvasive means. A long-term goal of the biomarker research is to enable screening of
10 high-risk individuals with sufficiently sensitive and specific non-invasive biomarkers to
11 identify disease at an early stage when therapeutic intervention might have a greater
12 potential to slow the progression of the disease or be curative. Other goals are to use
13 non-invasive biomarkers for monitoring the disease in patients treated for mesothelioma
14 and for diagnosing the disease. Non-invasive biomarkers, including osteopontin and
15 soluble mesothelin-related peptide, have been and continue to be evaluated, but none are
16 considered ready for routine clinical application [Cullen 2005; Scherpereel and Lee
17 2007].

18
19 Non-malignant asbestos-related diseases are diagnosed by considering three major
20 necessary criteria: (1) evidence of structural change consistent with asbestos-caused
21 effect (e.g., abnormality on chest image; and/or tissue histology); (2) evidence of
22 exposure to asbestos (e.g., history of occupational or environmental exposure with
23 appropriate latency; and/or asbestos bodies identified in lung tissue, sputum, or
24 bronchoalveolar lavage; and/or other concurrent marker of asbestos exposure such as
25 pleural plaques); and (3) exclusion of alternative diagnoses [ATS 2004]. The specificity
26 of an asbestosis diagnosis increases as the number of consistent clinical abnormalities
27 increases [ATS 2004]. In practice, only a small proportion of cases are diagnosed on the
28 basis of tissue histopathology, as lung biopsy is an invasive procedure with inherent risks
29 for the patient. Thus, following reasonable efforts to exclude other possible diagnoses,
30 the diagnosis of asbestosis usually rests on chest imaging abnormalities that are
31 consistent with asbestosis in an individual judged to have sufficient exposure and latency
32 since first exposure.

33
34 Chest radiography remains the most commonly used imaging method for screening
35 exposed individuals for asbestosis and for evaluating symptomatic patients.
36 Nevertheless, as with any screening tool, the predictive value of a positive chest
37 radiograph alone depends upon the underlying prevalence of asbestosis in the screened
38 population [Ross 2003]. A widely accepted system for classifying radiographic
39 abnormalities of the pneumoconioses was initially intended primarily for epidemiological
40 use, but has long been widely used for other purposes (e.g., to determine eligibility for
41 compensation and for medicolegal purposes) [ILO 2002]. A NIOSH-administered "B
42 Reader" Program trains and tests physicians for proficiency in the application of this
43 system [NIOSH 2007c]. Some problems with the use of chest radiography for
44 pneumoconioses have long been recognized [Wagner et al. 1993] and recent abuses have

1 garnered substantial attention [Miller 2007]. In response, NIOSH recently published
2 guidance for B Readers [NIOSH 2007d] and for the use of B Readers and ILO
3 classifications in various settings [NIOSH 2007e].
4

5 In developed countries, conventional film radiography is rapidly giving way to digital
6 radiography, and work is currently underway to develop digital standards and validate
7 their use in classifying digital chest radiographs under the ILO system [Franzblau et al.
8 2009; NIOSH 2008a]. Progress on developing technical standards for digital radiography
9 done for pneumoconiosis and ILO classification is underway [NIOSH 2008a]. In a
10 validation study involving 107 subjects with a range of chest parenchymal and pleural
11 abnormalities typical of dust-induced diseases, Franzblau et al. [2009] compared ILO
12 classifications based on digital radiographic images and corresponding conventional
13 chest x-ray films. The investigators found no difference in classification of small
14 parenchymal opacities. Minor differences were observed in the classification of large
15 parenchymal opacities, though more substantial differences were observed in the
16 classification of pleural abnormalities typical of asbestos exposure [Franzblau et al.
17 2009].
18

19 Computerized tomography, and especially high-resolution computed tomography
20 (HRCT), has proven more sensitive and more specific than chest radiography for the
21 diagnosis of asbestosis and is frequently used to help rule out other conditions [DeVuyst
22 and Gevenois 2002]. Standardized systems for classifying pneumoconiotic abnormalities
23 have been proposed for computed tomography, but have not yet been widely adopted
24 [Kraus et al. 1996; Huuskonen et al. 2001].
25

26 In addition to documenting structural tissue changes consistent with asbestos-caused
27 disease, usually assessed radiographically as discussed above, the diagnosis of asbestosis
28 relies on documentation of exposure [ATS 2004]. In clinical practice, exposure is most
29 often ascertained by the diagnosing physician from an occupational and environmental
30 history, assessed with respect to intensity and duration. Such a history enables a
31 judgment about whether the observed clinical abnormalities can be reasonably attributed
32 to past asbestos exposure, recognizing that severity of lung fibrosis is related to dose and
33 latency [ATS 2004]. The presence of characteristic pleural plaques, especially if
34 calcified, can also be used as evidence of past asbestos exposure [ATS 2004]. In a small
35 minority of cases, particularly when the exposure history is uncertain or vague or when
36 additional clinical assessment is required to resolve a challenging differential diagnosis,
37 past asbestos exposure is documented through mineralogical analysis of sputum,
38 bronchoalveolar lavage fluid, or lung tissue. Light microscopy can be used to detect and
39 count asbestos bodies (i.e., asbestos fibers that have become coated with iron-containing
40 hemosiderin during residence in the body and more generically referred to as ferruginous
41 bodies) in clinical samples. Electron microscopy (EM) can be used to detect and count
42 uncoated asbestos fibers in clinical samples. Methods for such clinical mineralogical
43 analyses often vary, valid background levels are difficult to establish, and the absence of
44 asbestos bodies cannot be used to rule out past exposure with certainty, particularly from

1 chrysotile exposure because chrysotile fibers are known to be less persistent in the lungs
2 than amphibole asbestos fibers [De Vuyst et al. 1998; ATS 2004].
3

4 **2.6 The NIOSH Recommendation for Occupational Exposure to Asbestos**

5

6 Evidence that asbestos causes lung cancer and mesothelioma in humans is well
7 documented [NIOSH 1976; IARC 1977, 1987a,b; EPA 1986; ATSDR 2001; HHS
8 2005a]. After initially setting an REL at 2 asbestos fibers per cubic meter of air (f/cm^3)
9 in 1972, NIOSH later reduced its REL to $0.1 f/cm^3$, measured as an 8-hour time-weighted
10 average (TWA) [NIOSH 1976]¹. This REL was set at the limit of quantification (LOQ)
11 for the phase contrast microscopy (PCM) analytical method for a 400-L sample, but risk
12 estimates indicated that exposure at $0.1 f/cm^3$ throughout a working lifetime would be
13 associated with a residual risk for lung cancer. A risk-free level of exposure to airborne
14 asbestos fibers has not been established.
15

16 In 1990, NIOSH [1990a] revised its REL, retaining the $0.1 f/cm^3$ limit but explicitly
17 encompassing EMPs from the nonasbestiform analogs of the asbestos minerals:
18

19 *NIOSH has attempted to incorporate the appropriate mineralogic*
20 *nomenclature in its recommended standard for asbestos and recommends the*
21 *following to be adopted for regulating exposures to asbestos:*

22 *The current NIOSH asbestos recommended exposure limit is 100,000*
23 *fibers greater than 5 micrometers in length per cubic meter of air, as determined*
24 *in a sample collected over any 100-minute period at a flow rate of 4L/min using*
25 *NIOSH Method 7400, or equivalent. In those cases when mixed fiber types occur*
26 *in the same environment, then Method 7400 can be supplemented with electron*
27 *microscopy, using electron diffraction and microchemical analyses to improve*
28 *specificity of the fiber determination. NIOSH Method 7402 ... provides a*
29 *qualitative technique for assisting in the asbestos fiber determinations. Using*
30 *these NIOSH microscopic methods, or equivalent, airborne asbestos fibers are*
31 *defined, by reference, as those particles having (1) an aspect ratio of 3 to 1 or*
32 *greater; and (2) the mineralogic characteristics (that is, the crystal structure and*
33 *elemental composition) of the asbestos minerals and their nonasbestiform*
34 *analogs. The asbestos minerals are defined as chrysotile, crocidolite, amosite*
35 *(cummingtonite-grunerite), anthophyllite, tremolite, and actinolite. In addition,*
36 *airborne cleavage fragments from the nonasbestiform habits of the serpentine*
37 *minerals antigorite and lizardite, and the amphibole minerals contained in the*
38 *series cummingtonite-grunerite, tremolite-ferroactinolite, and glaucophane-*

¹ The averaging time for the REL was later changed to 100 minutes in accordance with NIOSH Analytical Method #7400 [NIOSH 1994a]. This change in sampling time was first mentioned in comments and testimony presented by NIOSH to OSHA [NIOSH 1990a,b], and reaffirmed in comments to MSHA in 2002 with the explanation that the 100-minute averaging time would help "to identify and control sporadic exposures to asbestos and contribute to the overall reduction of exposure throughout the workshift" [NIOSH 2002].

1 2.6.1.1 Chrysotile

2
3 Chrysotile fibers consist of aggregates of long, thin, flexible fibrils that resemble scrolls
4 or cylinders, and the dimensions of individual chrysotile fibers depend on the extent to
5 which the material has been manipulated. Chrysotile fibers split along the fiber length
6 and undergo partial dissolution within the lungs after fibrillation [NRC 1984].
7 Longitudinal splitting of fibers after entering the lung represents one way that air sample
8 PCM counts may underestimate the cumulative dose of fibers in the lung.

9
10 Epidemiological studies of chrysotile in Quebec mines [McDonald and McDonald 1997]
11 and South Carolina textile mills [Dement et al. 1994; Hein et al. 2007] have produced
12 very different estimates of the risk of cancer associated with exposure to chrysotile fibers.
13 Several explanations for the difference in lung cancer risks observed in these two
14 different workplaces have been proposed. One suggested explanation is that the textile
15 workers were exposed to mineral oil. However, this explanation does not satisfactorily
16 explain the differences [Stayner et al. 1996]. Considering that the textile mill workers
17 were exposed to fibers considerably longer and thinner than those found in mines [Peto et
18 al. 1982; Dement and Wallingford 1990], a more likely explanation is that the difference
19 in risk may be due, at least in part, to dimensional differences in the particles to which
20 workers were exposed. It has also been proposed that exposures in the textile mills were
21 almost exclusively to chrysotile asbestos while exposures in the mines were to a mixture
22 of chrysotile asbestos and related nonasbestiform minerals [Wylie and Bailey 1992].
23 Stayner et al. [1997] also point out, in comparing a number of epidemiological studies,
24 that the variation in relative risk for lung cancer is often greater within an industry (e.g.,
25 mining or textile) than between varieties of asbestos.

26
27 Some have argued that pure chrysotile may not be carcinogenic and that increased
28 respiratory cancer among chrysotile workers can be explained by the presence of
29 tremolite asbestos as a contaminant of chrysotile [McDonald and McDonald 1997]. This
30 is referred to as the "amphibole hypothesis." However, several studies of workers using
31 chrysotile with very little contamination by tremolite have demonstrated strong
32 relationships between exposure to chrysotile and lung cancer. A study of chrysotile
33 asbestos workers in China [Yano et al. 2001] found an age- and smoking-adjusted
34 relative risk of 8.1 for lung cancer among highly exposed workers compared to workers
35 with low exposure to asbestos. The identified contamination of the chrysotile by
36 tremolite was less than 0.001%. In the South Carolina textile mill study, a strong
37 relationship between lung cancer and chrysotile exposure has been demonstrated
38 [Dement et al. 1994; Hein et al. 2007]. A recent reanalysis by transmission electron
39 microscopy (TEM) identified only 2 amphibole fibers among 18,840 fiber structures
40 (0.01%) in archived airborne dust samples from that textile mill study; the remainder
41 were identified as chrysotile [Stayner et al. 2007]. Additionally, in fiber burden studies
42 of human malignant mesothelioma cases, chrysotile fibers were often present in
43 mesothelioma tissue even in the absence of detectable amphibole fibers [Suzuki and
44 Yuen 2001].

1
2 A possible difference in risk for carcinogenicity between chrysotile and amphibole
3 asbestos exposures has been investigated in animal model studies. In a one-year rat
4 inhalation study, chrysotile samples were extremely fibrogenic and carcinogenic, with
5 pulmonary carcinomas developing in approximately 25% of animals and advanced
6 interstitial fibrosis in lung tissue in 10% of all older animals, while intrapleural injection
7 studies produced mesotheliomas in over 90% of animals [Davis et al. 1986]. It was
8 noted that very little chrysotile remained in the lungs of the animals that survived longest
9 following dust inhalation. From this it was suggested that chrysotile is very potent in
10 rodents but, except where exposure levels are very high and of long duration, may be less
11 hazardous to man because chrysotile fibers are removed from lung tissue more rapidly
12 than are amphibole fibers. Hodgson and Darnton [2000] reviewed the literature and
13 estimated that, at exposure levels seen in occupational cohorts, the exposure-specific risk
14 of mesothelioma from the three principal commercial asbestos types is broadly in the
15 ratio 1:100:500 for chrysotile, amosite, and crocidolite, respectively, and the risk
16 differential for lung cancer between chrysotile fibers and the two varieties of amphibole
17 asbestos fibers is between 1:10 and 1:50.

18 19 *2.6.1.2 Amphibole Asbestos and Other Fibrous Minerals*

20
21 There is little scientific debate that the asbestiform varieties of the five commercially
22 important amphibole asbestos minerals are carcinogenic and should be covered in
23 regulations to protect workers. However, concerns have been raised about whether the
24 current OSHA and MSHA asbestos definitions, which explicitly cover only the
25 asbestiform varieties of the six commercially important asbestos minerals, provide
26 sufficient worker protection from exposure to other fibrous minerals.

27
28 This concern is exemplified by exposures to winchite and richterite fibers at a vermiculite
29 mine near Libby, Montana, where exposures to these fibers have resulted in high rates
30 of lung fibrosis and cancer among exposed workers, similar to the occurrence of
31 asbestos-related diseases among asbestos-exposed workers in other industries [Amandus
32 and Wheeler 1987; Amandus et al. 1987a,b; McDonald et al. 2004; Sullivan 2007; Rohs
33 et al. 2008]. Workers at the mine and residents of Libby were exposed to fibers identified
34 (as defined using the 1997 IMA amphibole nomenclature) as the asbestiform amphiboles
35 winchite and richterite as well as tremolite asbestos [Meeker et al. 2003].

36
37 The recently updated NIOSH cohort study of Libby workers found elevated SMRs for
38 asbestosis (SMR 165.8; 95% CI 103.9-251.1), lung cancer (SMR 1.7; 95% CI 1.4-2.1),
39 cancer of the pleura (SMR 23.3; 95% CI 6.3-59.5) and mesothelioma [Sullivan 2007].
40 An exposure-response relationship with duration of employment and total fiber-years
41 cumulative exposure was demonstrated for both asbestosis and lung cancer. Significant
42 excess mortality from nonmalignant respiratory disease was observed even among
43 workers with cumulative exposure <4.5 fibers/cc-years (i.e., a worker's cumulative
44 lifetime exposure, if exposed to asbestos fibers at the current OSHA standard of 0.1 f/cm³

1 over a 45-year working life). Vermiculite from the Libby mine was used to produce
2 loose-fill attic insulation which remains in millions of homes around the U.S., and
3 homeowners and/or construction renovation workers (e.g., plumbers, cable installers,
4 electricians, telephone repair personnel, and insulators) are potentially exposed when this
5 loose-fill attic insulation is disturbed.

6
7 Because winchite and richterite are not explicitly listed among the six commercial
8 asbestos minerals, it is sometimes assumed that they are not included in the regulatory
9 definition for asbestos. However, some of what is now referred to as asbestiform
10 winchite and richterite using the 1997 IMA nomenclature would have been accurately
11 referred to as tremolite asbestos using the 1978 IMA nomenclature [Meeker et al. 2003].
12 Furthermore, an even greater portion of this richterite and winchite would have been
13 identified as tremolite asbestos using the optical methods of identification used prior to
14 1978. In fact, over the years, amphibole minerals from the Libby mine that are now
15 referred to as winchite and richterite have been identified by mineralogists as soda
16 tremolite [Larsen 1942], soda-rich tremolite [Boettcher 1966], and tremolite asbestos and
17 richterite asbestos [Langer et al. 1991; Nolan et al. 1991]; they were identified as
18 tremolite in reports of the Libby mine epidemiological studies conducted by NIOSH in
19 the 1980s [Amandus and Wheeler 1987; Amandus et al. 1987a,b].

20
21 Similar to the situation in Libby, MT, a study of a cluster of malignant mesothelioma
22 cases in eastern Sicily has implicated an etiological role for a fibrous amphibole in the
23 fluoro-edenite series, initially identified as in the tremolite-actinolite series [Comba et al.
24 2003]. In the face of past and future nomenclature changes in the mineralogical sciences,
25 workers need to be protected against exposures to pathogenic asbestiform minerals. The
26 health and regulatory communities will need to carefully define the minerals covered by
27 their policies and monitor the nomenclature changes to minimize the impact of these
28 changes on worker protections.

29 30 *2.6.1.3 Nonasbestiform Analogs of the Asbestos Varieties*

31
32 The current NIOSH REL for airborne asbestos fibers explicitly encompasses particles
33 from the nonasbestiform analogs of the asbestos minerals that meet the specified
34 dimensional criteria as determined microscopically.

35
36 The rationale for recommending that nonasbestiform analogs of the asbestos minerals be
37 encompassed within the policy definition of airborne asbestos fibers was first articulated
38 in NIOSH comments and testimony to OSHA [NIOSH 1990a,b]. In the 1990 testimony,
39 NIOSH based its recommendation on three elements:

- 40
41 • The first element comprised results of epidemiological studies of worker
42 populations exposed to EMPs from nonasbestiform mineral analogs of the
43 asbestos varieties (e.g., cleavage fragments). The 1990 testimony characterized

1 the existing evidence as equivocal for excess lung cancer risk attributable to
2 exposure to such nonasbestiform EMPs.

- 3
- 4 • The second element comprised results of animal carcinogenicity studies involving
5 experimental intrapleural or intraperitoneal administration of various mineral
6 particles. The 1990 testimony characterized the results of the studies as providing
7 strong evidence that carcinogenic potential depends on a mineral particle's length
8 and width and reasonable evidence that neither chemical composition nor
9 mineralogic origin are critical factors in determining a mineral particle's
10 carcinogenic potential.
 - 11
 - 12 • The third element comprised the lack of routine analytical methods to accurately
13 and consistently distinguish between asbestos fibers and nonasbestiform EMPs in
14 samples of airborne. The 1990 testimony argued that asbestiform and
15 nonasbestiform minerals can occur in the same area and that determining the
16 location and identification of tremolite asbestos, actinolite asbestos, and
17 anthophyllite asbestos within deposits of their nonasbestiform mineral analogs
18 can be difficult, resulting in mixed exposures for some mining operations and
19 downstream users of their mined commodities.
 - 20

21 Given the inconclusive epidemiological evidence for lung cancer risk associated with
22 exposure to cleavage fragments (see first bullet, above), NIOSH took a precautionary
23 approach and relied upon the other two elements to recommend that the 0.1 f/cm³ REL
24 for airborne asbestos fibers also encompass EMPs from the nonasbestiform analogs of the
25 asbestos minerals. In fact, the 1990 NIOSH testimony included an explicit assertion that
26 the potential risk of lung cancer from exposure to EMPs (of the nonasbestiform asbestos
27 analog minerals) warranted limiting such exposures. However, even if such EMPs were
28 not hazardous, the inability of analytical methods to accurately distinguish countable
29 particles as either asbestos fibers or cleavage fragments (of the nonasbestiform analog
30 minerals) presents a problem in the context of potentially mixed exposures (i.e., asbestos
31 fibers together with EMPs from the nonasbestiform analogs). NIOSH's 1990
32 recommendation provided a prudent approach to potentially mixed environments—
33 limiting the concentration of all countable particles that could be asbestos fibers to below
34 the REL would assure that the asbestos fiber component of that exposure would not
35 exceed the REL.

36

37 Some scientists and others have questioned NIOSH's rationale for including EMPs from
38 nonasbestiform amphibole minerals in its definition of "airborne asbestos fibers."
39 Mineralogists argue that these EMPs do not have the morphological characteristics
40 required to meet the mineralogical definition of "fibers"; acicular and prismatic
41 amphibole crystals and cleavage fragments generated from the massive habits of the
42 nonasbestiform analogs of the asbestos minerals are not true mineralogical "fibers."
43 Others have opined that the scientific literature does not demonstrate any clear health

1 risks associated with exposure to the nonasbestiform EMPs covered by the NIOSH
2 "airborne asbestos fiber" definition.

3
4 Whether or not to include EMPs from nonasbestiform analogs of the asbestos minerals in
5 federal regulatory asbestos policies has been the subject of long-standing debate. The
6 exposure-related toxicity and health effects associated with the various morphologies
7 (e.g., acicular, prismatic) of the nonasbestiform analogs of the asbestos minerals
8 continues to be a central point in the debate. In 1986, OSHA revised its asbestos standard
9 and included nonasbestiform anthophyllite, tremolite, and actinolite (ATA) as covered
10 minerals within the scope of the revised standard [OSHA 1986]. OSHA's decision to
11 include nonasbestiform ATA proved controversial. In a 1990 proposal to reverse this
12 revision, OSHA [1990] noted that there were "a number of studies which raise serious
13 questions about the potential health hazard from occupational exposure to nonasbestiform
14 tremolite, anthophyllite and actinolite," but that the "current evidence is not sufficiently
15 adequate for OSHA to conclude that these mineral types pose a health risk similar in
16 magnitude or type to asbestos."

17
18 In the preamble to the final rule removing nonasbestiform ATA from its asbestos
19 standard, OSHA [1992] stated that:

20 *various uncertainties in the data² and a body of data showing no carcinogenic*
21 *effect, do not allow the Agency to perform qualitative or quantitative risk*
22 *assessments concerning occupational exposures. Further, the subpopulations of*
23 *nonasbestiform ATA which, based on mechanistic and toxicological data, may be*
24 *associated with a carcinogenic effect, do not appear to present an occupational*
25 *risk. Their presence in the workplace is not apparent from the record evidence.*

26
27 In its 2005 proposed rule for asbestos, MSHA stated that substantive changes to its
28 asbestos definition were beyond the scope of the proposed rule and chose to retain its
29 definition of asbestos, which "does not include nonfibrous or nonasbestiform minerals"
30 [MSHA 2005]. These decisions are reflected in MSHA's final rule published in 2008
31 [MSHA 2008]. In formal comments during the rulemaking process, NIOSH agreed with
32 MSHA's decision not to modify its asbestos definition in the current rulemaking, stating
33 that "NIOSH is presently re-evaluating its definition of asbestos and nonasbestiform
34 minerals, and will work with other agencies to assure consistency to the extent possible"
35 [NIOSH 2005].

36 37 2.6.1.3.1 Epidemiological Studies

38
39 Epidemiological studies of populations with exposures to EMPs reported to be
40 nonasbestiform have been conducted in the talc mining region of upstate New York, the

² OSHA was referring to the scientific data on which NIOSH based its own carcinogenic health effect recommendation to OSHA.

1 Homestake gold mine in South Dakota; and the taconite mining region of northeastern
2 Minnesota. The findings from these investigations are reviewed below.

3
4 *Studies of New York Talc Miners and Millers*

5 Workers exposed to talc have long been recognized to have an increased risk of
6 developing pulmonary fibrosis, often referred to as talc pneumoconiosis [Siegel et al.
7 1943; Kleinfeld et al. 1955]. Talc-exposed workers have also been reported to have an
8 increased prevalence of pleural plaques [Siegel et al. 1943].

9
10 Several more recent epidemiological studies and reviews have been conducted of workers
11 employed in talc mines and mills in upstate New York [Brown et al. 1979, 1990; Gamble
12 1993; Kleinfeld et al. 1967, 1974; Lamm and Starr 1988; Lamm et al. 1988; Stille and
13 Tabershaw 1982; Honda et al. 2002; Gamble and Gibbs 2008].

14
15 Excessive rates of mesothelioma have been reported for Jefferson County, which (along
16 with adjacent St Lawrence County) is a major site of the New York talc industry [Vianna
17 et al. 1981; Enterline and Henderson 1987; Hull et al. 2002]. In a study of all
18 histologically confirmed mesothelioma cases reported to New York State's tumor registry
19 from 1973–1978, Vianna et al. [1981] reported 6 cases from Jefferson County, resulting
20 in a mesothelioma rate for that county more than twice that of New York State (excluding
21 New York City). In a national study of mesothelioma mortality from 1966 through 1981,
22 Enterline and Henderson [1987] reported 4 mesothelioma cases in Jefferson County
23 females (0.6 expected) and 7 cases in Jefferson County males (1.4 expected), giving that
24 county mesothelioma rates that were the 2nd and 6th highest county-specific rates in the
25 nation for females and males, respectively (both $p < 0.01$). More recently, Hull et al.
26 [2002] updated the Enterline and Henderson mesothelioma mortality analysis for
27 Jefferson County, reporting 5 new male cases (2 expected) and 3 new female cases (0.5
28 expected) through 1997 and describing Jefferson County mesothelioma death rates as “5–
29 10 times the background rate.” A potential limitation of the Enterline and Henderson
30 [1987] and Hull et al. [2002] mesothelioma death rates is that they relied on ICD code
31 163 (“malignant neoplasms of the pleura, mediastinum, and unspecified sites”) as a
32 surrogate identification for malignant mesothelioma. That code lacked specificity and
33 sensitivity for mesothelioma; in a study of Massachusetts deaths, many non-
34 mesothelioma malignancies involving the pleura were assigned code 163 and most
35 mesotheliomas were not assigned code 163 [Davis et al. 1992]. The more recent ICD-10
36 system, which has been used since 1999 to code death certificate data in the United
37 States, includes a discrete code for malignant mesothelioma. Based on that new ICD-10
38 code, the age-adjusted death rates (per million population) for 1999–2004 were 12.9
39 (based on 5 mesothelioma deaths) for Jefferson County and 10.9 (based on 5
40 mesothelioma deaths) for St. Lawrence County. These are similar to the overall U.S.
41 mesothelioma death rates for this same period (based on a total of 15,379 mesothelioma
42 deaths) of 11.4 per million [NIOSH 2007b].

1 An excess of lung cancer has also been reported in several epidemiological studies of
2 New York talc mines and mills [Kleinfeld et al. 1967, 1974; Brown et al. 1990; Lamm
3 and Starr 1988; Stille and Tabershaw 1982; Lamm et al. 1988; Honda et al. 2002]. The
4 most extensive research has been conducted on workers at the talc mine and mills owned
5 by RT Vanderbilt Company, Inc. (RTV), located in St. Lawrence County. A significant
6 excess of mortality from nonmalignant respiratory disease (NMRD) has been consistently
7 reported in these studies. These studies have also generally demonstrated an
8 approximately two- to three-fold increase in lung cancer mortality among these workers
9 [Brown et al. 1990; Honda et al. 2002; Lamm et al. 1988]. The lung cancer excess has
10 been reported to be particularly high among workers with more than 20 years since their
11 first exposure (latency), which is a pattern consistent with an occupational etiology
12 [Brown et al. 1979, 1990]. Authors of several studies have questioned whether the
13 excess of lung cancer observed in these studies is due to employment at the RTV mines
14 and mills or to other factors [Honda et al. 2002; Lamm et al. 1988; Stille and Tabershaw
15 1982]. Attributing these findings to employment in the RTV mine is difficult because
16 there were numerous mines operating in these counties and the mineralogic composition
17 of the ores varied substantially [Peterson et al. 1993]. A high smoking rate among the
18 workers at the RTV mine and mills has been suggested as one possible explanation for
19 the excess lung cancer mortality [Kelse 2005; Gamble 1993]. However, it is generally
20 considered implausible that confounding by smoking in occupational cohort studies could
21 explain such a large (i.e., ~2–3 fold) increase in lung cancer mortality [Steenland et al.
22 1984; Axelson and Steenland 1988; Axelson 1989].

23
24 The most persuasive argument against a causal interpretation of these findings is that the
25 lung cancer excess in this study population did not increase with duration and measures
26 of exposure to talc dust [Lamm et al. 1988; Stille and Tabershaw 1982; Honda et al.
27 2002]. Also, the excess of lung cancer in this cohort has been reported to be limited to
28 workers with short employment (<1 year) [Lamm et al. 1988] and to workers who have
29 been employed in other industries prior to working in the RTV mine and mills [Lamm et
30 al. 1988; Stille and Tabershaw 1982]. The latter observation could be explained by there
31 simply being too few workers and inadequate follow-up of workers who have only
32 worked at RTV to provide the statistical power necessary to demonstrate an increased
33 lung cancer risk. For example, in one of the studies only 10% of the decedents were
34 reported to have not worked in other industries prior to their employment at RTV [Stille
35 and Tabershaw 1982].

36
37 In the most recent study of RTV miners and millers, Honda et al. [2002] examined lung
38 cancer mortality in relation to quantitative estimates of exposure to respirable talc dust
39 [Oestenstad et al. 2002]. As in previous studies, mortality from lung cancer was found to
40 be significantly elevated [standardized mortality ratio (SMR)=2.3, 95% confidence
41 interval (95%CI)=1.6–3.3]. However, the excess of lung cancer mortality was found to
42 be most pronounced in short-term workers (<5 years) and inversely related to cumulative
43 exposure to respirable dust ($\text{mg}/\text{m}^3\text{-d}$). In contrast, exposure-response relationships were

1 observed in this study between cumulative exposure to respirable dust and NMRD and
2 pulmonary fibrosis.

3
4 A plausible explanation that has been offered for the lack of exposure-response in these
5 studies is that the observed excess of lung cancer was a result of exposures from
6 employment prior to starting work at RTV. It has been suggested that many of these
7 workers may have had prior employment in neighboring talc mines in upstate New York
8 with similar exposures to talc [NIOSH, 1980]. Not considering exposures at these other
9 mines could have substantially impacted results of exposure-response analyses.
10 Exposures to talc dust may also have been substantially higher in the neighboring mines
11 than in the RTV mine [Kelse 2005]. Because RTV workers may have had exposures to
12 talc dust in other mines, their exposures may have been underestimated, which could
13 explain the observed lack of an exposure-response relationship in the epidemiological
14 studies of RTV workers. There is also evidence to suggest that RTV workers may have
15 been exposed to lung carcinogens from prior work in non-talc industries [Lamm et al.
16 1988].

17
18 Gamble [1993] conducted a nested lung cancer case-control study of the RTV cohort to
19 further explore whether factors unrelated to exposures at RTV, such as smoking and
20 exposures from prior employment, might be responsible for the observed excess of lung
21 cancer among RTV workers. Cases and controls were identified from 710 workers who
22 were employed between 1947 and 1958 and vital status was ascertained through 1983.
23 All individuals with lung cancer as the underlying cause of death were included as cases
24 (n=22). Three controls (n=66) for each case were selected from members of the cohort
25 who had not died of NMRD or accidents, and were matched to cases based on dates of
26 birth and hire. Controls were also required to have survived for as long as their matched
27 case. Information on smoking and work histories was obtained by interviewing the case
28 (if alive) or relatives. An attempt was made to verify information on previous
29 employment by checking personnel records and by contacting previous employers. A
30 panel of epidemiologists and industrial hygienists classified previous non-talc
31 employment with regard to the probability of occupational exposure to a lung cancer risk.

32
33 As in previous investigations of the RTV cohort, Gamble [1993] found that the risk of
34 lung cancer decreased with increasing duration of employment at RTV. This was true
35 among both smokers and non-smokers, and also when individuals with inadequate time
36 since first exposure (<20 years) and short duration of employment were excluded. Lung
37 cancer risk was also found to decrease with increasing probability of exposure to lung
38 carcinogens from non-talc employment. A positive exposure-response relationship was
39 evident when non-RTV talc exposures were included in the analysis, although this
40 relationship was not statistically significant.

41
42 This study by Gamble [1993] does not provide support for the argument that prior
43 employment in non-talc industries was responsible for the excess of lung cancer observed
44 among RTV workers. The author interpreted his findings as providing support for the

1 argument that the excess of lung cancer was due to confounding by smoking based on the
2 fact that smoking was strongly associated with lung cancer risk and on the observation
3 that the exposure-response relationship with talc was more strongly negative (inverse) in
4 analyses restricted to smokers than among all study subjects. However, it is no surprise
5 that an association was observed between smoking and lung cancer, and the fact that the
6 negative (inverse) exposure-response trend was stronger among smokers does not explain
7 why the cohort as a whole experienced much higher lung cancer rates than expected.
8

9 Only two cases of pleural mesothelioma have been reported in the cohort studies of RTV
10 miners and millers [Honda et al. 2002]. It is unclear whether these cases are attributable
11 to exposure to talc at the RTV mine and mills. One of the cases had only worked for a
12 short time in a job with minimal talc exposure, had previously worked for many years in
13 the construction of a talc mine, and had subsequently worked on repairing oil heating
14 systems. The other case developed only 15 years after first exposed to RTV talc.
15 Mesothelioma has more typically been observed to develop at least 20 years from the
16 time of first exposure.
17

18 NIOSH [1980] reported that dust from this mine contains chrysotile, tremolite, and
19 anthophyllite asbestos. However, the identification of these minerals as asbestos or their
20 nonasbestiform analogs has been the subject of debate. In an industrial hygiene
21 assessment conducted at RTV mines by NIOSH [1980], X-ray diffraction and
22 petrographic microscopic analyses of talc product samples found them to contain 4.5–
23 15% anthophyllite (some of which was categorized as asbestos). In contrast, a paper
24 prepared by Kelse [2005] reported the percentage by weight of talc from the RTV mine
25 in upstate New York as 1–5% nonasbestiform anthophyllite. Based on airborne samples
26 collected by NIOSH [1980] at the mine and mill and analyzed by TEM, 65% of the
27 EMPs that were longer than 5 μm were anthophyllite and 7% were tremolite, with much
28 of the tremolite determined to be from a non-fibrous habit. Kelse [2005] reported that up
29 to 1.8% of the minerals were from an asbestiform habit, though the asbestiform
30 component was reported not to be asbestos. Serpentine and amphibole minerals typically
31 develop through the alteration of other minerals. Consequently, they may exist as
32 partially altered minerals having variations in elemental compositions. Minerals
33 undergoing this alteration are often frequently called “transitional minerals.” Thus the
34 elemental composition of individual mineral particles can vary within a mineral deposit
35 containing transitional minerals, which could account for differences in the reported
36 composition of talc from the RTV mine.
37

38 A major limitation of the epidemiological studies of RTV talc workers is the lack of an
39 exposure-response analysis based on direct measurements of airborne EMP
40 concentrations. Most of the studies used tenure as a surrogate for exposure, and the
41 exposure metric used in the Honda et al. [2002] study was respirable dust, which may not
42 be correlated with exposure to EMPs. Relationships between health outcomes and
43 exposure to an agent of interest can be attenuated when a nonspecific exposure indicator
44 is used as a surrogate for exposure to the agent of interest [Blair et al. 2007; Friesen et al.

1 2007]. Thus, when the exposure index used to assess the effect of EMPs is based on a
2 surrogate measure, such as respirable dust, rather than on specific measurement of EMP
3 concentrations, the lack of an exposure-response relationship between the exposure index
4 and the health outcome must be considered suspect, particularly where the composition
5 of a mixed exposure varies by work area.

6
7 Finally, a cohort study of Vermont talc miners and millers has some relevance for
8 interpreting the findings from the studies of New York talc workers [Selevan et al. 1979].
9 The available evidence indicates that Vermont talc is free of asbestos fibers. A
10 statistically significant excess of NMRD mortality was observed among the millers
11 (SMR=4.1, 95%CI=1.6–8.4), but not among the miners (SMR=1.6, 95%CI=0.20–9.6), in
12 this study. In contrast, respiratory cancer mortality was found to be significantly elevated
13 among the miners (SMR=4.3, 95%CI=1.4–10), but not among the millers (SMR=1.0,
14 95%CI=0.12–4.0). The authors suggested that their respiratory cancer findings might be
15 due to non-talc exposures, such as radon progeny, because exposures to talc dust were
16 higher among millers than miners. The pattern of excess of respiratory cancer observed
17 in this study is similar to that reported in studies of RTV miners and millers. It has been
18 argued [Lamm and Starr 1988] that this provides evidence against the hypothesis that the
19 lung cancer excess among RTV miners is related to exposure to asbestos or
20 rionasbestiform EMPs, since these were not known to be present in Vermont talc.

21
22 In summary, an excess of pulmonary fibrosis and pleural plaques is recognized to have
23 occurred among workers exposed to talc. Mesothelioma rates have been reported to be
24 significantly elevated in Jefferson County, which is the site of some of the talc industry in
25 New York and is located adjacent to St. Lawrence County, where the New York talc
26 industry is most concentrated. However, death data reported for 1999–2004 do not
27 suggest a particularly high rate of mesothelioma in that county. Also, aspects of the few
28 cases of mesothelioma that have been carefully evaluated in the studies of New York talc
29 miners make it unclear whether the cases are attributable to employment in the talc
30 industry. Lung cancer mortality has been consistently reported to be elevated in studies
31 of New York talc miners. However, whether this excess is attributable to exposures to
32 talc is questionable because the lung cancer excess was generally found to be most
33 pronounced in short-term workers and did not increase with cumulative exposure to talc
34 dust. Chance or confounding from smoking is highly unlikely to fully explain the large
35 lung cancer excess observed in these studies. These findings may be at least partly
36 explained by employment in other industries, including other mines in upstate New York.

37 38 *Studies of Homestake Gold Miners*

39 Three groups of investigators have conducted retrospective cohort studies of miners at the
40 Homestake gold mine in South Dakota with somewhat different and overlapping cohort
41 definitions. Gillam et al. [1976] studied 440 white males who were employed as of 1960
42 and who had worked underground for, at least 5 years in the mine. McDonald et al.
43 [1978] conducted a retrospective cohort study of 1,321 men who had retired and worked
44 for at least 21 years in the mine as of 1973 and were followed for vital status until 1974.

1 Brown et al. [1986] conducted a retrospective cohort study of 3,328 miners who had
2 worked for at least 1 year between 1940 and 1965 with follow-up of vital status to 1977.
3 Follow-up of this same cohort was subsequently updated to 1990 by Steenland and
4 Brown [1995]. Exposures of potential concern at this mine include crystalline silica,
5 radon progeny, arsenic, and nonasbestiform EMPs. The longer ($>5\ \mu\text{m}$) nonasbestiform
6 EMPs have been reported to be primarily cummingtonite-grunerite (69%), but tremolite-
7 actinolite (15%) and other nonasbestiform amphibole varieties (16%) were also detected
8 [Zumwalde et al. 1981]. Most of the EMPs observed by TEM (70–80%) were shorter
9 than $5\ \mu\text{m}$; for the entire population of EMPs, the geometric mean length was $3.2\ \mu\text{m}$ and
10 the geometric mean diameter was $0.4\ \mu\text{m}$.

11
12 There is very little evidence of an excess of mesothelioma in the studies of Homestake
13 gold miners. One case of mesothelioma with “low” dust exposure was reported in the
14 study by McDonald et al. [1978]. Slight excesses of cancers of the peritoneum (4 cases;
15 $\text{SMR}=2.8$, $95\%\text{CI}=0.76\text{--}7.2$) and other respiratory cancer (3 cases: $\text{SMR}=2.5$,
16 $95\%\text{CI}=0.52\text{--}7.4$) were reported in the most recent study [Steenland and Brown 1995].
17 These categories might be expected to include cases of mesothelioma; however,
18 mesothelioma was not mentioned on the death certificates for these cases.

19
20 Significant excesses in mortality from tuberculosis and pneumoconiosis (mainly silicosis)
21 were observed in all of the studies. An excess of respiratory cancer (10 cases observed,
22 $\text{SMR}=3.7$, $95\%\text{CI}=1.8\text{--}6.7$) was reported in the earliest study by Gillam et al. [1976].
23 Respiratory cancer mortality was not found to be elevated (34 cases, $\text{SMR}=1.0$,
24 $95\%\text{CI}=0.71\text{--}1.4$) and there was only weak evidence that it increased with level of
25 exposure in the study by McDonald et al. [1978]. A slight excess of lung cancer (115
26 cases, $\text{SMR}=1.1$, $95\%\text{CI}=0.94\text{--}1.4$) was reported in the most recent study based on
27 comparison with U.S. mortality rates [Steenland and Brown 1995]. This lung cancer
28 excess was more pronounced when county rates ($\text{SMR}=1.3$, $95\%\text{CI}=1.0\text{--}1.5$) and even
29 more so when South Dakota state rates ($\text{SMR}=1.6$, $95\%\text{CI}=1.3\text{--}1.9$) were used as the
30 referent. The excess was also increased (based on U.S. rates: $\text{SMR}=1.3$, $95\%\text{CI}=1.0\text{--}1.6$)
31 when the analysis was restricted to individuals with at least 30 years of time since first
32 exposure (latency). Lung cancer mortality was not found to increase with estimated
33 cumulative exposure to dust in this study, though a clear exposure-response trend was
34 observed for pneumoconiosis. The limited available data on smoking habits indicated
35 that miners in this cohort smoked slightly more than the U.S. general population in a
36 1960 survey.

37
38 Taken together, the studies of Homestake gold miners provide, at best, weak evidence of
39 an excess risk of lung cancer. Although small excesses of lung cancer have been reported
40 in the most recent studies of the Homestake gold miners, the increased mortality has not
41 been found to increase with measures of cumulative dust exposure. The uncertainty of
42 the relationship between contemporary dust and EMP exposures hinders the usefulness of
43 historical dust measurement data in estimating EMP exposures [Zumwalde et al. 1981].
44 Thus the lack of exposure-response reported in these studies for cancer is largely

1 uninformative with respect to the hypothesis that nonasbestiform EMPs are associated
2 with increased risk of respiratory diseases in this population.
3

4 *Studies of Taconite Miners*

5 There has been a long history of concern about a potential association between exposures
6 associated with the taconite iron ore industry in northeastern Minnesota and the risk of
7 respiratory cancers and diseases. This concern started in 1973, when amphibole fibers
8 were found in the Duluth water supply and were traced to tailings that had been disposed
9 of in Lake Superior by the Reserve Mining Company. Extensive sampling and analysis
10 of areas of the Peter Mitchell taconite iron ore mines was recently reported by Ross et al.
11 [2007], who reported finding “no asbestos fibers of any type” in the mines. However,
12 they did find and describe fibrous ferroactinolite, fibrous ferrian sepiolite, fibrous
13 grunerite-ferroactinolite, and fibrous actinolite in ore samples, some of which was very
14 thin ($<0.01 \mu\text{m}$) with a very high aspect ratio. They estimated fibrous amphibole material
15 to represent “a tiny fraction of one percent of the total rock mass of this taconite deposit”
16 [Ross et al. 2007].
17

18 Several epidemiological studies have examined mortality of miners working in the
19 taconite mines and mills of Minnesota. Higgins et al. [1983] published the earliest study,
20 which examined the mortality of approximately 5,700 workers employed at the Reserve
21 Mining Company between 1952 and 1976 and followed up to 1976. Overall mortality
22 (SMR=0.87) and mortality from respiratory cancer (15 cases, SMR=0.84) were both less
23 than expected. Respiratory cancer mortality was not found to be increased among
24 workers with at least 15 years since first exposure (latency) and did not increase with
25 estimated cumulative exposure to dust. The maximum follow-up of this cohort was 24
26 years, which is probably too short to be able to detect increased mortality from lung
27 cancer or mesothelioma.
28

29 Cooper et al. [1988, 1992] have reported on the mortality experience of 3,431 miners and
30 millers who were employed in the Erie or Minntac mines and mills for at least 3 months
31 between 1947 and 1958. Follow-up of the cohort, initially to 1983 [Cooper et al. 1988],
32 was extended to 1988 in their more recent update [Cooper et al. 1992]. Comparisons
33 were made with white male mortality rates for Minnesota and for the U.S. population.
34 Mortality from respiratory cancer was found to be slightly less than expected in this study
35 (106 cases, based on Minnesota rates: SMR=0.92, 95%CI=0.75–1.1). Respiratory cancer
36 mortality was close to the expected value (46 cases, based on Minnesota rates:
37 SMR=0.99, 95%CI=0.72–1.3) among workers with more than 20 years since first
38 exposure (latency).
39

40 A statistically significant excess of mesothelioma has been reported in northeastern
41 Minnesota, which is the area in which the taconite mining and milling industry is located
42 [MDH 2007]. In its most recent report, the Minnesota Department of Health (MDH)
43 reported that a total of 159 cases occurred in this region during the period of 1988 to
44 2006. The mesothelioma rate in males was approximately twice the expected rate based

1 on the rest of the state (146 cases, rate ratio (RR)=2.1, 95%CI=1.8–2.5), while the rate in
2 females was less than expected (RR=0.72, 95%CI=0.38–1.2). The fact that the excess of
3 mesothelioma was only observed among males strongly suggests an occupational
4 etiology. In addition to the taconite industry, a plant producing asbestos ceiling tiles
5 (Conwed Corporation) was located in the northeastern Minnesota region. From 1958–
6 1965 amosite was used at Conwed, and from 1966–1974 chrysotile was used [Mandel
7 2008]. The MDH has initiated epidemiological studies of mesothelioma incidence
8 among workers at the Conwed Corporation and at the iron mines in northeastern
9 Minnesota. The records from a cohort of approximately 72,000 iron miners and from
10 5,700 Conwed workers have been linked with a mesothelioma data registry. Between
11 1988 and 2007, a total of 58 mesothelioma cases have been identified among the miners
12 and 25 cases have been identified among the Conwed workers. Because only 3 of the 58
13 mesothelioma cases identified in the miner cohort had also been employed at Conwed, it
14 is unlikely that the mesothelioma excess in miners could be explained by asbestos
15 exposures during employment at the Conwed ceiling tile facility [MDH 2007].
16

17 Brunner et al. [2008] have recently reported findings from an MDH study of
18 mesothelioma cases occurring among iron miners between 1988 and 1996. The job
19 histories of the cases were reviewed for evidence of exposure to commercial asbestos.
20 Mining jobs were identified from company personnel files. Non-mining employment
21 information was obtained from worker application files, worker compensation records,
22 and obituaries. Potential asbestos exposures for jobs held in the mining industry were
23 identified by conducting interviews of 350 workers representing 122 occupations and 7
24 different mining companies. To estimate the probability and intensity of potential
25 exposure to commercial asbestos in each of the jobs, an expert panel rated the potential
26 for asbestos exposure based on these interviews, available job descriptions from the
27 relevant time period, and their knowledge of the mining environment. Fifteen of 17 iron
28 miners known to have developed mesothelioma were judged to have sufficiently good
29 work histories for the study. Eleven of the cases were reported to have had probable
30 exposure, and 3 were reported to have possible exposure to commercial asbestos. The
31 asbestos exposures were from non-mining jobs (4 cases), mining jobs (4 cases), or both
32 (6 cases). The findings from this study suggest that the excess of mesothelioma observed
33 among taconite miners might be explained by exposure to commercial asbestos rather
34 than from the nonasbestiform amphibole EMPs generated during iron ore processing.
35 However, this being a case series, it was not possible to determine whether commercial
36 asbestos exposure was different in the cases than in the cohort as a whole or in a control
37 group. This study also did not include the 41 additional mesothelioma cases that have
38 been reported by the MDH since 1996 [MDH 2007].
39

40 In summary, the results from cohort mortality studies of taconite miners and millers in
41 Minnesota have not provided any evidence of an increased risk of respiratory cancer or
42 mesothelioma. This appears to be somewhat in conflict with reports from the MDH that
43 mesothelioma incidence is significantly elevated among males (but not females) in
44 northeastern Minnesota and that a large number of these cases were workers in the

1 Minnesota taconite industry. There is some evidence that these cases could, at least in
2 part, be related to exposures to commercial asbestos that occurred in or outside of the
3 taconite mining industry, but further research on this question is needed. The MDH is
4 currently working with researchers at the University of Minnesota, School of Public
5 Health on a mesothelioma case-control study, a respiratory morbidity study, and a
6 mortality study of the iron miners of northeastern Minnesota [MDH 2007].

7
8 *Summary of Epidemiological Studies of Cohorts Exposed to Nonasbestiform EMPs*

9 The results from studies of populations reportedly exposed to nonasbestiform EMPs do
10 not provide clear answers regarding the toxicity of these EMPs. There are a number of
11 features of these studies that limit their usefulness for answering these questions. First,
12 the populations in these studies were exposed to a complex mixture of particles.
13 Nonasbestiform EMPs generally represented only a small component of airborne
14 exposures, which included other minerals such as silica that are known to cause lung
15 diseases. Thus, although an excess of pneumoconiosis has been observed in the studies
16 of Homestake gold miners and New York talc workers, the extent to which these findings
17 are attributable to their exposures to nonasbestiform EMPs cannot be determined. A
18 potential limitation of the New York talc studies is that if the EMPs do include
19 asbestiform minerals as reported in the NIOSH [1980] study, it is difficult to determine
20 whether the observed health effects are from asbestiform or other EMPs.

21
22 Another major limitation of these studies is that they lack adequate information on past
23 exposure to EMPs. An excess of respiratory cancer was observed in the occupational
24 studies of New York talc workers and a small excess was observed in the most recent
25 study of Homestake gold miners. In both studies, the excess of respiratory cancer was
26 not found to increase with cumulative exposure to dust. Relationships between health
27 outcomes and exposure to an agent of interest can be attenuated when a nonspecific
28 exposure indicator is used as a surrogate for exposure to that agent [Blair et al. 2007;
29 Friesen et al. 2007]. Thus, when the exposure index used to assess the effect of EMPs is
30 based on a surrogate measure, such as respirable dust, rather than on specific
31 measurement of EMP concentrations, the lack of an exposure-response relationship
32 between the exposure index and the health outcome must be considered suspect,
33 particularly where the composition of a mixed exposure varies by work area.
34 Interpretation of findings from the New York talc studies has been further complicated by
35 the employment of the workers elsewhere, including employment at other talc mines in
36 the area. Lack of positive findings from exposure-response analyses in the New York
37 talc studies of RTV miners and millers could also have resulted from exposure
38 misclassification—possible under-ascertainment of exposure to talc and other mineral
39 particles caused by not considering exposures at neighboring talc mines.

40
41 The reliability of death certificate information is another major limitation, particularly for
42 the diagnosis of mesothelioma. Mesothelioma did not have a discrete ICD code until the
43 10th revision of the ICD, used for U.S. death certificate data only since 1999. This likely
44 explains the discordance between the apparent recent lack of excess mesothelioma deaths

1 in an upstate New York county in which talc mines and mills have been located and the
2 excess “mesothelioma” death rates previously reported in that same county. This may
3 explain the apparent contradiction between the lack of an excess of mesothelioma in the
4 cohort studies of taconite miners, and the excess of mesothelioma that has been reported
5 in the more recent studies based on a mesothelioma registry in northeastern Minnesota.

6
7 Finally, the lack of information on cigarette smoking habits of the studied workers is a
8 major issue in interpreting the findings for respiratory cancer in these studies. Concerns
9 about cigarette smoking in occupational cohort studies is generally based on the
10 assumption that blue collar workers smoke more than the general population. However,
11 the extent of this bias is generally not expected to be able to account for more than a 50%
12 increase in lung cancer risk and is unlikely to explain the 2- to 3-fold risk reported in the
13 New York talc studies. Confounding by smoking could conceivably explain the small
14 excess of lung cancer that has been reported in the most recent study of Homestake gold
15 miners [Steenland and Brown 1995]. However, smoking may have introduced a negative
16 bias in some of these studies. Cigarette smoking has been reported to have been banned
17 in the Homestake gold mines [Brown et al. 1986] and in the underground taconite mines
18 [Lawler et al. 1985]. Preventing workers from smoking at work could have negatively
19 biased the lung cancer findings in these studies.

20
21 Because of the study limitations described above, the findings from these studies should
22 best be viewed as providing inconclusive as opposed to negative evidence regarding the
23 health effects associated with exposures to nonasbestiform EMPs. To be more
24 informative, additional studies of these populations would need improved
25 characterizations of exposure to EMPs, smoking status, and exposures associated with
26 other employment. Additional studies of these populations should be pursued if these
27 improvements are deemed feasible.

28 29 2.6.1.3.2 Animal Studies

30
31 In NIOSH’s rationale for its 1990 recommendation that the REL for airborne asbestos
32 fibers encompass cleavage fragments from the nonasbestiform analogs of the asbestos
33 minerals, discussion of results of animal carcinogenicity studies cited several original
34 studies and reviews [Stanton et al. 1977, 1981; Wagner et al. 1982; Muhle et al. 1987;
35 Pott et al. 1974, 1987; Lippmann 1988]. NIOSH [1990a] concluded that the cited papers
36 provided evidence indicating that fiber dimension (and not fiber composition) was the
37 major determinant of carcinogenicity for mineral fibers, stating that:

38 *Literature reviews by Lippmann [1988] and Pott et al. [1987] enhance the*
39 *hypothesis that any mineral particle can induce cancer and mesothelioma if it is*
40 *sufficiently durable to be retained in the lung and if it has the appropriate aspect*
41 *ratio and dimensions. Similarly, Wagner [1986] concluded that all mineral*
42 *particles of a specific diameter and length size range may be associated with*
43 *development of diffuse pleural and peritoneal mesotheliomas.*

1 That general conclusion notwithstanding, a study by Smith et al. [1979] that was not cited
2 by NIOSH in 1990 addressed the specific question of carcinogenicity of EMPs from
3 nonasbestiform amphiboles. Pleural tumor induction by intrapleural (IP) injection
4 challenge in hamsters was compared for various challenge materials including two
5 asbestiform tremolites and two nonasbestiform (prismatic) tremolitic talcs. In contrast to
6 the two asbestiform tremolites, which induced tumors in 22% and 42% of challenged
7 hamsters at the higher dose, no tumors resulted following challenge with either of the two
8 nonasbestiform tremolites [Smith et al. 1979]. In its rule-making, OSHA noted several
9 limitations of the study, including the small number of animals in the study, the early
10 death of many animals, and the lack of systematic characterization of fiber size and
11 aspect ratio [OSHA 1992]. One of the nonasbestiform tremolitic talcs was later analyzed
12 and confirmed to have tremolitic chemical composition and 13% "fibers" as defined by a
13 3:1 aspect ratio [Wylie et al. 1993].
14

15 Since 1990, another carcinogenicity study of nonasbestiform amphibole minerals has
16 been published. An IP injection study in rats used six samples of tremolite, including
17 three asbestiform samples that induced mesothelioma in 100%, 97%, and 97% of
18 challenged animals [Davis et al. 1991]. Two nonasbestiform tremolite samples resulted
19 in mesotheliomas in 12% and 5% of the animals, at least the former incidence being
20 above expected background levels. Another sample that was predominantly
21 nonasbestiform but contained a small amount of asbestiform tremolite resulted in
22 mesothelioma in 67% of animals. Of note, the nonasbestiform material associated with
23 the 12% mesothelioma incidence and this latter material contained an approximately
24 equal number of EMPs longer than 8 μm and thinner than 0.5 μm .
25

26 Studies of *in vitro* assays of various biological responses, some published before and
27 some after 1990, have also found relative toxicities of asbestiform and nonasbestiform
28 minerals that generally parallel the differences observed in the *in vivo* IP injection studies
29 of tumorigenicity [Wagner et al. 1982; Woodworth et al. 1983; Hansen and Mossman
30 1987; Marsh and Mossman 1988; Sesko and Mossman 1989; Janssen et al. 1994;
31 Mossman and Sesko 1990] A recent review of the literature concluded that low aspect
32 ratio cleavage fragments of amphiboles are less potent than asbestos fibers [Mossman
33 2008].
34

35 In summary, there is more literature now than in 1990 pertaining to differential animal
36 carcinogenicity and toxicity of EMPs from nonasbestiform amphiboles (e.g., acicular
37 crystals, prismatic crystals, cleavage fragments). More detailed discussion of these
38 studies, including discussion of important limitations of the studies, can be found in
39 Section 2.7.4 of this document.
40

41 2.6.1.3.3 Analytical Limitations 42

43 The third element that served as a basis for NIOSH's recommendation in 1990 was the
44 inability to accurately and consistently distinguish asbestos fibers and nonasbestiform

1 EMPs in samples of airborne particulate. The 1990 NIOSH testimony argued that
2 asbestiform and nonasbestiform minerals can occur in the same geological area and that
3 mixed airborne exposures to asbestos fibers and EMPs from the nonasbestiform analog
4 minerals can occur at mining operations. The potential for mixed exposures can also
5 occur downstream if the mined commodity contains both asbestiform and nonasbestiform
6 minerals.

7
8 The 1990 NIOSH testimony further pointed out the lack of routine analytical methods for
9 air samples that can accurately and consistently determine whether an individual EMP
10 that meets the dimensional criteria of a countable particle is an asbestos fiber or a
11 nonasbestiform EMP (e.g., acicular crystals, prismatic crystals, cleavage fragments).

12
13 Two analytical components of the NIOSH REL for airborne asbestos fibers are applied to
14 air samples, the microscopic methods and the counting rules. The microscopic methods
15 include:

- 16
17 • *Phase contrast microscopy (PCM)* — Analytical Method 7400 “A rules” —
18 Asbestos and Other Fibers by PCM [NIOSH 1994a] is used to count all particles
19 that are longer than 5 μm and have a length-to-width ratio equal to or greater than
20 3:1.
- 21
22 • *Transmission electron microscopy (TEM)* — Analytical Method 7402 —
23 Asbestos by TEM [NIOSH 1994b] is used as a supplement to the PCM method
24 when there is uncertainty about the identification of elongate particles (EPs) that
25 are counted. When TEM analysis is used for particle identification, only those
26 EPs that are identified as “asbestos” and meet the dimensional criteria used by
27 PCM ($>0.25 \mu\text{m}$ width and $>5\mu\text{m}$ length) are counted as asbestos fibers. PCM
28 counts can be adjusted to yield corrected asbestos fiber counts by multiplying
29 them by the proportion of fibers determined by TEM to be asbestos.

30
31 There are several limitations of the use of PCM and TEM for asbestos analysis. PCM is
32 stated to be limited to observing EPs with widths $>0.25 \mu\text{m}$ and is not equipped for
33 particle identification. TEM, while capable of resolving EPs with widths as small as
34 $0.001 \mu\text{m}$, frequently cannot differentiate nonasbestiform from asbestiform EMPs when
35 the elemental composition is the same or when present in a heterogeneous mix of
36 unknown particles. Important limitations of TEM are that partial lengths of long fibers
37 that intersect grid bars can be hidden due to the small field of view; likewise, because
38 only a small portion of the filter sample is being analyzed some uncertainty may exist in
39 determining airborne fiber concentrations. Another limitation of both methods is that
40 high concentrations of background dust collected on samples may interfere with fiber
41 counting by PCM and particle identification by TEM.

42

1 Thus, the current PCM and TEM methods used for routine exposure assessment lack the
2 capability to accurately count, size, and identify all EMPs collected on airborne samples.
3 Further discussion of the analytical limitations and possible improvements are discussed
4 in Section 2.8.

6 ***2.6.2 Some Minerals of Potential Concern Not Covered by the NIOSH REL***

8 By analogy to asbestos, there is reason to be concerned about potential for health risks
9 associated with inhalational exposure to other fibrous minerals not covered by asbestos
10 policies promulgated by federal agencies.

12 Erionite is perhaps the most worrisome known example [HHS 2005b]. An epidemic of
13 malignant mesothelioma affecting several villages in Central Turkey has been studied for
14 several decades [Baris et al. 1981]. Homes and other buildings in those villages were
15 traditionally constructed of blocks of local volcanic stone containing erionite, a fibrous
16 zeolite mineral. A recently published prospective mortality study has documented that
17 mesothelioma accounts for over 40% of deaths among those residing in the affected
18 villages [Baris and Grandjean 2006]. This localized epidemic of malignant mesothelioma
19 produced an opportunity for a pedigree study that indicates a strong genetic influence on
20 erionite-caused mesothelioma [Dogan et al. 2006]. As with exposure to asbestos, there is
21 evidence that exposure to erionite causes other malignant tumors [Baris et al. 1996] and
22 pleural plaques [Karakoca et al. 1997] in addition to mesothelioma. Likewise, as with
23 amphiboles, the mineralogy of zeolites, including erionite, appears to be complicated and
24 subject to misclassification [Dogan and Dogan 2008]. While no clear epidemic of
25 erionite-caused disease has been documented elsewhere, the mineral occurs in the
26 intermountain west of the United States and a recent publication purports to be the first to
27 report a case of erionite-associated malignant mesothelioma in North America [Kliment
28 et al. 2009].

30 The International Agency for Research on Cancer (IARC) has considered evidence
31 relevant to carcinogenicity for several EMPs [IARC 1987a, 1997]. Only for erionite has
32 IARC made an assessment that the evidence was sufficient to determine that it is a human
33 carcinogen (i.e., Group 1) [IARC 1987a]. Based on studies in rats, palygorskite
34 (attapulgite) fibers longer than 5 μm were determined to be possibly carcinogenic to
35 humans (Group 2B) [IARC 1997]. In experimental animals the evidence was limited for
36 the carcinogenicity of long sepiolite fibers (>5 μm) and inadequate to assess
37 carcinogenicity of non-erionite fibrous zeolites (including clinoptilolite, mordenite, and
38 phillipsite) and wollastonite (Group 3) [IARC 1997]. A Group 3 determination means
39 that “the available studies are of insufficient quality, consistency or statistical power to
40 permit a conclusion regarding the presence or absence of a causal association, or no data
41 on cancer in humans are available” [IARC 1997]. These Group 3 determinations
42 highlight the need for additional research on these non-asbestos EMPs.

2.7 Determinants of Particle Toxicity and Health Effects

Current recommendations for assessing occupational and environmental exposures to asbestos fibers rely primarily on dimensional and mineralogical characteristics. Dimension, which impacts the deposition of EMPs in the lung, lung clearance mechanisms, and retention time in the lung, is an important determinant of toxicity. However, other particle characteristics, such as durability in lung fluids, chemical composition, and surface activity, may also play important roles in causing respiratory diseases. Research to elucidate what roles these EMP characteristics play in causing biological responses may help to provide better evidence-based recommendations for asbestos fibers and other EMPs.

2.7.1 Deposition

Deposition of airborne particles in the respiratory system is defined as the loss of particles from the inspired air during respiration. Clearance pertains to the removal of these deposited particles by diverse processes over time, whereas retention is the temporal persistence of particles within the respiratory system [Morrow 1985]. The deposition of inhaled particles in the respiratory tract is a function of their physical characteristics (dimension and density), the anatomical and physiological parameters of the airways, and the rate and depth of respiration [Yu et al. 1986]. While particle chemical composition does not play a role in deposition, respiratory clearance of all particle types is dependent on both physical and chemical characteristics of the particle. In addition, surface charge and hydrophilicity, as well as adsorbed materials (e.g., coatings on synthetic fibers) and other physical and chemical factors, determine whether small particles and fibers will agglomerate into larger, non-respirable masses [ILSI 2005].

Depending on their physical characteristics, inhaled particles are differentially deposited in one of the following three respiratory system compartments: the extra-thoracic region consisting of the anterior and posterior nose, mouth, pharynx, and larynx; the bronchial region consisting of the trachea, bronchi, and bronchioles down to and including the terminal bronchioles; and the alveolar-interstitial region consisting of the respiratory bronchioles, alveolar ducts, and alveolar sacs.

Important parameters for the deposition of airborne particles are their aerodynamic and thermodynamic properties. Below a particle size of 0.5 μm aerodynamic equivalent diameter (AED), thermodynamic properties prevail. The AED of EPs is mostly determined by their geometric diameter and density. Deposition of EPs in an airway is strongly related to the orientation of the particle with respect to the direction of the air flow and is affected by the interrelationship of four major deposition mechanisms: impaction, interception, sedimentation, and diffusion [Asgharian and Yu 1988]. In a study to assess EP deposition in the tracheobronchial region, Zhou et al. [2007] evaluated the deposition efficiencies of carbon fibers (3.66 μm diameter) using two human airway

1 replicas that consisted of the oral cavity, pharynx, larynx, trachea, and 3 to 4 generations
2 of bronchi. Carbon fiber deposition was found to increase with the Stokes number,
3 indicating that inertial impaction is the dominant mechanism. Also, fiber deposition in
4 the tracheobronchial region was lower than that of spherical particles at a given Stokes
5 number, indicating a greater likelihood for small-width EPs to move past the upper
6 respiratory tract and reach the lower airways where diffusional deposition predominates
7 [Yu et al.1986]. These results were confirmed by results of later studies evaluating the
8 deposition of asbestos using a similar tracheobronchial cast model [Sussman et al.
9 1991a,b]. The probability of deposition of a particle in a specific location in the airways
10 is not the same as the probability of penetration to that region, and for particles in a
11 certain range of aerodynamic diameters the difference between penetration and
12 deposition may be substantial [ICRP 1994].
13

14 **2.7.2 Clearance and Retention**

15

16 A variety of mechanisms are associated with the removal of deposited particles from the
17 respiratory tract [Warheit 1989]. Physical clearance of insoluble particles deposited in
18 the lung is an important physiological defense mechanism that usually serves to moderate
19 any risk that might otherwise be associated with exposure to particles. Inhaled particles
20 that deposit on respiratory tract surfaces may be physically cleared by the
21 tracheobronchial mucociliary escalator or nasal mucus flow to the throat, and then may
22 be either expectorated or swallowed. Clearance depends upon the physicochemical
23 properties of the inhaled particles, the sites of deposition, and respiratory anatomy and
24 physiology. For example, inhaled insoluble particles with larger AEDs tend to deposit on
25 the nasopharyngeal mucus and are generally cleared by sneezing or nose blowing or by
26 flow into the oropharynx where they are swallowed. Insoluble particles with smaller
27 AEDs tend to deposit lower in the respiratory tract, with associated longer retention
28 times. Those deposited in the alveolar region are subject to longer retention times than
29 those deposited on the bronchial region [Lippmann and Esch 1988].
30

31 The most important process for removal of insoluble particles from the airways is
32 mucociliary clearance, which involves a moving layer of mucus by the action of ciliated
33 airway cells that line the trachea, bronchi, and terminal bronchioles [Warheit 1989]. The
34 mucociliary transport system is sensitive to a variety of agents, including cigarette smoke
35 and ozone [Vastag et al. 1985]. These toxicants affect the speed of mucus flow and
36 consequent particle clearance by altering ciliary action and/or modifying the properties
37 and/or amount of mucus. Chronic exposure to cigarette smoke has been shown to cause a
38 prolonged impairment of particulate clearance from the bronchial region. This impaired
39 clearance is associated with increased retention of asbestos fibers in the bronchi, where
40 they stimulate inflammatory processes in the bronchial epithelium [Churg et al. 1992;
41 Churg and Stevens 1995].
42

43 Because the alveolar region of the lung does not possess mucociliary clearance
44 capability, particles (generally $<2 \mu\text{m}$ AED) deposited in this region are cleared at a

1 much slower rate than particles deposited in the bronchial region. Particles that are
2 soluble may dissolve and be absorbed into the pulmonary capillaries, while insoluble
3 particles may physically translocate from the alveolar airspace [Lippmann et al. 1980;
4 Lippmann and Schlesinger 1984; Schlesinger 1985]. Most insoluble EPs that deposit in
5 the alveolar regions are phagocytized (i.e., engulfed) by alveolar macrophages.
6 Macrophages contain lysosomes packed with digestive enzymes, such as acid hydrolases,
7 at acidic pH levels. Lysosomal contents are capable of digesting many—though not all—
8 types of phagocytized particles. Alveolar macrophages that have phagocytized particles
9 tend to migrate to the bronchoalveolar junctions, where they enter onto the mucociliary
10 escalator for subsequent removal from the lung [Green 1973]. It has been postulated by
11 some investigators that dissolution of particles within macrophages is a more important
12 determinant of long-term clearance kinetics for many mineral dusts than is mucociliary
13 transport and the migratory potential of lung macrophages [Brain et al. 1994]. However,
14 there are circumstances which can disrupt the normal phagosomal function of alveolar
15 macrophages. One such type of circumstance involves the toxic death of macrophages
16 initiated by highly reactive particle surfaces (e.g., crystalline silica particles). Another
17 such circumstance involves overwhelming the capacity of macrophages by an extreme
18 burden of deposited particles, sometimes referred to as “overload,” even by particles that
19 would be considered “inert” at lower doses. A third type of circumstance, typified by
20 asbestos fibers, involves EPs that, even though having a small enough AED (defined
21 primarily by particle width) to permit deposition in the alveolar region, cannot be readily
22 phagocytized because particle length exceeds macrophage capacity. When alveolar
23 macrophages attempt to phagocytize such EPs, they cannot completely engulf them
24 (sometimes referred to as “frustrated phagocytosis”) and lysosomal contents are released
25 into the alveolar space. “Frustrated phagocytosis” can initiate a process in which reactive
26 oxygen species (ROS) are generated, stimulating the induction of tumor necrosis factor-
27 alpha (TNF- α). TNF- α is considered an inflammatory and fibrogenic cytokine that plays
28 an important role in the pathogenesis of pulmonary fibrosis [Blake et al. 1998].

29
30 All three types of disruption of normal macrophage function contribute to decreased
31 particle clearance rates and can result in inflammation of the alveolar spaces. In addition,
32 particles that are not phagocytized in the alveoli can translocate to the lung interstitium,
33 where they may be phagocytized by interstitial macrophages or transported through the
34 lymphatics to pulmonary lymph nodes [Lippmann et al. 1980; Lippmann and Schlesinger
35 1984; Schlesinger 1985; Oberdorster et al. 1988]. Tran and Buchanan [2000] have
36 reported findings suggesting that sequestration of particles in the interstitial compartment
37 is more prominent in exposed humans than is the observed retention of particles due to
38 overload in animal studies. The importance of interstitialization in humans is consistent
39 with the kinetic differences observed in lung clearance rates in humans and rats. The
40 first-order rate coefficient for alveolar clearance is approximately 1 order of magnitude
41 faster in rats than in humans [Snipes 1996], which may allow for greater interstitialization
42 of particles in humans at all levels of lung dust burden. These findings indicate that
43 adjustment of kinetic differences in particle clearance and retention is required when
44 using rodent data to predict lung disease risks in humans and that current human lung

1 models underestimate working lifetime lung dust burdens in certain occupational
2 populations [Kuempel et al. 2001].

3
4 Evidence from *in vivo* studies in rodents and *in vitro* studies indicates that EPs (vitreous
5 glass and EMPs) with a length equal to or greater than the diameter of rodent lung
6 macrophages (about 15 μm) are most closely linked to biological effects observed in
7 rodent lungs [Blake et al. 1998]. Alveolar macrophages appear to be capable of
8 phagocytizing and removing EPs shorter than approximately 15 μm , either by transport to
9 the mucociliary system or to local lymph channels. With increasing length above
10 approximately 15 μm , alveolar macrophages appear to be increasingly ineffective at
11 physical removal, resulting in differential removal rates for EPs of different lengths.
12 While EP lengths greater than 15 μm appear to be associated with toxicity in
13 experimental studies with rodents, a "critical" length for toxicity in humans is probably
14 greater than 15 μm [Zeidler-Erdelyi et al. 2006]. For long EPs that cannot be easily
15 cleared by macrophages, biopersistence in the lung is influenced by the ease with which
16 the EPs break into shorter lengths.

17 18 **2.7.3 Biopersistence and other Potentially Important Particle Characteristics**

19
20 The differences in crystalline structure between amphibole asbestos fibers and amphibole
21 cleavage fragments have been hypothesized to account for apparent differences in
22 toxicological response to these particles. It has been observed that cleavage fragments
23 which meet the dimensional criteria for countable particles under federal regulatory
24 policies for asbestos fibers are generally shorter and wider than asbestos fibers [Siegrist
25 and Wylie 1980; Wylie 1988]. This dimensional difference between populations of
26 asbestos fibers and populations of cleavage fragments might contribute to generally
27 shorter biopersistence in the lung for cleavage fragments compared to asbestos fibers.
28 Asbestos fibers also tend to separate longitudinally once deposited in the lung, thus
29 increasing the total number of retained fibers without an accompanying reduction in
30 lengths of the retained fibers [NRC 1984]. In contrast, cleavage fragments tend to break
31 transversely due to dissolution of their weaker crystalline structure, resulting in shorter
32 particles that can be more easily cleared through phagocytosis and mucociliary clearance
33 [Zoltai 1981]. The impact of these structural differences on solubility in lung fluids
34 warrants study, because substantial differences in solubility in lung fluids between
35 asbestos fibers and other EMPs (including amphibole cleavage fragments) could translate
36 into differences in toxicity.

37 38 **2.7.3.1 Biopersistence**

39
40 Dissolution of EPs in the lung is a poorly understood process that is dependent on particle
41 characteristics, biological processes, and concomitant exposure to other particulates. The
42 ability of an EP to be retained and remain intact in the lung is considered an important
43 factor in the process of an adverse biological response. EPs of sufficient length that
44 remain intact and are retained in the lung are thought to pose the greatest risk for

1 respiratory disease. The ability of an EP to reside long-term in the lung is generally
2 referred to as “biopersistence.” Biopersistence of EPs in the lung is a function of site and
3 rate of deposition, rates of clearance by alveolar macrophages and mucociliary transport,
4 solubility in lung fluids, breakage rate and breakage pattern (longitudinal or transverse),
5 and rates of translocation across biological membranes. The rates of some of these
6 processes can affect the rates of other processes. For example, a high rate of deposition
7 in the alveolar region could potentially overwhelm macrophage clearance mechanisms
8 and increase the rate of translocation to the lung interstitium.

9
10 The persistence of an EP in the lung is influenced by changes that may occur in its
11 dimension, surface area, chemical composition, and surface chemistry. Differences in
12 any of these characteristics can potentially result in differences in clearance and retention
13 and affect toxic potential. For example, EPs too long to be effectively phagocytized by
14 alveolar macrophages will tend to remain in the alveolar compartment and be subjected
15 to other clearance mechanisms, including dissolution, breakage, and translocation to
16 interstitial sites and subsequently to pleural and other sites.

17
18 The durability of EPs residing in the lung is an important characteristic influencing
19 biopersistence. An EP’s durability is generally measured by its ability to resist
20 dissolution and mechanical disintegration after being subjected to lung extra-cellular fluid
21 (approximately pH 7) and lysosomal fluids (approximately pH 5). EPs that are more
22 soluble will be less biopersistent, and thicker EPs may take longer to dissolve than
23 thinner EPs, all else being equal. For example, long, thin EPs that are not very durable
24 could dissolve and/or fragment into shorter EPs, increasing their probability of being
25 cleared from the lung and thus potentially decreasing lung retention time and risk for
26 fibrotic or neoplastic effects. Some EPs, such as certain types of glass fibers, are fairly
27 soluble in lung fluid and are cleared from the lung in a matter of days or months. Other
28 EPs, such as amphibole asbestos, can remain in the lung for decades. It has been
29 suggested that some types of EPs may alter the mobility of macrophages and the
30 translocation of EPs to the pleura or lymph nodes [Davis 1994]. No relationship has been
31 established between biopersistence of EPs in the lung and the risk of induction of genetic
32 and epigenetic changes that may lead to cancer [Barrett 1994]. While some evidence
33 indicates that durability may be a determinant of toxicity for various SVFs, EMPs need to
34 be evaluated to determine whether they conform to this paradigm [ILSI 2005].

35
36 Measurement of the biopersistence of various EMPs has been suggested as a means for
37 estimating their relative potential hazard. Short-term inhalation and intratracheal
38 instillation studies have been used to determine the biopersistence of various SVFs and
39 asbestos fibers. Animal inhalation studies are preferred over animal tracheal instillation
40 studies to assess biopersistence because they more closely mimic typical human
41 exposure. The European Commission has adopted specific testing criteria that permit the
42 results from either short-term biopersistence studies or chronic animal studies to be used
43 as a basis for determining carcinogenicity [European Commission 1997].
44

1 Several animal inhalation studies have indicated that oncogenic potential of long SVFs
2 can be determined by their biopersistence [Mast et al. 2000; Bernstein et al. 2001;
3 Moolgavkar et al. 2001]. It has been suggested that a certain minimum persistence of
4 long EPs is necessary before even minute changes appear in the lungs of exposed animals
5 [Bernstein et al. 2001]. Furthermore, Moolgavkar et al. [2001] have suggested that fiber-
6 induced cancer risk, in addition to being a linear function of exposure concentration, is
7 also a linear function of the weighted half-life of fibers observed in inhalation studies
8 with rats. Also, dosimetry models for rodents and humans indicate that, on a normalized
9 basis, fiber clearance rates are lower in humans than in rats [Maxim and McConnell
10 2001] and that fibers frequently sequester in the interstitial compartment of humans
11 [Snipes 1996; Tran and Buchanan 2000]. Thus, results from chronic inhalation studies
12 with rodents exposed to EPs may underestimate risks for humans and adjustment for
13 kinetic differences in particle clearance and retention in rats is required to predict lung
14 disease risks in humans [Kuempel et al. 2001].

15
16 Studies using *in vitro* assays have been conducted with various SVFs and silicate
17 minerals to determine the dissolution rate in simulated lung and lysosomal fluids [Hume
18 and Rimstidt 1992; Werner et al. 1995; Hesterberg and Hart 2000; Jurinski and Rimstidt
19 2001]. *In vitro* dissolution studies can provide a rapid and more controlled alternative to
20 classical long-term toxicity testing in animals and could provide useful information when
21 performed as companion experiments with *in vivo* studies if conditions of exposure and
22 test agent can be made similar. The design of *in vitro* assays is intended to mimic the
23 biological conditions that exist in the lung once the EP comes into contact with lung
24 tissue or macrophages. While uncertainties exist about the specific physiological
25 processes that occur in the lung, results from *in vitro* assays can provide some insight into
26 the chemical reactions that influence EP dissolution. For example, it appears that EP
27 (e.g., glass fibers) dissolution occurs more readily when the EP is in contact with a fluid
28 that is under-saturated with respect to the EP's composition. The condition of under-
29 saturation must be maintained at the EP's surface for dissolution to continue. If an EP is
30 surrounded by a saturated or super-saturated solution (compared to the EP composition),
31 then no further dissolution occurs.

32
33 The results from many *in vitro* experiments demonstrate different patterns of dissolution
34 for most of the tested EP types (i.e., glass, asbestos) under various test conditions. This
35 effect was most notable in those experiments where different pH conditions were used.
36 Fluid pH appears to influence the creation of complexes from the leached elements of the
37 EP, which in turn alters the rate of solubility. Chrysotile fibers tend to dissolve readily in
38 acids because of the preferential leaching of Mg from the fiber. The leaching of Mg from
39 tremolite and anthophyllite and Na from crocidolite also occurs more readily in acid
40 conditions.

41
42 Rate of EP dissolution has also been observed to be affected by differing internal and
43 surface structures. EPs with porous or rough surfaces have larger surface areas compared
44 to smooth EPs with the same gross dimensions. These larger surface areas interact more

1 readily with the surrounding medium because of the greater number of sites where solute
2 molecules can be absorbed. EMPs with cleavage plane surfaces will contain varying
3 degrees of defects; the higher the number of surface defects, the greater the potential
4 instability of the particle. Dissolution of these types of EMPs is typically initiated where
5 surface vacancies or impurities are present [Searl 1994]. Chrysotile asbestos is an
6 example of a sheet silicate made up of numerous fibrils comprised of tightly bound rolled
7 layers of Mg hydroxide. These Mg hydroxide layers are readily leached by acid solutions
8 within human tissues [Spurny 1983], causing disintegration of the fibril's crystalline
9 structure. In contrast, the amphibole asbestos minerals are chain silicates with a
10 crystalline structure comprised of alkali and alkali earth metals that are tightly bound,
11 making the fibers less susceptible to dissolution. In contrast to the crystalline structure of
12 the asbestos fibers, some high-temperature glass fibers are more stable than chrysotile
13 fibers because they are comprised of silicate chains, sheets, and frameworks [Searl 1994].
14 The absence of cleavage planes or structural defects in glass fibers limits the degree to
15 which fluids can penetrate their interior to promote dissolution. Chrysotile fibers were
16 found to be less durable in rat lungs than some high-temperature SVFs [Bellmann et al.
17 1987; Muhle et al. 1987] but more durable in physiological solutions than some
18 refractory ceramic fibers (RCFs) [Scholze and Conradt 1987].

19
20 EP surface characteristics (e.g., structural defects, porous surfaces) and composition not
21 only influence the rate of dissolution, but also affect the manner in which dissolution
22 occurs. In some instances, surface dissolution will cause alterations in internal structure
23 sufficient to cause mechanical breakage. In some studies, slagwools and rockwools
24 exposed to water developed irregular surfaces, creating stress fractures which caused
25 transverse breakage [Bellmann et al. 1987]. Similar occurrences of glass fiber breakage
26 have been observed when there was leaching of alkaline elements [Searl 1994].

27
28 Results from *in vitro* and short-term *in vivo* studies conducted with various EMPs and
29 SVFs provide some confirmation that persistence of EPs in the lung is influenced by
30 particle durability [Bernstein et al. 1996]. However, other evidence suggests that,
31 because of the relatively short biodurability of chrysotile fibers, any damage to the lung
32 tissue caused by chrysotile fibers must be initiated soon after exposure [Hume and
33 Rimstidt 1992], suggesting that biopersistence of EPs in the lung may be only one of
34 many factors that contribute to biological response. A better understanding of the factors
35 that determine the biological fate of EMPs deposited in the lung is critical to
36 understanding the mechanisms underlying differences in toxic potential of various EMPs
37 of different dimensions and compositions. Because biopersistence of EMPs is thought to
38 play an important role in the development of disease, it may eventually prove to be an
39 important characteristic to incorporate into occupational safety and health policies
40 concerning exposures to EMPs.

1 2.7.3.2 Other Potentially Important Particle Characteristics

2
3 Surface composition and surface-associated activities have been suggested as factors
4 affecting the potential for disease induction by EMPs (e.g., asbestos)[Bonneau et al.
5 1986; Kane 1991; Jaurand 1991; Fubini 1993]. For non-elongate respirable mineral
6 particles (e.g., crystalline silica), surface composition and surface interactions can
7 directly and profoundly affect *in vitro* toxicities and *in vivo* pathogenicity; they can also
8 directly cause membranolytic, cytotoxic, mutagenic, or clastogenic damage to cells, and
9 have been shown to induce fibrogenic activities in animals and humans. Investigation is
10 warranted to confirm that these effects of surface composition and surface interactions
11 also apply to EMPs. One strategy is to determine the effects of well-characterized
12 surface modification of different types of EMPs on cell-free interactions with biological
13 materials, *in vitro* cellular cytotoxicities or genotoxicities, and pathology in animal
14 models.

15
16 Surface properties of mineral fibers and other EMPs may have direct impact on cytotoxic
17 or genotoxic mechanisms responsible for fibrogenic or carcinogenic activity. Chemical
18 surface modification of asbestos fibers has been shown to affect their cytotoxicity [Light
19 and Wei 1977a,b; Jaurand et al. 1983; Vallyathan et al. 1985]. While asbestos fibers
20 clearly can be carcinogenic, they are not consistently positive in genotoxicity assays;
21 their principal damage is chromosomal rather than gene mutation or DNA damage
22 [Jaurand 1991]. One study linked cytotoxicity with *in vitro* mammalian cell
23 transformation [Hesterberg and Barrett 1984]; thus, surface factors affecting cytotoxicity
24 might affect potential for inducing some genotoxic activities. However, surface
25 modification of a well-characterized sample of chrysotile fibers by depleting surface Mg
26 while retaining fiber length did not result in a significant quantitative difference for *in*
27 *vitro* micronucleus induction between the native and surface-modified materials, both of
28 which were positive in the assay [Keane, et al. 1999].

29
30 The surface of mineral fibers and other EMPs also might be an indirect but critical factor
31 in the manifestation of pathogenic activity. EMP surfaces may be principal determinants
32 of EMP durability under conditions of *in vivo* dissolution in biological fluids. As such,
33 they would be a controlling factor in biopersistence, critical to the suggested mechanisms
34 of continuing irritation or inflammatory response in causing fibrosis or neoplastic
35 transformation.

36 37 2.7.4 Animal and In Vitro Toxicity Studies

38
39 Over the last half-century, *in vivo* animal model studies have explored induction of
40 cancer, mesothelioma, and pulmonary fibrosis by asbestos fibers and other EMPs
41 following intrapleural, intraperitoneal, or inhalation challenge. Numerous cell-free, *in*
42 *vitro* cellular, and *in vivo* short-term animal model studies have been pursued, attempting
43 to: (1) examine tissue and cellular responses to EMPs and impact of EMP conditioning
44 on these responses; (2) identify and evaluate interactions and mechanisms involved in

1 pathogenesis; and (3) seek morphological or physicochemical EMP properties controlling
2 those mechanisms. These short-term studies provide an evolving basis for design or
3 interpretation of higher-tier chronic exposure studies of selected EMPs.
4

5 Some of the short-term studies have addressed:

- 6 • the general question of extrapolating human health effects from *in vivo* animal
7 model studies;
- 8 • the physiological relevance of *in vitro* cellular studies of EMP toxicities;
- 9 • the association of EMP dimensions with pathology demonstrated in animal
10 model studies;
- 11 • the potential mechanisms and associated EMP properties responsible for
12 initiating cell damage;
- 13 • the extensive information now available on a “central dogma” of subsequent
14 intracellular biochemical pathway stimulation leading to toxicity or
15 intercellular signaling in disease promotion; and
- 16 • the use of these mechanistic paradigms to explain specific questions of:
 - 17 ○ differences between the activities of asbestiform and nonasbestiform
18 EMPs, including seemingly anomalous differences between some *in vitro*
19 and *in vivo* EMP activities;
 - 20 ○ differences between the activities of erionite fibers and amphibole
21 asbestos fibers; and
 - 22 ○ the possibility of EMP-viral co-carcinogenesis.

23
24 Several reviews and recommendations for animal model and cellular studies on these
25 issues have been developed by expert workshops and committees. Early studies on the
26 carcinogenicity of asbestos and erionite fibers were reviewed by IARC [1977, 1987a,b]
27 and SVFs were reviewed more recently [IARC 2002]. Short-term *in vivo* and *in vitro*
28 studies to elucidate mechanisms of fiber-induced genotoxicity and genetic mechanisms
29 affecting fiber-induced lung fibrosis have been extensively reviewed. A review for the
30 EPA by an international working group assembled in 2003 provides an update on short-
31 term assay systems for fiber toxicity and carcinogenic potential [ILSI 2005], and two
32 additional reviews discuss the fiber genotoxicity literature up to the current decade
33 [Jaurand 1997; Schins 2002]:
34

35 2.7.4.1 Model Systems Used to Study EMP Toxicity

36
37 The paucity of human health effects information for some new synthetic EPs has led to
38 renewed considerations of the value and limitations of animal model studies, and the
39 question of the interpretability of intrapleural, intraperitoneal, or inhalation challenge
40 methods of animal model tests to make predictions of human health effects [IARC 2002].
41 One analysis concluded that rat inhalation is not sufficiently sensitive for prediction of
42 human carcinogenicity by EMPs other than asbestos fibers [Muhle and Pott 2000].
43 Another review concluded that there are significant interspecies differences between the

1 mouse, hamster, rat, and human, with the available evidence suggesting that the rat is
2 preferable as a model for the human, noting that rats develop fibrosis at comparable lung
3 burdens, in fibers per gram of dry lung, to those that are associated with fibrosis in
4 humans. The review suggested that, on a weight-of-evidence basis, there is no reason to
5 conclude that humans are more sensitive to fibers than rats with respect to the
6 development of lung cancer [Maxim and McConnell 2001]. However, others suggest
7 that, because inhaled particles frequently sequester in the interstitial compartment of
8 humans, alveolar clearance is approximately one order of magnitude slower in humans
9 than in rats [Snipes 1996; Tran and Buchanan 2000]. Those comparisons imply that
10 results of inhalation studies with rats exposed to particles underestimate the risk for
11 humans and that adjustment for kinetic differences in particle clearance and retention in
12 rats is required to predict lung disease risks in humans [Kuempel et al. 2001].
13

14 How the results of *in vitro* tests which use cells or organ cultures apply to humans has
15 been questioned because of differences in cell types and species-specific responses. It is
16 difficult to isolate and maintain epithelial or mesothelial cells for use as models.
17 Interpretation of *in vitro* test results may be limited because *in vitro* models may not
18 consider all processes, such as clearance or surface conditioning, which occur *in vivo*. A
19 major deficiency of *in vitro* systems is that biopersistence is not easily addressed. In
20 addition to the usual exposure metric of mass, experimental designs should also include
21 exposure metrics of EMP number and surface area [Mossman 2008; Wylie et al. 1997].
22

23 As frequently performed, *in vitro* assays of mineral particle-induced damage, measured
24 by cell death or cytosolic or lysosomal enzyme release, do not adequately model or
25 predict the results of *in vivo* challenge or epidemiological findings. For example,
26 respirable aluminosilicate clay dust is as cytotoxic as quartz dust in such *in vitro* assays,
27 while quartz, but not clay, is strongly fibrogenic *in vivo* [Vallyathan et al. 1988].
28

29 2.7.4.2 Studies on Effects of Fiber Dimension

30

31 Early animal inhalation studies found that chrysotile fibers induced fibrosis, hyperplasia
32 of lung epithelial cells, and carcinomas in mice [Nordman and Sorge 1941] and tumors in
33 rats [Gross et al. 1967]. Another study found lung carcinomas and mesotheliomas in rats
34 inhalationally exposed to asbestos fiber samples of amosite, anthophyllite, crocidolite,
35 and chrysotile [Wagner et al. 1974]. The effects of fiber length, width, and aspect ratio
36 on carcinogenicity were addressed in a seminal study using a pleural surface implantation
37 method of challenge in the rat [Stanton et al. 1977, 1981]. Tests were performed on 72
38 durable EPs: 13 crocidolites; 22 glasses; 8 aluminum oxide sapphire whiskers; 7 talcs; 7
39 dawsonites; 4 wollastonites; 2 asbestos tremolites; an amosite; 2 attapulgitites; 2
40 halloysites; a silicon carbide whisker; and 3 titanates. The incidence of malignant
41 mesenchymal neoplasms a year after implantation correlated best with EPs that were
42 longer than 8 μm and no wider than 0.25 μm , with relatively high correlations with EPs
43 longer than 4 μm and no wider than 1.5 μm . This suggested that carcinogenicity of
44 durable EPs depends on dimension, and durability, rather than physicochemical

1 properties. This is sometimes referred to as the “Stanton hypothesis” and has been the
2 subject of continuing research. Reanalysis of the dimensions of seven of the crocidolite
3 samples used in the 1981 study found that tumor probability was significantly correlated
4 with the number of index particles (defined as particles longer than 8 μm and no wider
5 than 0.25 μm), but the coefficient was low enough to suggest that factors other than size
6 and shape play a role in carcinogenic effects of durable EPs [Wylie et al. 1987]. Further
7 analysis confirmed the number of such index particles as the primary dimensional
8 predictor of tumor incidence, but the correlation was increased when the data were
9 analyzed by separate mineral types [Oehlert 1991]. These analyses suggested that
10 mineral type is important, which is counter to the “Stanton hypothesis.”

11
12 Data from animal models exposed by instillation or inhalation of EMPs of defined size
13 distributions have been reviewed, along with human lung fiber burden data and
14 associated effects, to conclude that: (1) asbestosis is most closely associated with the
15 surface area of retained EMPs; (2) mesothelioma is most closely associated with numbers
16 of EMPs longer than about 5 μm and thinner than about 0.1 μm ; and (3) lung cancer is
17 most closely associated with EMPs longer than about 10 μm and thicker than about 0.15
18 μm [Lippmann 1988]. A more recent review of the response to asbestos fibers of various
19 lengths in animal models, along with data from studies of human materials, concluded
20 that asbestos fibers of all lengths induce pathological responses, and suggested caution
21 when attempting to exclude any subpopulation of inhaled asbestos fibers, based on their
22 length, from being considered contributors to the development of asbestos-related
23 diseases [Dodson et al. 2003].

24 25 2.7.4.3 Initiation of Toxic Interactions

26
27 A first question in seeking a full understanding of EMP properties and mechanisms
28 responsible for fibrosis, lung cancer, or mesothelioma risks is the identity of initiating
29 toxic interactions and the morphological, physical, or chemical properties of EMPs
30 controlling them. Among proposed initiating mechanisms are: (1) EMP surfaces generate
31 ROS (even *in vitro* in the absence of cells), which are the primary toxicants to cells; (2)
32 EMP surfaces are directly membranolytic or otherwise directly cytotoxic or genotoxic to
33 components of the cell, as are some non-elongate mineral particles, and that damage can
34 cause necrosis, apoptosis, mutation, or transformation directly or by responsive cellular
35 production of secondary reactive intermediates; and (3) EMP morphology itself can result
36 in “frustrated phagocytosis” with an anomalous stimulation or release of ROS or other
37 toxic reactive species.

38 39 2.7.4.3.1 Reactive Oxygen Species

40
41 Asbestos fibers can generate ROS or reactive nitrogen species in *in vitro* systems through
42 direct aqueous-phase surface chemical reactions, as well as by stimulating secondary
43 release of reactive species from cells. Electron spin resonance using spin-trapping
44 techniques found that crocidolite, chrysotile, and amosite asbestos fibers were all able to

1 catalyze the generation of toxic hydroxyl radicals in a cell-free system containing
2 hydrogen peroxide, a normal byproduct of tissue metabolism, and that the iron chelator
3 desferroxamine inhibited the reaction, indicating a major role for iron in the catalytic
4 process [Weitzman and Graceffa 1984]. ROS generated by some EMP surfaces in cell-
5 free media may provide toxicants to initiate cell structural or functional damage,
6 including chromosomal or DNA genetic damage or aneuploidy from spindle apparatus
7 damage. They also may activate cellular signaling pathways that promote cell
8 proliferation or transformation. Research has investigated the possible roles of iron in
9 this reactivity and the roles of released versus surface-borne iron.

10
11 Asbestos fibers can cause lipid peroxidation in mammalian cells and artificial membranes
12 that can be prevented by removal of catalytic iron. Reduction of crocidolite cytotoxicity
13 by certain antioxidants (including superoxide dismutase (SOD), a depletor of superoxide
14 anion (SO⁻); catalase, a scavenger of hydrogen peroxide (H₂O₂); dimethylthiourea
15 (DMTU), a scavenger of the hydroxyl radical ([•]OH); and desferroxamine, an iron
16 chelator) suggested that iron is involved in the generation of ROS through a modified
17 Haber-Weiss Fenton-type reaction resulting in the production of hydroxyl radical (e.g.,
18 from SO and H₂O₂ generated during phagocytosis) [Goodlick and Kane 1986; Shatos et
19 al. 1987]. Such scavenging or chelation prevented DNA strand breakage in cells *in vitro*
20 by crocidolite fibers [Mossman and Marsh 1989].

21
22 In a cell-free study of five natural and two synthetic fibers, erionite, JM code 100 glass
23 fibers, and glass wool were the most effective initiators of hydroxyl radical formation,
24 followed by crocidolite, amosite, and chrysotile fibers. Hydroxyl radical formation
25 activity showed positive correlations with tumor rates in rats challenged by intrapleural
26 injection and with human mesothelioma mortality rates, but not with tumor rates in rats
27 challenged by intraperitoneal injection [Maples and Johnson 1992]. SO-produced ROS
28 then might induce DNA oxidative damage, measured as elevated 8-
29 hydroxydeoxyguanosine (8-OHdG). In cell-free systems, the crocidolite-induced
30 increase of 8-OHdG in isolated DNA was enhanced by addition of H₂O₂ and diminished
31 by addition of desferroxamine [Faux et al. 1994]. However, de-ironized crocidolite fibers
32 incubated in a cell-free system induced twice the 8-OHdG oxidative damage to DNA as
33 untreated crocidolite fibers. In parallel rat exposures, the combination of de-ironized
34 crocidolite fibers plus Fe₂O₃ resulted in mesothelioma in all animals compared to half the
35 animals injected with crocidolite fibers alone and none of the animals injected with Fe₂O₃
36 alone [Adachi et al. 1994]. Other research suggested that unreleased fiber-surface-bound
37 iron is important to the reactivity; long fibers of amosite and crocidolite both caused
38 significant dose-dependent free radical damage to cell-free phage DNA, suppressible by
39 the hydroxyl radical scavenger mannitol and by desferroxamine, but short RCFs and
40 man-made vitreous fibers (MMVFs) did not, while releasing large quantities of Fe(III)
41 iron [Gilmour et al. 1995]. Crocidolite fibers induced mutations in peritoneal tissue *in*
42 *vivo* in rats, most prominently guanine-to-thymine (G-to-T) transversions known to be
43 induced by 8-OHdG; this was interpreted as strong evidence for the involvement of ROS
44 or reactive nitrogen species in crocidolite-induced mutagenesis *in vivo*, consistent with *in*

1 *in vitro* and cell-free studies [Unfried et al. 2002]. In contrast to glass fiber, crocidolite fiber
2 intratracheal instillation in rats increased 8-OHdG levels in DNA at one day and in its
3 repair enzyme activity at seven days. This *in vivo* activity is consistent with asbestos-
4 and MMVF-induced increases of 8-OHdG oxidative damage *in vitro* [Yamaguchi et al.
5 1999].

6 7 2.7.4.3.2 Membrane Interactions

8
9 Many mineral particles, elongate or not, can directly cause membranolysis or other
10 cytotoxic responses without necessarily invoking extracellular generation of ROS.
11 Mechanisms of cell damage by EMPs independent of ROS formation have been proposed
12 to involve direct interactions of particle surface functional groups (e.g., silicon or
13 aluminum or magnesium) with lipoproteins or glycoproteins of the cell membrane. It has
14 been suggested that silica particle cytotoxicity to macrophages is due to distortion and
15 disruption of secondary lysosomal membranes by phagocytosed particles whose surface
16 silanol groups hydrogen-bond to membrane lipid phosphates, but that chrysotile-induced
17 cellular release of hydrolytic enzymes is due to surface magnesium interacting ionically
18 with sialic acid residues of membrane glycoproteins, inducing cation leakage and osmotic
19 lysis [Allison and Ferluga 1977]. Chrysotile fibers cause lysis of red blood cells. EM
20 indicates that cell membranes become wrapped around the fibers and that cell distortion
21 and membrane deformation correlate with an increase in the intracellular ratio of sodium
22 to potassium ions. Cell pretreatment with neuraminidase prevents fiber-cell binding,
23 suggesting mediation by cell membrane glycoproteins [Brody and Hill 1983]. However,
24 chrysotile and crocidolite fibers both induced increased membrane rigidity in model
25 unilamellar vesicles made of saturated dipalmitoyl phosphatidylcholine (DPPC),
26 suggesting that lipid peroxidation is not involved in membrane rigidity induced by
27 asbestos [Gendek and Brody 1990]. Silicate slate dust and chrysotile fibers both induced
28 hemolysis *in vitro* and peroxidation of polyunsaturated membrane lipids. However,
29 poly(2-vinylpyridine N-oxide) (PVPNO) and DPPC surface prophylactic agents
30 suppressed lysis but not peroxidation, while SOD and catalase did the reverse; and lysis
31 was much faster than peroxidation. This suggested that membrane lysis and peroxidation
32 are independent processes [Singh and Rahman 1987]. However, either mechanism may
33 be involved in membrane damage by EMPs; and seemingly disparate findings suggest
34 uncharacterized details of EMP properties or of cellular or mineral conditioning under
35 test conditions may be important.

36
37 In *in vitro* studies, quartz dust and chrysotile fibers induced loss of viability and release
38 of lactate dehydrogenase (LDH) from alveolar macrophages. DPPC reduced these
39 activities of the quartz but not of the asbestos [Schimmelpfeng et al. 1992]. DPPC is
40 adsorbed from aqueous dispersion in approximately equal amounts on a surface area
41 basis, about 5 mg phospholipid per square meter, by asbestos fibers [Jaurand et al. 1980]
42 and by non-fibrous silicate particles [Wallace et al. 1992]; this is close to the value
43 predicted by mathematical modeling of an adsorbed bilayer [Nagle 1993]. In the case of
44 silica or clay membranolytic dusts, this adsorption fully suppresses their activity until

1 toxicity is manifest as the prophylactic surfactant is digested from the particle surface by
2 lysosomal phospholipase enzyme, with mineral-specific rates of the process suggesting a
3 basis for differing fibrogenic potentials of different types of mineral particles [Wallace et
4 al. 1992].

5
6 Samples of intermediate-length and short-length NIEHS chrysotile were compared, with
7 and without DPPC lung surfactant pre-treatment, for micronucleus induction in Chinese
8 hamster lung V79 cells *in vitro*. Increase in micronuclei frequency and multi-nuclear cell
9 frequency were induced by all samples, with the greatest micronucleus induction by
10 untreated intermediate-length chrysotile fibers and with greater activity for untreated
11 versus treated short chrysotile fibers. Cell viability was greater for treated fibers [Lu et
12 al. 1994]. NIEHS intermediate-length chrysotile was mildly acid-treated to deplete
13 surface-borne magnesium while only slightly affecting fiber length. Challenge of
14 Chinese hamster lung fibroblast cells, *in vitro* for micronucleus induction found no
15 significant difference between the treated and untreated samples, supporting a model of
16 chemically non-specific chromosomal and spindle damage effects [Keane et al. 1999].
17 Chrysotile fiber induction of mucin secretion in a tracheal cell culture was inhibited by
18 using lectins to block specific carbohydrate residues on the cell surface; leached
19 chrysotile was inactive, suggesting that the surface cationic magnesium of chrysotile was
20 responsible for interaction with cell surface glycolipids and glycoproteins [Mossman et
21 al. 1983]. However, complete removal of accessible sialic acid residues from
22 erythrocytes did not inhibit hemolysis by chrysotile fibers, suggesting that chrysotile
23 fibers can induce lysis by interaction with some other component of the cell [Pelé and
24 Calvert 1983].

25 26 2.7.4.3.3 Morphology-mediated Effects

27
28 A third possible mechanism for damage by EMP principally involves morphology. The
29 possibility of "frustrated phagocytosis" is suggested by the Stanton hypothesis of an over-
30 riding significance of particle dimension for disease induction by durable EPs. A general
31 concept is that EMPs longer than a phagocytic cell's linear dimensions can not be
32 completely incorporated in a phagosome. Recruitment of membrane from the Golgi
33 apparatus or endoplasmic reticulum may provide extensive addition to the plasma
34 membrane for a cell's attempted invagination to accommodate a long EMP in a
35 phagosomal membrane [Aderem 2002]. However, because of the length of the EMP
36 relative to the dimensions of the cell, the final phagosomal structure is topologically an
37 annulus extending fully through the cell, rather than an enclosed vacuole fully within the
38 cell. Following uptake of non-elongate particles, there is a maturation of the phagosomal
39 membrane; the initial phagosomal membrane is that of the cell's external plasmalemma,
40 which cannot kill or digest phagocytosed material. After sealing of the fully invaginated
41 phagosomal vesicle in the interior of the cell, there is a rapid and extensive change in the
42 membrane composition [Scott et al. 2003]. This involves, in part, an association with
43 lysosomal vesicles and exposure of particles within the secondary phagosome or
44 phagolysosome to lytic enzymes and adjusted pH conditions. Failure to close the

1 phagosome, as occurs in frustrated phagocytosis, is speculated to induce dysfunction of
2 the system. Conventional phagocytosis of non-elongate particles can lead to a respiratory
3 or oxidative burst of membrane-localized NADPH oxidase of SO radicals, which may be
4 converted to H₂O₂, hydroxyl radicals, and other toxic reactive products of oxygen. If
5 these are released extracellularly in connection with frustrated phagocytosis, they are
6 potentially harmful to the tissue [Bergstrand 1990].

7
8 Failure to complete normal phagocytosis may affect the duration or intensity of the
9 phagocytic response. It may also affect the generation or release of reactive species or
10 membranolytic digestive enzymes into the still-exterior annulus. Another possible affect
11 is to alter the maturation of the annular frustrated phagocytic membrane from the normal
12 structural and functional evolution of a closed phagolysosomal vesicle fully interior to the
13 cell. Even in the response to such a frustrated phagocytosis, there might be some mineral
14 specificity beyond morphology alone for EMP-induced release of reactive species.
15 Amosite fibers, MMVF, silicon carbide fibers, and RCF-1 fibers all stimulated modest
16 release of SO which was not dose-dependent in isolated rat alveolar macrophages.
17 However, when IgG, a normal component of lung lining fluid, was adsorbed onto the
18 fiber surfaces, such release was strongly enhanced for all but the silicon carbide fibers.
19 SO release correlated with adsorptive capacity for IgG of the fibers, except for the
20 amosite, which required only poorly adsorbed IgG for strong activity, suggesting some
21 mineral specificity beyond morphology alone for the EMP-induced cellular respiratory
22 burst [Hill et al. 1996].

23 24 2.7.4.3.4 Cellular Responses to Initiation of Toxicity

25
26 Subsequent to initiating damage, either by direct or induced ROS generation, or by direct
27 membranolysis generated by interactions of mineral surface sites with membrane lipids
28 or glycoproteins, or by not-fully-defined toxic response to morphology-based frustrated
29 phagocytosis, a standard model for subsequent complex cellular response has evolved
30 and has been the subject of extensive and detailed analyses [Mossman et al. 1997]. EMP-
31 generated primary toxic stimuli to the cell are subject to signal transduction by mitogen-
32 activated protein kinase (MAPK), beginning an intracellular multiple kinase signal
33 cascade which then induces transcription factors in the nucleus such as activator protein
34 (AP)-1 or nuclear factor kappa beta (NF-κB), which in turn regulate the transcription of
35 mRNA from genes for TNF-α or other cytokines involved in cell proliferation or
36 inflammation.

37
38 Fibers of the six asbestos minerals generate MAPK in lung epithelium *in vitro* and *in*
39 *vivo*, increasing AP-1 transcription activation, cell proliferation, death, differentiation, or
40 inflammation. This is synergistic with cigarette smoke [Mossman et al. 2006].
41 Macrophage release of oxidants or mitogenic factors through such a pathway could then
42 cause cell proliferation or DNA damage [Driscoll et al. 1998]. In contrast to MMVF-10
43 and RCF-4, amosite and two other carcinogenic fibers (silicon carbide and RCF-1)
44 produced significant dose-dependent translocation of NF-κB to the nucleus in A549 lung

1 epithelial cells. It was hypothesized that carcinogenic fibers have greater free radical
2 activity, which produces greater oxidative stress and results in greater translocation of
3 NF- κ B to the nucleus for the transcription of pro-inflammatory genes (e.g., cytokines)
4 [Brown et al. 1999]. Crocidolite induced AP-1 *in vitro* in JB6 cells and induced AP-1
5 transactivation in pulmonary and bronchial tissue after intratracheal instillation in
6 transgenic mice, apparently mediated by activation of MAPK [Ding et al. 1999].
7 Chrysotile challenge to blood monocytes co-cultured with bronchial epithelial cells
8 resulted in elevated levels in epithelial cells of protein-tyrosine kinase activity, NF- κ B
9 activity, and mRNA levels for interleukin (IL)-1 β , IL-6, and TNF- α . Protein-tyrosine
10 kinase activity, NF- κ B activity, and mRNA synthesis were inhibited by antioxidants,
11 suggesting ROS-dependent NF- κ B-mediated transcription of inflammatory cytokines in
12 bronchial epithelial cells [Drumm et al. 1999].

13
14 Chemokines known to be associated with particle-induced inflammation were found to be
15 secreted by mesothelial cells after amosite challenge to cultured rat pleural mesothelial
16 cells, and were found in pleural lavage of rats challenged *in vivo* [Hill et al. 2003].

17
18 Fibers from both crocidolite (asbestiform riebeckite) and nonfibrous milled riebeckite
19 increased phosphorylation and activity of a MAPK cascade in association with induction
20 of an inflammatory state of rat pleural mesothelial cells and progenitor cells of malignant
21 mesothelioma. Amelioration by pre-incubation with vitamin E indicated this to be an
22 oxidative stress effect [Swain et al. 2004]. Lung lysate, cells from bronchoalveolar
23 lavage, and alveolar macrophages and bronchiolar epithelial cells from lung sections
24 from rats exposed to crocidolite or chrysotile fibers contained nitrotyrosine and
25 phosphorylated extracellular signal-regulated kinases (ERKs); nitrotyrosine is a marker
26 for peroxynitrite which activates ERK signaling pathways, altering protein function
27 [Iwagaki 2003]. *In vitro* challenge of human bronchiolar epithelial cells with crocidolite
28 or chrysotile fibers induced tissue factor (TF) mRNA expression and induced NF- κ B and
29 other transcription factors that bind the TF gene promoter. TF *in vivo* is involved in
30 blood coagulation with inflammation and tissue remodeling [Iakhiaev et al. 2004].
31 Asbestos fibers activate an ERK pathway *in vitro* in mesothelial and epithelial cells.
32 Crocidolite challenge to mice results in phosphorylation of ERK in bronchiolar and
33 alveolar type II epithelial cells, epithelial cell hyperplasia, and fibrotic lesions. Epithelial
34 cell signals through the ERK pathway lead to tissue remodeling and fibrosis [Cummins et
35 al. 2003].

36
37 Crocidolite and erionite fibers, but not non-fibrous milled riebeckite, up-regulated
38 expression of epidermal growth factor receptor (EGFR) in rat pleural mesothelial cells *in*
39 *vitro*. Cell proliferation was co-localized subsequent to EGFR, suggesting initiation of a
40 cell-signaling cascade to cell proliferation and cancer [Faux et al. 2000]. "Long" amosite
41 fibers were more active than "short" amosite fibers in causing: (1) damage to nude DNA;
42 (2) *in vitro* cytotoxicity in a human lung epithelial cell line; (3) free radical reactions; (4)
43 inhibition of glycerol-6-phosphate dehydrogenase and pentose phosphate pathways; (5)

1 decrease in intracellular reduced glutathione; (6) increase in thiobarbituric acid reaction
2 substances; and (7) leaking of LDH [Riganti et al. 2003].
3

4 An important paradox or seeming failure of *in vitro* studies concerns mesothelioma.
5 While chrysotile or amphibole asbestos fibers clearly induce malignant mesothelioma *in*
6 *vivo*, they do not transform primary human mesothelial cells *in vitro*, while erionite fibers
7 do. Asbestos fibers can induce some genotoxic changes; crocidolite fibers induced
8 cytogenotoxic effects, including increased polynucleated cells and formation of 8-OHdG
9 in a phagocytic human mesothelial cell line, but did not induce cytogenotoxic effects in a
10 non-phagocytic human promyelocytic leukemia cell line [Takeuchi et al. 1999].
11 Tremolite, erionite, RCF-1, and chrysotile fiber challenges of human-hamster hybrid
12 A(L) cells found chrysotile fibers to be significantly more cytotoxic. Mutagenicity was
13 not seen at the hypoxanthine-guanine phosphoribosyltransferase (HPRT) locus for any of
14 the fibers. Erionite and tremolite fibers induced dose-dependent mutations at the gene
15 marker on the only human chromosome in the hybrid cell. Erionite was the most
16 mutagenic type of fiber. RCF-1 fibers were not mutagenic, in seeming contrast to their
17 known induction of mesothelioma in hamsters [Okayasu et al. 1999]. Crocidolite fibers
18 induced significant but reversible DNA single-strand breaks in transformed human
19 pleural mesothelial cells; TNF- α induced marginal increases; co-exposure to crocidolite
20 fibers and TNF- α caused greater damage than fibers alone. Antioxidant enzymes did not
21 reduce the DNA damage, suggesting a mechanism of damage other than by free radicals
22 [Ollikainen et al. 1999]. Crocidolite fibers were also very cytotoxic to the cells;
23 presumably cell death may prevent the observation of cell transformation. *In vitro*
24 challenge to mesothelial cells and to fibroblast cells by crocidolite fibers, but not by glass
25 wool, induced dose-dependent cytotoxicity and increased DNA synthesis activity
26 [Cardinali et al. 2006]. Crocidolite fibers were found to induce TNF- α secretion and
27 receptors in human mesothelial cells, and TNF- α reduced cytotoxicity of crocidolite
28 fibers by activating NF- κ B and improving cell survival and permitting expression of
29 cytogenetic activity [Yang et al. 2006]. Erionite fibers transformed immortalized non-
30 tumorigenic human mesothelial cells *in vitro* only when exposed in combination with IL-
31 1 β or TNF- α [Wang et al. 2004]. Erionite fibers were poorly cytotoxic but induced
32 proliferation signals and high growth rate in hamster mesothelial cells. Long-term
33 exposure to erionite fibers resulted in transformation of human mesothelial cells *in vitro*,
34 but exposure to asbestos fibers did not transform those cells [Bertino et al. 2007]. *In vitro*
35 challenge of mesothelial cells to asbestos fibers induced cytotoxicity and apoptosis, but
36 not transformation. *In vitro* challenge of human mesothelial cells to asbestos fibers
37 induced the ferritin heavy chain of iron-binding protein, an anti-apoptotic protein, with
38 decrease in H₂O₂ and other ROS and resistance to apoptosis [Aung et al. 2007]. This was
39 seen also in a human malignant mesothelial cell line.
40

41 The question of a co-carcinogenic effect of asbestos fibers with a virus has been raised.
42 Most malignant mesotheliomas are associated with asbestos exposures, but only a
43 fraction of those exposed develop mesothelioma, indicating that other factors may play a
44 role. It has been suggested that simian virus 40 (SV40) and asbestos fibers may be co-

1 carcinogens. SV40 is a DNA tumor virus that causes mesothelioma in hamsters and has
2 been detected in several human mesotheliomas. Asbestos fibers appear to increase
3 SV40-mediated transformation of human mesothelial cells *in vitro* [Carbone et al. 2002].
4 In an *in vivo* demonstration of co-carcinogenicity of SV40 and asbestos fibers, mice
5 containing high copy number of SV40 viral oncogene rapidly developed fast-growing
6 mesothelioma following asbestos challenge. Transgenic copy number was proportional
7 to cell survival and *in vitro* proliferation [Robinson et al. 2006].
8

9 Various mechanisms exist to protect cells and tissues against oxidants, and it is
10 conceivable that genetic and acquired variations in these systems may account for
11 individual variation in the response to oxidative stress [Driscoll et al. 2002]. Similarly,
12 species differences in antioxidant defenses or the capacity of various defenses may
13 underlie differences in response to xenobiotics that act, in whole or part, through
14 oxidative mechanisms. Oxidative mechanisms of response to xenobiotics is especially
15 relevant to the respiratory tract, which is directly and continually exposed to an external
16 environment containing oxidant pollutants (e.g., ozone, oxides of nitrogen) and particles
17 which may generate oxidants as a result of chemical properties or by stimulating
18 production of cell-derived oxidants. In addition, exposure to particles or other pollutants
19 may produce oxidative stress in the lung by stimulating the recruitment of inflammatory
20 cells. For example, the toxicity of asbestos fibers likely involves the production of
21 oxidants, such as hydroxyl radical, SO, and H₂O₂. Studies have also shown that asbestos
22 fibers and other mineral particles may act by stimulating cellular production of ROS and
23 reactive nitrogen species. In addition to direct oxidant production, exposure to asbestos
24 and SVFs used in high-dose animal studies stimulates the recruitment and activation of
25 macrophages and polymorphonuclear leukocytes that can produce ROS through the
26 activity of NADPH oxidase on their cell membranes. Developing an understanding of
27 the oxidative stress/NF-κB pathway for EMP-mediated inflammation and the interplay
28 between exposure-induced oxidant production, host antioxidant defenses, and inter-
29 individual or species variability in defenses may be very important for developing
30 appropriate risk assessments of inhaled EMPs [Donaldson and Tran 2002].
31

32 2.7.4.4 Studies Comparing EMPs from Amphiboles with Asbestiform versus 33 Nonasbestiform Habits 34

35 Smith et al. [1979] compared tumor induction after IP injection in hamsters of two
36 asbestiform tremolites, two nonasbestiform prismatic tremolitic talcs, and one tremolitic
37 talc of uncertain asbestiform status. No tumors were observed following the
38 nonasbestiform tremolite challenge, in contrast to the asbestiform tremolites. However,
39 tumors were observed from the tremolitic talc of uncertain amphibole status. In rule-
40 making, OSHA [1992] noted the small number of animals in the study, the early death of
41 many animals, and the lack of systematic characterization of particle size and aspect
42 ratio. Subsequent analyses (by chemical composition) performed on the nonasbestiform
43 tremolitic talc from the study, which was not associated with mesothelioma, found 13%
44 of particles had at least a 3:1 aspect ratio [Wylie et al. 1993]. A prismatic,

1 nonasbestiform tremolitic talc and an asbestiform tremolite from the study were analyzed
2 for aspect ratio [Campbell et al. 1979]. They analyzed 200 particles of the asbestiform
3 tremolite sample and found 17% had an aspect ratio of 3:1 or greater and 9.5% had an
4 aspect ratio greater than 10:1. Analysis of 200 particles of the prismatic tremolite found
5 2.5% had an aspect ratio of 3:1 or greater and 0.5% (one particle) had an aspect ratio
6 greater than 10:1.

7
8 Wagner et al. [1982] challenged rats by IP injection using tremolite asbestos, a prismatic
9 nonasbestiform tremolite, or a tremolitic talc considered nonasbestiform containing a
10 limited number of long fibers. Only the tremolite asbestos produced tumors;
11 mesothelioma was found in 14 of 37 animals. The authors speculated that tumor rate
12 may have risen further if the testing period had not been shortened due to infection-
13 induced mortality. On a per microgram of injected dose basis, the asbestiform sample
14 contained 3.3×10^4 non-fibrous particles, 15.5×10^4 fibers, and 56.1×10^3 fibers $>8 \mu\text{m}$
15 long and $<1.5 \mu\text{m}$ wide. Corresponding values for the prismatic amphibole were $20.7 \times$
16 10^4 , 4.8×10^4 , and 0. Tremolitic talc values were 6.9×10^4 , 5.1×10^4 , and 1.7×10^3 .
17 Infection-reduced survival prevented evaluation of a crocidolite-exposed positive control.

18
19 Another IP injection study with the rat used six samples of tremolite of different
20 morphological types [Davis et al. 1991]. For three asbestiform samples, mesothelioma
21 occurred in 100%, 97%, and 97% of the animals, at corresponding doses of 13.4×10^9
22 fibers / 121×10^6 fibers with length $>8 \mu\text{m}$ and diameter $<0.25 \mu\text{m}$; $2.1 \times 10^9 / 8 \times 10^6$;
23 and $7.8 \times 10^9 / 48 \times 10^6$, respectively. For an Italian tremolite from a non-asbestos source
24 and containing relatively few asbestiform fibers ($1.0 \times 10^9 / 1 \times 10^6$), mesothelioma was
25 found in two-thirds of the animals, with delayed expression. For two nonasbestiform
26 tremolites ($0.9 \times 10^9 / 0$; $0.4 \times 10^9 / 0$), tumors were found in 12% and 5% of the animals,
27 respectively; at least the former was above expected background levels. The Italian
28 sample resulting in 67% mesothelioma incidence contained only one-third the number of
29 EMPs $>8 \mu\text{m}$ long compared to the nonasbestiform sample associated with 12%
30 mesothelioma, and those two samples contained an approximately equal number of fibers
31 with length $>8 \mu\text{m}$ and width $<0.5 \mu\text{m}$. The preparation of the three asbestiform samples
32 and the Italian sample were essentially identical. However, the two nonasbestiform
33 samples associated with low mesothelioma incidence required significantly different pre-
34 treatment, the first requiring multiple washing and sedimentation and the second grinding
35 under water in a micronizing mill. It was noted that those two nonasbestiform samples
36 and the Italian sample contained minor components of long, thin asbestiform tremolite
37 fibers. This study suggested that carcinogenicity may not depend simply on the number
38 of EMPs and called for methods of distinguishing "carcinogenic tremolite fibers" from
39 non-fibrous tremolite dusts that contain similar numbers of EMPs of similar aspect ratios
40 [Davis et al. 1991]. It has been suggested that the response observed for the Italian
41 tremolite is of a pattern expected for a low dose of highly carcinogenic asbestos tremolite
42 [Addison 2007].
43

1 A recent review of past studies of varieties of tremolite and the limitations of earlier
2 studies (e.g., their use of injection or implantation versus inhalation) suggested that,
3 based on observed differences in the carcinogenicity of tremolite asbestos and
4 nonasbestiform prismatic tremolite, differences in carcinogenicity of amphibole asbestos
5 fibers and nonasbestiform amphibole cleavage fragments are sufficiently large to be
6 discernable even with the study limitations [Addison and McConnell 2008]. The authors
7 also concluded the evidence supports a view that shorter, thicker cleavage fragments of
8 the nonasbestiform amphiboles are less hazardous than the thinner asbestos fibers
9 [Addison and McConnell 2008].

10
11 In summary, several types of animal studies have been conducted to assess the
12 carcinogenicity and fibrogenicity of asbestiform and nonasbestiform tremolite fibers and
13 other EMPs. Tremolite asbestos was found to be both fibrogenic and carcinogenic in rats
14 by inhalation. However, the data for other particle forms of tremolite and for other
15 amphiboles in general are much more limited, and is based primarily on mesotheliomas
16 produced by intrapleural administration studies in rats. These studies bypass the lung
17 entirely, and thus provide no information on the test material's potential for causing lung
18 tumors. In addition, they have often been criticized for employing a non-physiological
19 route of administration. Some of the older studies [Smith et al. 1979; Wagner et al. 1982]
20 are difficult to interpret due to inadequate characterization of the tremolite preparation
21 that was used, although the studies do tend to show fewer tumors from prismatic
22 tremolite than from asbestiform tremolite. Unfortunately, doses used in most animal
23 studies are generally reported in terms of mass (e.g., 10, 25, or 40 mg/rat). Unless the
24 test preparations are well characterized in terms of fiber counts and fiber size
25 distributions, it is difficult to relate the mass-based dose in the animals to fiber count
26 measurements used to assess human occupational exposures. Where semi-quantitative
27 fiber count and size distribution data are given, as in the Davis et al. [1991] study, it is
28 evident that the prismatic tremolite samples contain fewer countable fibers per 10 mg
29 dose than the asbestiform tremolite samples. Although the prismatic tremolite samples
30 clearly generated fewer mesotheliomas than the asbestiform tremolite samples, it is not
31 apparent whether the tumorigenic potency per fiber is lower for the nonasbestiform
32 tremolites.

33
34 Cellular *in vitro* assays used LDH release, beta-glucuronidase release, cytotoxicity, and
35 giant cell formation to compare two nonasbestiform and one asbestiform tremolites,
36 finding relative toxicities parallel to the differences seen in an *in vivo* rat IP injection
37 study of tumorigenicity using the same samples [Wagner et al. 1982]. *In vitro* cellular or
38 organ tissue culture studies showed squamous metaplasia and increased DNA synthesis
39 in tracheal explant cultures treated with long glass fibers or with crocidolite or chrysotile
40 fibers, while cleavage fragments from their nonasbestiform analogues, riebeckite and
41 antigorite, were not active [Woodworth et al. 1983]. For alveolar macrophages *in vitro*,
42 crocidolite fibers induced the release of ROS an order of magnitude greater than cleavage
43 fragments from nonasbestiform riebeckite [Hansen and Mossman 1987]. Similar
44 differences were observed in hamster tracheal cells for:

- 1 • induction of ornithine decarboxylase, an enzyme associated with mouse skin cell
- 2 proliferation and tumor promotion [Marsh and Mossman 1988];
- 3 • stimulating survival or proliferation in a colony-forming assay using those
- 4 hamster tracheal epithelial cells [Sesko and Mossman 1989];
- 5 • activation of proto-oncogenes in tracheal epithelial and pleural mesothelial cells
- 6 *in vitro* [Janssen et al. 1994]; and
- 7 • cytotoxicity [Mossman and Sesko 1990].

8
9 A recent review concludes that a large body of work shows that asbestos fibers have been
10 most active in a number of *in vitro* bioassays comparing activities of a variety of asbestos
11 fibers and other nonpathogenic fibers or particles, while cleavage fragments of
12 amphiboles are less potent than asbestos fibers [Mossman 2008].

13
14 These are a fraction of the extensive number of studies that have provided detailed
15 information on some of the biomolecular mechanisms induced in cells by EMP exposure,
16 suggesting some bases underlying applied questions of relative toxicities and
17 pathogenicities of asbestiform and nonasbestiform EMPs. Seemingly contradictory
18 implications between some experiments suggest that new methods for preparation and
19 characterization of EMPs may be needed. Also, careful attempts to identify *in vitro* and
20 *in vivo* conditions which may unexpectedly influence the initiation or promotion of cell
21 damage and progression to disease may aid the further elucidation of EMP properties and
22 conditions of exposure determining disease risk.

23
24 The number of animal studies of nonasbestiform amphibole dusts is limited. To date this
25 research has found generally significant differences in pathogenicity between
26 nonasbestiform and asbestiform amphiboles. Within these studies, there are few findings
27 of biological effects or tumorigenicity induced by samples classified as nonasbestiform,
28 and there are rational hypotheses as to the cause of those effects. There are general
29 fundamental uncertainties concerning EMP properties and biological mechanisms that
30 determine mineral particle toxicities and pathogenicities, and specifically concerning the
31 similarities or differences in disease mechanisms between EMPs from asbestiform versus
32 nonasbestiform amphiboles. *In vitro* studies have generally found differences in specific
33 toxic activities between some asbestiform and nonasbestiform amphibole EMPs, although
34 *in vitro* systems are not yet able to predict relative pathogenic risk for mineral fibers and
35 other EMPs. This suggests a focus of research to determine if and when nonasbestiform
36 amphibole EMPs are active for tumorigenicity or other pathology, if there is a threshold
37 for those activities, and if distinguishing conditions or properties that determine such
38 pathogenicity can be found.

39 40 **2.7.5 Thresholds**

41
42 Discussions of thresholds for adverse health effects associated with exposure to asbestos
43 fibers and related EMPs have focused on the characteristics of dimension, including

1 length, width, and the derived aspect ratio, as well as concentration. Although other
2 particle characteristics discussed above may impact these thresholds, or may have
3 thresholds of their own that impact the toxicity of EMPs, they are not well discussed in
4 the literature. The following discussion is focused on thresholds for dimension and
5 concentration.

6
7 The seminal work of Stanton et al. [1981] laid the foundation for much of the information
8 on dimensional thresholds. Their analyses found that malignant neoplasms in exposed
9 rats were best predicted by the number of EMPs longer than 8 μm and thinner than 0.25
10 μm . However, the number of EMPs in other size categories having lengths greater than 4
11 μm and widths up to 1.5 μm were also highly correlated with malignant neoplasms.
12 Also, some samples with relatively larger proportions of shorter particles, such as the
13 tremolites, produced high rates of tumors. Lippmann [1988, 1990] reviewed the
14 literature and suggested that lung cancer is most closely associated with asbestos fibers
15 longer than 10 μm and thicker than 0.15 μm , while mesothelioma is most closely
16 associated with asbestos fibers longer than 5 μm and thinner than 0.1 μm . Evidence from
17 animal studies and some *in vitro* studies suggests that short asbestos fibers (e.g., <5 μm
18 long) may play a role in fibrosis, but are of lesser concern than longer asbestos fibers for
19 cancer development.

20
21 Berman et al. [1995] statistically analyzed aggregate data from 13 inhalation studies in
22 which rats were exposed to 9 types of asbestos (4 chrysotiles, 3 amosites, a crocidolite,
23 and a tremolite asbestos) to assess fiber dimension and mineralogy as predictors of lung
24 tumor and mesothelioma risks. Archived samples from the studies were reanalyzed to
25 provide detailed information on each asbestos structure, including mineralogy (i.e.,
26 chrysotile, amosite, crocidolite, or tremolite), size (i.e., length and width, each in 5
27 categories), type (i.e., fiber, bundle, cluster, or matrix), and complexity (i.e., number of
28 identifiable components of a cluster or matrix). Multiple concentrations (each for
29 asbestos structures with different specified characteristics) were calculated for the
30 experimental exposures. While no univariate index of exposure adequately described
31 lung tumor incidence observed across all inhalation studies, certain multivariate indices
32 of exposure did adequately describe outcomes. Fibers and bundles longer than 5 μm and
33 thinner than 0.4 μm contributed to lung tumor risk; very long (≥ 40 μm) and very thick
34 (≥ 5 μm) complex clusters and matrices possibly contributed. While structures <5 μm
35 long did not contribute to lung tumor risk, potency of thin (<0.4 μm) structures increased
36 with increasing length above 5 μm and structures ≥ 40 μm long were estimated to be
37 about 500 times more potent than structures between 5 and 40 μm long. With respect to
38 lung tumor risk, no difference was observed between chrysotile and amphibole asbestos.
39 With respect to mesothelioma risk, chrysotile was found to be less potent than amphibole
40 asbestos. While the Berman et al. [1995] analysis was limited to studies of asbestos
41 exposure, similar statistical approaches may be adaptable to assess study outcomes from
42 exposures to a broader range of EMPs beyond asbestos.

43

1 In addressing the issue of a length threshold, the Health Effects Institute [HEI 1991]
2 concluded that asbestos fibers <5 μm long appear to have much less carcinogenic activity
3 than longer fibers and may be relatively inactive. A panel convened by the ATSDR
4 [2003] concluded that “given findings from epidemiological studies, laboratory animal
5 studies, and *in vitro* genotoxicity studies, combined with the lung’s ability to clear short
6 fibers, the panelists agreed that there is a strong weight of evidence that asbestos and
7 SVFs shorter than 5 μm are unlikely to cause cancer in humans.” Also, an EPA [2003]
8 peer consultant panel “agreed that the available data suggest that the risk for fibers <5 μm
9 long is very low and could be zero.” They also generally agreed that the width cut-off
10 should be between 0.5 and 1.5 μm , but deserved further analysis.

11
12 However, Dodson et al. [2003] have argued that it is difficult to rule out the involvement
13 of short (<5 μm) asbestos fibers in causing disease because exposures to asbestos fibers
14 are overwhelmingly comprised of fibers shorter than 5 μm and fibers observed in the
15 lung and in extrapulmonary locations are also overwhelmingly shorter than 5 μm . For
16 example, in a study of malignant mesothelioma cases, Suzuki and Yuen [2002] and
17 Suzuki et al. [2005] found that the majority of asbestos fibers in lung and mesothelial
18 tissues were shorter than 5 μm .

19
20 NIOSH investigators have recently evaluated the relationship between the dimensions
21 (i.e., length and width) of airborne chrysotile fibers and risks for developing lung
22 cancer or asbestosis by updating the cohort of chrysotile-exposed textile workers
23 previously studied by Dement et al. [1994], Stayner et al. [1997], and Hein et al. [2007].
24 Archived airborne samples collected at this chrysotile textile plant were re-analyzed by
25 TEM to generate exposure estimates based on bivariate fiber-size distribution [Dement et
26 al. 2008]. TEM analysis of sampled fibers found all size-specific categories (35
27 categories were assigned based on combinations of fiber width and length) to be highly
28 statistically significant predictors of lung cancer and asbestosis [Stayner et al. 2007]. The
29 smallest fiber size-specific category was thinner than 0.25 μm and $\leq 1.5 \mu\text{m}$ long. The
30 largest size-specific category was thicker than 3.0 μm and $>40 \mu\text{m}$ long. Both lung
31 cancer and asbestosis were most strongly associated with exposures to thin fibers (<0.25
32 μm), and longer fibers (>10 μm) were found to be the strongest predictors of lung cancer.
33 A limitation of the study is that cumulative exposures for the cohort were highly
34 correlated across all fiber-size categories, which complicates the interpretation of the
35 study results.

36
37 In addition to length and width, an important parameter used to define EMPs is the aspect
38 ratio. The use of the 3:1 length:width aspect ratio as the minimum to define an EMP was
39 not established on scientific bases such as toxicity or exposure potential. Rather the
40 decision was based on the ability of the microscopist to determine the elongate nature of
41 a particle [Holmes 1965], and the practice has been carried through to this day. As
42 bivariate analyses are conducted, the impact of aspect ratio, in addition to length and
43 width, on toxicity and health outcomes needs to be addressed.

44

1 As discussed in Section 2.4.2, the nature of occupational exposures to asbestos has
2 changed over the last several decades. Once dominated by chronic exposures in textile
3 mills, friction product manufacturing, and cement pipe fabrication, current occupational
4 exposures to asbestos in the United States are primarily occurring during maintenance
5 activities or remediation of buildings containing asbestos. These current occupational
6 exposure scenarios frequently involve short-term, intermittent exposures. The generally
7 lower current exposures give added significance to the question of whether or not there is
8 an asbestos exposure threshold below which workers would incur no risk of adverse
9 health outcomes.

10
11 Risk assessments of workers occupationally exposed to asbestos were reviewed by
12 investigators sponsored by the Health Effects Institute [1991]. They found that dose-
13 specific risk is highly dependent on how the measurement of dose (exposure) was
14 determined. A common problem with many of the epidemiological studies of workers
15 exposed to asbestos was the quality of the exposure data. Few studies have good
16 historical exposure data and those data which were available are mostly area samples
17 with concentrations reported as millions of particles per cubic foot of air (mppcf).
18 Although correction factors were used to convert exposures measured in mppcf to f/cm^3 ,
19 the conversions were often based on more recent exposure measurements collected at
20 concentrations lower than those prevalent in earlier years. In addition, a single
21 conversion factor was typically used to estimate exposures throughout a facility, which
22 may not accurately represent differences in particle sizes and counts at different processes
23 in the facility.

24
25 More recently, the concept of a concentration threshold has been reviewed by Hodgson
26 and Darnton [2000]. It is generally accepted that lung fibrosis requires relatively heavy
27 exposure to asbestos and that the carcinogenic response of the lung may be an extension
28 of the same inflammatory processes that produce lung fibrosis. Some evidence for a
29 threshold is provided by an analysis of a chrysotile-exposed cohort, which suggests a
30 potential threshold dose of about 30 f/mL-yr to produce radiologically evident fibrosis
31 [Weill 1994]. Another study of necropsy material from textile workers exposed to
32 chrysotile shows a distinct step increase in fibrosis for exposures in the 20–30 f/mL-yr
33 range [Green et al. 1997]. However, a study of textile mill workers exposed to chrysotile
34 did not find evidence for significant concentration thresholds for either asbestosis or lung
35 cancer [Stayner et al. 1997]. Hodgson and Darnton [2000] pointed out that any evidence
36 suggesting a threshold for chrysotile would likely not apply to amphibole asbestos
37 because radiologically evident fibrosis has been documented among workers exposed to
38 amphibole asbestos at low levels (<5 f/mL-yr). They concluded that if a concentration
39 threshold exists for amphiboles, it is very low.

40
41 For mesothelioma, Hodgson and Darnton [2000] identified cohorts with high rates of
42 mesothelioma at levels of exposure below those at which increased lung cancer has been
43 identified; in some studies, the proportion of mesothelioma cases with no likely asbestos

1 exposure is much higher than expected. Hodgson and Darnton [2000] concluded that
2 these studies support a non-zero risk, even from brief, low-level exposures:
3

4 Animal studies using intraperitoneal and intrapleural injection of asbestos fibers cited by
5 Ilgren and Browne [1991] suggest a possible threshold concentration for mesothelioma.
6 However, it is not clear how this would be useful to determine a threshold for inhalation
7 exposure in humans.
8

9 **2.8 Analytical Methods**

10
11 Available analytical methods can characterize the size, morphology, elemental
12 composition, crystal structure, and surface composition of bulk materials and individual
13 airborne particles. There are two separate paradigms for selecting among these methods
14 for their use or further development for application to EMPs: one is for their support of
15 standardized surveys or compliance assessments of workplace exposures to EMPs;
16 another is for their support of research to identify physicochemical properties of EMPs
17 that are critical to predicting toxicity or pathogenic potential for lung fibrosis, cancer, or
18 mesothelioma. The former refers to analytical methods that can be applied to samples of
19 airborne particles, while the latter can be used to characterize airborne particles and bulk
20 materials.
21

22 Cost, time, availability, standardization requirements, and other pragmatic factors limit
23 the selection of analytical methods for standardized analysis of field samples for the first
24 set of uses. Additionally, those uses require methods with an historic established
25 association with disease risk. Principal among these analyses for standardized industrial
26 hygiene use is an optical microscopy method — PCM (e.g., the NIOSH Method 7400 or
27 equivalent) [NIOSH 1994a]. Under the current NIOSH REL for airborne asbestos fibers,
28 particles are counted if they are EMPs (i.e., mineral particles with an aspect ratio
29 [length:width] of 3:1 or greater) of the covered minerals and they are longer than 5 μm
30 when viewed microscopically using NIOSH Method 7400 or its equivalent. The
31 assumption when using this method is that all particles meeting the dimensional criteria
32 are airborne asbestos fibers because PCM cannot identify the chemistry or crystalline
33 structure of a particle. This assumption may be appropriate in situations where the
34 majority of particles are reasonably assumed to be one of the minerals included in the
35 airborne asbestos fiber REL. Electron microscopy can be used to determine the actual
36 proportion of the total particles that are covered by the airborne asbestos fiber REL, and
37 this proportion can be used to adjust the count from PCM (NIOSH Method 7402)
38 [NIOSH 1994b]. Such counts are known as PCM-equivalents or PCMe. Note that this is
39 not the same procedure as counting particles that would meet the PCM criteria under the
40 electron microscope. Methods for performing counts under both scanning electron
41 microscopy (SEM) [ISO 2002] and transmission electron microscopy (TEM) [U.S. Code
42 of Federal Regulations 2001] have been developed. However, only a few countries (e.g.
43 Germany, Austria, Netherlands and Switzerland) use SEM routinely for counting. The
44 EPA uses TEM for counting.

1
2 Characterization of bulk minerals is a process known as petrographic analysis.
3 Petrographic analysis includes a number of techniques including polarized light
4 microscopy (PLM), electron microscopy (scanning electron microscopy [SEM], or
5 transmission electron microscopy [TEM]), x-ray diffraction (XRD), x-ray fluorescence
6 (XRF), and electron microprobe analysis. Other techniques, such as infra-red and Raman
7 spectroscopy and surface area measurements, can also be used. Some of these techniques
8 can also be applied to individual airborne particles. If it is determined that the toxicity of
9 EMPs has a basis in properties that can be measured by one or more of these techniques,
10 then it may be possible to tailor analytical procedures in the future to more precisely
11 estimate risk.

12
13 Care should be taken in developing or applying new analytical methods to the analysis of
14 asbestos for standardized and compliance assessments. The use of new or different
15 analytical methods to assess exposures must be carefully evaluated and validated to
16 ensure that they measure exposures covered by the health protection standard. The
17 sampling and analytical methods for assessing *workplace* exposures to EMPs have
18 different constraints from methods used to assess *environmental* exposures. NIOSH is
19 focused on developing and validating methods for assessing workplace exposures to
20 EMPs and provides assistance in developing environmental exposure methods, where
21 possible, and appropriate through its relationships with other federal agencies.

22 23 **2.8.1 NIOSH Sampling and Analytical Methods for Standardized Industrial Hygiene** 24 **Surveys**

25
26 The analytical components of NIOSH's REL for asbestos exposure take on substantial
27 significance because the current REL was set on the basis of the limit of quantification
28 (LOQ) of the PCM method using a 400-L sample, rather than solely on estimates of the
29 health risk. Had a lower LOQ been possible, a lower REL may have been proposed to
30 further reduce the risk of occupational cancer among asbestos-exposed workers. With
31 the change from an 8-hour TWA to a 100-minute TWA, and advances in sampling pump
32 capabilities, using sampling pumps at the 16 L/min maximum flow rate of the method for
33 100 minutes provides a 1600-L sample, which would allow quantitation of about 0.04
34 f/cm³, provided there is no excessive interference from other dust.

35
36 PCM was designated as the principal analytical method for applying the REL because it
37 was thought to be the most practical and reliable available method, particularly for field
38 assessments. The particle counting rules specified for PCM analysis of air samples result
39 in an index of exposure which has been used with human health data for risk assessment.
40 PCM-based counts do not enumerate all EMPs because very thin particles, such as
41 asbestos fibrils, are typically not visible by PCM when using NIOSH Method 7400. The
42 ratio of countable EPs to the total number of EPs collected on air samples can therefore
43 vary for samples collected within the same workplace, as well as between different
44 workplaces where the same or different asbestos materials are handled [Dement and

1 Wallingford 1990]. The result of this is that equivalent PCM asbestos exposure
2 concentrations determined at different work places would be considered to pose the same
3 health risk, when, in fact, those risks may be different due to unknown amounts of
4 unobserved fibers on the samples. It is commonly stated that particles thinner than about
5 0.2–0.25 μm typically cannot be observed with PCM because they are below the
6 resolution limits of the microscope. However, the results for PCM counts may also vary
7 depending on the index of refraction of the object being examined. When the index of
8 refraction of the particle is similar to that of the filter substrate or mounting medium, the
9 ability to resolve particles is less than when the refractive index of the particle differs
10 from that of the substrate [Kenny and Rood 1987]. When a microscope is calibrated
11 appropriately for NIOSH Method 7400, and triacetin is used as the mounting medium,
12 calculation and experiment have indicated that chrysotile fibers as thin as 0.15 μm can be
13 resolved [Rooker et al. 1982], which implies that amphibole fibers thinner than 0.2 μm
14 and with higher refractive index may actually be visible and potentially counted.

15
16 Individual asbestos fibrils range in width from <10 nm (0.01 μm) for chrysotile up to 40
17 nm (0.04 μm) or more for amosite. Thus, individual asbestos fibrils are not likely to be
18 visible under PCM. However, asbestos particles of 3:1 aspect ratio and longer than 5 μm
19 are not usually individual fibrils, but fibrillar bundles that are much wider than fibrils
20 [Hwang and Gibbs 1981; further data cited in Walton 1982], so that the number of
21 particles meeting these criteria counted under PCM has not generally been found to differ
22 greatly from the number of particles meeting the same criteria counted under the electron
23 microscope [Lynch et al. 1970; Hwang and Gibbs 1981; Marconi et al. 1984; Dement and
24 Wallingford 1990]. Also, silicate mineral particles thinner than the resolution of PCM in
25 NIOSH Method 7400 are in the same size range as the deposition minimum observed for
26 small particles in human respirable particle studies. Current standards for assessing
27 particle dose are based on particle penetration into the human respiratory system which
28 may overestimate deposition [ISO 1995a]. More recently, proposals have been
29 developed to account for deposition [Vincent 2005]. In addition, a single large bundle
30 may be the source of a great many fibrils in the lung because the larger fibrillar bundles
31 are known to split apart into individual fibrils in the lung. For these reasons, asbestos
32 particles visible by PCM may contribute more to risk than those that are not visible,
33 lending credibility to PCM counts as an index of risk.

34
35 Another aspect of NIOSH Method 7400 is that two sets of counting rules are specified
36 depending on the type of fiber analysis. The rules for counting particles for asbestos
37 determination, referred to as the “A” rules, instruct the microscopist to count EPs of any
38 width that are longer than 5 μm and have an aspect ratio of at least 3:1. However, EPs
39 wider than 3 μm are not likely to reach the thoracic region of the lung when inhaled. The
40 “B” counting rules, which are used to evaluate airborne exposure to other EPs, specify
41 that only EPs thinner than 3 μm and longer than 5 μm should be counted [NIOSH
42 1994a]. The European Union is moving toward a standardized PCM method for
43 evaluating asbestos exposures using counting rules recommended by the World Health

1 Organization (WHO), which specify counting only EPs thinner than 3 μm and with a 3:1
2 or larger aspect ratio [WHO 1997; European Parliament and Council 2003].

3 4 **2.8.2 Analytical Methods for Research**

5
6 For research purposes, it may be important for a more expansive set of analyses to be
7 considered. However, EMPs thinner than the limit of spatial resolution of the optical
8 microscope are thought to be important etiologic agents for disease, so other detection
9 and measurement methods may be needed for improved investigations of the relationship
10 between fiber dimension and disease outcomes.

11
12 TEM has much greater resolving power than optical microscopy, on the order of 0.001
13 μm . Additionally, TEM has the ability to semi-quantitatively determine elemental
14 composition by using EDS. Incident electrons excite electronic states of atoms of the
15 sample, and the atoms decay that excess energy either by emitting an X-ray of frequency
16 specific to the element (X-ray spectroscopy) or by releasing a secondary electron with
17 equivalent kinetic energy (an Auger electron). Furthermore, TEM can provide some
18 level of electron diffraction (ED) analysis of particle mineralogy by producing a mineral-
19 specific diffraction pattern based on the regular arrangement of the particle's crystal
20 structure [Egerton 2005].

21
22 The greater spatial resolving power and the crystallographic analysis abilities of TEM
23 and TEM-ED are used in some cases for standardized workplace industrial hygiene
24 characterizations. TEM methods (e.g., NIOSH 7402) are used to complement PCM in
25 cases where there is apparent ambiguity in EMP identification [NIOSH 1994b] and,
26 under the Asbestos Hazardous Emergency Response Act of 1986, the EPA requires that
27 TEM analysis be used to ensure the effective removal of asbestos from schools [EPA
28 1987]. Each of these methods employs specific criteria for defining and counting
29 visualized fibers and report different fiber counts for a given sample. These data
30 subsequently can be independently interpreted according to different definitional criteria,
31 such as those developed by the International Organization for Standardization (ISO),
32 which provides methods ISO 10312 and ISO 13794 [ISO 1995b, 1999].

33
34 Improved analytical methods that have become widely available should be re-evaluated
35 for complementary research applications or for ease of applicability to field samples.
36 Scanning electron microscopy (SEM) is now generally available in research labs and
37 commercial analytical service labs. SEM resolution is on the order of ten times that of
38 optical microscopy, and newly commercial field emission SEM (FESEM) can improve
39 this resolution to about 0.01 μm or better, near that of TEM. SEM-EDS and SEM-
40 wavelength dispersive spectrometers (WDS) can identify the elemental composition of
41 particles. It is not clear that SEM-backscatter electron diffraction analysis can be adapted
42 to crystallographic analyses equivalent to TEM-ED capability. Ease of sample collection
43 and preparation for SEM analysis compared to TEM, and some SEM advantages in
44 visualizing fields of EMPs and EMP morphology, suggest that SEM methods should be

1 re-evaluated for EMP analyses both for field sample analyses and for research [Goldstein
2 2003].

3
4 Research on mechanisms of EMP toxicity includes concerns for surface-associated
5 factors. To support this research, elemental surface analyses can be performed by
6 scanning Auger spectroscopy on individual particles with widths near the upper end of
7 SEM resolution. In scanning Auger spectroscopy, the Auger electrons stimulated by an
8 incident electron beam are detected; the energy of these secondary electrons is low,
9 which permits only secondary electrons from near-surface atoms to escape and be
10 analyzed, thus analyzing the particle elemental composition to a depth of only one or a
11 few atomic layers [Egerton 2005]. This method has been used in some pertinent research
12 studies (e.g., assessing effects on toxicity of leaching Mg from chrysotile fiber surfaces)
13 [Keane et al. 1999]. Currently, this form of analysis is time-consuming and not ideal for
14 the routine analysis of samples collected from field studies.

15
16 Surface elemental composition and limited valence state information on surface-borne
17 elements can be obtained by X-ray photoelectron spectroscopy (XPS or ESCA), albeit
18 not for individual particles. XPS uses X-ray excitation of the sample, rather than electron
19 excitation as used in SEM-EDS or TEM-EDS. The X-rays excite sample atom electrons
20 to higher energy states, which then can decay by emission of photoelectrons. XPS
21 detects these element-specific photoelectron energies, which are weak and therefore
22 emitted only near the sample surface, similar to the case of Auger electron surface
23 spectroscopy. In contrast to scanning Auger spectroscopy, XPS can in some cases
24 provide not only elemental but also valence state information on atoms near the sample
25 surface. However, in XPS the exciting X-rays cannot be finely focused on individual
26 fibers, so analysis is made of an area larger than single particle [Watts and Wolstenholme
27 2003]. Thus, analysis of a mixed-composition dust sample would be confounded; so XPS
28 is applicable only to some selected or prepared homogeneous materials or to pure field
29 samples.

30 31 ***2.8.3 Differential Counting and Other Proposed Analytical Approaches for*** 32 ***Differentiating EMPs***

33
34 When used to assess asbestos fiber counts in mixed exposures, the use of PCM to
35 determine concentrations of airborne fibers from asbestos minerals cannot ensure that
36 EMPs from nonasbestiform minerals are excluded. Reliable and reproducible analytical
37 methods are not available for air samples to distinguish between asbestos fibers and
38 EMPs from nonasbestiform analogs of the asbestos minerals. The lack of reliable and
39 validated analytical methods that can make these distinctions on individual fibers in air
40 samples is clearly a major limitation in applying the airborne asbestos fiber definitions of
41 federal agencies.

42
43 A technique referred to as “differential counting,” suggested as an approach to
44 differentiate between asbestiform and nonasbestiform EMPs, is mentioned in a non-

1 mandatory appendix to the OSHA asbestos standard. That appendix points out that the
2 differential counting technique requires “a great deal of experience” and is “discouraged
3 unless legally necessary.” It relies heavily on subjective judgment and does not appear to
4 be commonly used except for samples from mines. In this technique, EMPs that the
5 microscopist judges as nonasbestiform (e.g., having the appearance of cleavage
6 fragments) are not counted; any EMPs not clearly distinguishable as either asbestos or
7 nonasbestos using differential counting are to be counted as asbestos fibers. One effect
8 of using differential counting is to introduce an additional source of variability in the
9 particle counts caused by different “reading” tendencies between microscopists. The
10 technique has not been formally validated and has not been recommended by NIOSH.

11
12 For counting airborne asbestos fibers in mines and quarries, ASTM has proposed
13 “discriminatory counting” that incorporates the concepts of differential counting. The
14 proposed method uses PCM and TEM in a tiered scheme. Air samples are first analyzed
15 by PCM. If the initial PCM fiber count exceeds the MSHA permissible exposure limit
16 (PEL), TEM is performed to determine an equivalent PCM count of regulated asbestos
17 fibers only. If the initial PCM count is greater than one-half the PEL but less than the
18 PEL, discriminatory counting is then performed. Discriminatory counts are restricted to
19 fiber bundles, fibers longer than 10 μm , and fibers thinner than 1.0 μm . If the
20 discriminatory count is at least 50% of the initial PCM fiber count, TEM is performed to
21 determine an equivalent PCM count of regulated asbestos fibers only. These results are
22 then compared to regulatory limits [ASTM 2006].

23
24 ASTM has begun an interlaboratory study (ILS#282) to determine the interlaboratory
25 precision of “binning” fibers into different classes based on morphology [Harper et al.
26 2007]. The first part of the validation process was to evaluate samples of ground massive
27 or coarsely crystalline amphiboles and air samples from a taconite mine which have
28 amphibole particulates, where the majority are characterized as cleavage fragments.
29 Almost none of the observed particles met the Class 1 criteria (i.e., potentially
30 asbestiform based on curved particles and/or fibril bundles). Many particles were
31 classified as Class 2 (i.e., potentially asbestiform based on length $>10 \mu\text{m}$ or width <1
32 μm), although their morphology suggested they were more likely cleavage fragments.
33 Using alternative criteria for Class 2 (length $>10 \mu\text{m}$ and width $<1 \mu\text{m}$), the number of
34 Class 2 particles was greatly reduced. However, evidence from the literature [Dement et
35 al. 1976; Griffis et al. 1983; Wylie et al. 1985; Siegrist and Wylie 1980; Beckett and
36 Jarvis 1979; Myojo 1999] indicates that as much as 50% of airborne asbestos fibers are
37 $<10 \mu\text{m}$ long. The proportion of asbestos fibers in the length “bin” bracketed by 5 μm
38 and 10 μm was also quite large (about 30%), and the adoption of the alternate Class 2
39 criteria as length $>10 \mu\text{m}$ and width $<1 \mu\text{m}$ would cause this proportion of asbestos fibers
40 to be classified as nonasbestiform and excluded from counts of asbestos fibers [Harper et
41 al. 2008b].

42
43 Other procedures have been suggested with the intent of ensuring that the counts on air
44 samples do not include cleavage fragments [IMA-NA 2005; NSSGA 2005]. These

1 procedures include reviewing available geological information and/or results from
2 analysis of bulk materials to establish that asbestos is present in the sampled
3 environment, or specifying dimensional criteria to establish that airborne particulates
4 have population characteristics typical of asbestos fibers (e.g., mean particle aspect ratios
5 exceeding 20:1).
6

7 For research purposes, it is critically important that an analytical method that is able to
8 clearly distinguish between asbestiform and nonasbestiform EMPs be developed,
9 validated, and used. Whether any of these suggested procedures would ensure adequate
10 health protection for exposed workers is unclear, and the practical issues associated with
11 implementing these supplemental procedures are also undetermined.
12

13 **2.9 NIOSH's 1990 Recommendation for Occupational Exposure to Asbestos**

14

15 The NIOSH REL for asbestos has been described in NIOSH publications and in formal
16 comments and testimony submitted to the Department of Labor. The recommendation
17 was based on the Institute's understanding in 1990 of potential hazards, the ability of the
18 analytical methods to distinguish and count fibers, and the prevailing mineral definitions
19 used to describe covered minerals.
20

21 **2.9.1 Comments to OSHA [NIOSH 1990a]**

22

23 *The NIOSH definition of minerals to be included in the regulatory standard for*
24 *asbestos is as follows:*
25

26 *Asbestos is defined as chrysotile, crocidolite, amosite (cummingtonite-grunerite),*
27 *anthophyllite, tremolite, and actinolite. The nonasbestiform habits of the*
28 *serpentine minerals antigorite and lizardite, and the amphibole minerals*
29 *contained in the series cummingtonite-grunerite, tremolite-ferroactinolite, and*
30 *glaucophane-riebeckite shall also be included provided they meet the criteria for*
31 *a fiber as ascertained on a microscopic level. A fiber is defined as a particle with*
32 *an aspect ratio of 3:1 or larger and having a length >5 μm .*
33

34 *The determinations of airborne fiber concentrations are made microscopically*
35 *and can be determined using NIOSH Method 7400 [PCM], or its equivalent. In*
36 *those cases when asbestos and other mineral fibers occur in the same*
37 *environment, then Method 7400 can be supplemented by the use of NIOSH*
38 *Method 7402 [TEM], or its equivalent, to improve specificity of the mineral*
39 *determination.*
40
41
42
43
44

2.9.2 Testimony at OSHA Public Meeting [NIOSH 1990b]

NIOSH has attempted to incorporate the appropriate mineralogical nomenclature in its recommended standard for asbestos and recommends the following to be adopted for regulating exposures to asbestos:

The current NIOSH asbestos recommended exposure limit is 100,000 fibers greater than 5 micrometers in length per cubic meter of air, as determined in a sample collected over any 100-minute period at a flow rate of 4L/min. This airborne fiber count can be determined using NIOSH Method 7400, or equivalent. In those cases when mixed fiber types occur in the same environment, then Method 7400 can be supplemented with electron microscopy, using electron diffraction and microchemical analyses to improve specificity of the fiber determination. NIOSH Method 7402 ... provides a qualitative technique for assisting in the asbestos fiber determinations. Using these NIOSH microscopic methods, or equivalent, airborne asbestos fibers are defined, by reference, as those particles having (1) an aspect ratio of 3 to 1 or greater; and (2) the mineralogical characteristics (that is, the crystal structure and elemental composition) of the asbestos minerals and their nonasbestiform analogs. The asbestos minerals are defined as chrysotile, crocidolite, amosite (cummingtonite-grunerite), anthophyllite, tremolite, and actinolite. In addition, airborne cleavage fragments³ from the nonasbestiform habits of the serpentine minerals antigorite and lizardite, and the amphibole minerals contained in the series cummingtonite-grunerite, tremolite-ferroactinolite, and glaucophane-riebeckite shall also be counted as fibers provided they meet the criteria for a fiber when viewed microscopically.

2.9.3 Clarification of the NIOSH Recommended Exposure Limit

As described in the preceding sections, uncertainty remains concerning the adverse health effects that may be caused by nonasbestiform EMPs encompassed by NIOSH since 1990 in the REL for asbestos. In addition, current analytical methods still cannot reliably differentiate between fibers from the asbestos minerals and other EMPs in mixed-dust environments. NIOSH recognizes that its descriptions of the REL since 1990 have created confusion and caused many to infer that the additional covered minerals were included by NIOSH in its definition of "asbestos." NIOSH wishes to make clear that such nonasbestiform minerals are not "asbestos" or "asbestos minerals." NIOSH also wishes to minimize any potential future confusion by no longer referring to particles from the nonasbestiform analogs of the asbestos minerals as "asbestos fibers." However, as

³ NIOSH intended the term "cleavage fragment" to include all elongate particles from the nonasbestiform habits of the specified serpentine minerals and amphibole minerals. This includes more particle types, such as acicular and prismatic crystals, than the more restrictive meaning of "cleavage fragments" used by mineralogists.

1 the following clarified REL makes clear, particles that meet the specified dimensional
2 criteria remain countable under the REL for the reasons stated above, even if they are
3 derived from the nonasbestiform analogs of the asbestos minerals.

4
5 Using terms defined in this *Roadmap*, the NIOSH REL is now clarified as follows:

6
7 The **NIOSH REL** for airborne asbestos fibers and related elongate mineral particles
8 (EMPs) is 0.1 countable EMPs from one or more covered minerals per cubic centimeter
9 averaged over 100 minutes, where:

- 10 • a *countable elongate mineral particle (EMP)* is any fiber or fragment of a mineral
11 longer than 5 μm with a minimum aspect ratio of 3:1 when viewed
12 microscopically using NIOSH Analytical Method #7400 ('A' rules) or its
13 equivalent; and
- 14 • a *covered mineral* is any mineral having the crystal structure and elemental
15 composition of: one of the asbestos varieties (chrysotile, riebeckite asbestos
16 [crocidolite], cummingtonite-grunerite asbestos [amosite], anthophyllite asbestos,
17 tremolite asbestos, and actinolite asbestos) or one of their nonasbestiform analogs
18 (the serpentine minerals antigorite and lizardite, and the amphibole minerals
19 contained in the cummingtonite-grunerite mineral series, the tremolite-
20 ferroactinolite mineral series, and the glaucophane-riebeckite mineral series).

21
22 This clarification of the NIOSH REL for airborne asbestos fibers and related EMPs
23 results in *no change* in counts made as defined by NIOSH Method 7400 ('A' rules).
24 However, it clarifies definitionally that EMPs included in the count are not necessarily
25 asbestos fibers

26
27 The existing NIOSH REL established in 1990 remains subject to change based on
28 research findings that shed light on the toxicity of nonasbestiform amphibole EMPs
29 covered by the REL and on the toxicity of other EMPs outside the range of those
30 minerals currently covered by the REL. In addition, due to changes by the IMA in 1978
31 [Meeker et al. 2003] in how minerals (e.g., amphiboles) are to be identified and classified
32 (optical microscopy to chemistry-based), a more extensive clarification of specific
33 minerals covered by the NIOSH REL may be warranted. That more extensive
34 clarification of covered minerals is beyond the scope of this *Roadmap*, but will be
35 addressed through additional efforts by NIOSH to encompass contemporary
36 mineralogical terminology within the REL.

37 38 **2.10 Summary of Key Issues**

39
40 For fibers from the asbestos minerals, an important question that remains unanswered is
41 "What are the important dimensional and physicochemical determinants of
42 pathogenicity?" Evidence from epidemiological and animal studies indicates that the risk
43 for asbestosis and lung cancer decreases with decreasing exposure concentrations and

1 that the potency of asbestos is reduced as the fiber length decreases. However, the results
2 from lung burden studies indicate the presence of short asbestos fibers at disease sites,
3 and positive correlations between lung cancer and exposure to short asbestos fibers make
4 it difficult to rule out a role for short asbestos fibers in causing disease.

5
6 Understanding the determinants of toxicity of EMPs from varieties of asbestos minerals
7 and of erionite, a fibrous zeolite, as well as of non-elongate mineral particles such as
8 quartz, may help to elucidate some of these issues. The results of human, animal, and *in*
9 *vitro* studies performed to date on a limited number of nonasbestiform EMPs are not
10 sufficient to conclude that exposures to EMPs from this large and highly variable group
11 of minerals are not capable of causing substantial adverse health outcomes. Additional
12 data are needed to develop risk assessments. There is a general lack of occupational
13 exposure data on nonasbestiform EMPs, making it difficult to assess the range of particle
14 characteristics, including dimension, in occupational settings with exposures to
15 nonasbestiform EMPs. The few studies that have assessed biopersistence or durability
16 suggest that nonasbestiform EMPs are not as biopersistent as asbestiform fibers of the
17 same dimension, but more information is needed to systematically assess the ranges and
18 importance of biopersistence in determining toxicity. Any assessment of risk needs to
19 address the influence of dimension, so studies that systematically compare effects of
20 asbestiform and nonasbestiform particles of similar dimensions from the same mineral
21 (e.g., crocidolite and nonasbestiform riebeckite) are needed for a variety of mineral types.

22
23 An important need is to identify and develop methods of analysis that can be used or
24 modified to assess occupational exposures to EMPs and that are capable of differentiating
25 EMPs based on particle characteristics demonstrated to be important in causing disease.
26 The current PCM method is inadequate for assessing exposures to fibers in mixed-dust
27 environments which are likely to predominate for the foreseeable future, and it lacks the
28 capability to measure the important physical and chemical parameters of fibers thought to
29 be associated with toxicity. For routine use in assessing compliance with regulations, the
30 limited availability, high relative cost, and long turnaround times associated with EM
31 methods will need to be addressed to provide an alternative to the PCM method. Until
32 these issues are addressed, improvements in PCM methodologies should be pursued. In
33 epidemiological and toxicological research, EM methods will need to be used to carefully
34 characterize the exposure materials. Also, the results of toxicological and
35 epidemiological studies may identify additional determinants of particle toxicity that
36 warrant evaluation to determine whether they can be incorporated into sampling and
37 analytical methods used to assess the health risks of exposure to EMPs.

38
39 Section 3 of this *Roadmap* presents a framework for proposed research intended to
40 address these scientific issues and inform future public health policies and practices.

3 FRAMEWORK FOR RESEARCH

3.1 Strategic Research Goals and Objectives

Strategic goals and objectives for a multi-disciplinary research program on mineral fibers and other EMPs are identified below. Shown in brackets following each goal and objective is the number of the section of this *Roadmap* in which the goal or objective is subsequently discussed.

I. Develop a broader understanding of the important determinants of toxicity for asbestos fibers and other EMPs [3.2].

- Conduct *in vitro* studies to ascertain what physical, chemical, surface properties, and other particle characteristics influence the toxicity of asbestos fibers and other EMPs [3.2.1]; and
- Conduct animal studies to ascertain what physical and chemical properties, surface properties, and other particle characteristics influence the toxicity of asbestos fibers and other EMPs [3.2.2]

II. Develop information and knowledge on occupational exposures to asbestos fibers and other EMPs and related health outcomes [3.3].

- Assess available occupational exposure information relating to various types of asbestos fibers and other EMPs [3.3.1].
- Collect and analyze available information on health outcomes associated with exposures to various types of asbestos fibers and other EMPs [3.3.2].
- Conduct selective epidemiologic studies of workers exposed to various types of asbestos fibers and other EMPs [3.3.3]; and
- Improve clinical tools and practices for screening, diagnosis, treatment, and secondary prevention of diseases caused by asbestos fibers and other EMPs [3.3.4].

III. Develop improved sampling and analytical methods for asbestos fibers and other EMPs [3.4].

- Reduce inter-operator and inter-laboratory variability of the current analytical methods used for asbestos fibers [3.4.1];
- Develop analytical methods with improved sensitivity to visualize thinner EMPs to ensure a more complete evaluation of airborne exposures [3.4.2];
- Develop a practical analytical method for air samples to differentiate between exposures to asbestiform fibers from the asbestos minerals and exposures to EMPs from their nonasbestiform analogs [3.4.3];
- Develop analytical methods to assess durability of EMPs [3.4.4]; and
- Develop and validate size-selective sampling methods for EMPs [3.4.5].

3.2 Approach to Conducting Interdisciplinary Research

Within each of the goals and objectives laid out in this framework, a more detailed research program will have to be developed. Research conducted to support these three research goals must be planned and conducted using an interdisciplinary approach between the toxicological, epidemiological, exposure assessment, medical, analytical, and mineralogical disciplines. The research must also be integrated to optimize resources, facilitate the simultaneous collection of data, and ensure, to the extent feasible, that the research builds toward a resolution of the key issues. An aim of the research is to acquire a level of mechanistic understanding that can provide the basis for developing biologically-based models for extrapolating results of animal inhalation and other types of *in vivo* studies to exposure conditions typically encountered in the workplace. The information gained from such research can then be used by regulatory agencies and occupational health professionals to implement appropriate exposure limits and risk management programs for monitoring worker exposure and health. Much of this research may be accomplished by NIOSH, other federal agencies, or other stakeholders. Any individual research project undertaken should be designed to ensure that the results can be interpreted and applied within the context of other studies in the overall program and lead to outcomes useful for decision-making and policy-setting.

1 **3.3 National Reference Repository of Minerals and Information System**
2

3 To support the needed research, a national reference repository of samples of asbestos
4 and related minerals will be required, and a database of relevant information should be
5 developed. Minerals vary in composition and morphology by location and origin, and
6 differences within the same mineral type can be significant. Currently, no national
7 repository exists to retain, document, and distribute samples of asbestiform and
8 nonasbestiform reference minerals for research and testing. These reference samples
9 should be well-characterized research-grade materials that are made available to the
10 research community so they can be used for testing and standardization. This will allow
11 minerals to be chosen for study in such a way as to match properties (e.g., morphology,
12 dimension). To accomplish this research, exhaustive characterization of the samples
13 including contaminants is necessary. Detailed characterizations of particles that may
14 affect biological activities (e.g., surface composition, durability, morphology, and surface
15 properties) are needed. The use of these samples in research would facilitate meaningful
16 comparisons and reduce uncertainties in the interpretation of results between and among
17 studies.
18

19 The characterization of minerals should include, among other properties: (1) purity of the
20 mineral; (2) particle morphology (range of dimensions and sizes); (3) surface area; (4)
21 surface chemistry; and (5) surface reactivity. The particle characteristics identified by
22 Hochella [1993] should be considered for particle characterization. Care must be taken to
23 ensure that a sufficient amount of the studied material is available, not only for current
24 studies, but also as reference material for possible future studies. The information
25 developed from all of these efforts should be entered into a database which can serve as a
26 tool for selection of minerals for testing and validation of toxicological tests, as well as to
27 assist in identification of worker populations for possible epidemiological studies.
28

29 The development of a comprehensive, publicly available information system
30 incorporating all studies of the toxicity, exposures, and health effects of asbestos and
31 related minerals could help enhance the development of the research programs, avoid
32 duplication of effort, and enhance interpretation of the information generated. The
33 information system should include all pertinent information about the methods, doses or
34 exposures, mineral information, particle characteristics, and other information deemed
35 pertinent.
36

37 **3.4 Develop a Broader Understanding of the Important Determinants of Toxicity for**
38 **Asbestos Fibers and Other EMPs**
39

40 To address this objective, one of the first steps will be to identify the range of minerals
41 and mineral habits needed to systematically address the mineral characteristics that may
42 determine particle toxicity. Care must be taken to ensure that mineralogical issues in a
43 study are adequately addressed. Information on both crystalline lattice structure and
44 composition are needed to define a mineral species because information on either alone is

1 insufficient to describe the properties of a mineral. For example, nonasbestiform
2 riebeckite and asbestiform riebeckite (crocidolite) share the same elemental composition
3 but have different crystalline lattices. EMPs from nonasbestiform riebeckite are not
4 flexible. Crocidolite fibers generally have chain-width defects, which explain the
5 flexibility of crocidolite fibers. These chain-width defects also affect diffusion of cations
6 and dissolution properties, both of which can explain greater release of iron into
7 surrounding fluid by crocidolite than by nonasbestiform riebeckite [Guthrie 1997].
8

9 In addition to elemental content and crystalline lattice, the particle characteristics
10 identified by Hochella [1993] should be considered for particle characterization. For
11 example, the current paradigm for fiber pathogenicity does not discriminate between
12 different compositions of biopersistent fibers, except insofar as composition determines
13 biopersistence. There are instances of two biopersistent fiber types, erionite [Wagner et
14 al. 1985] and silicon carbide [Davis et al. 1996], that show a special proclivity to cause
15 mesothelioma for reasons that are not easily explained by the current paradigm because
16 biopersistence and distributions of fiber lengths are not substantially different than the
17 amphiboles. The biochemical basis of the enhanced pathogenicity of these two fiber
18 types has not been elucidated. This suggests that some fiber types may possess surface or
19 chemical reactivity that imparts added pathogenicity over and above what would be
20 anticipated for long biopersistent fibers. Because of the many variations in elemental
21 composition, crystalline structure, and other characteristics of these minerals, it will be
22 impossible to study all variants. Therefore, a strategy will need to be developed for
23 selecting minerals for testing. Included in this strategy should be consideration of
24 occupationally relevant minerals and habits, availability of appropriate and well-
25 characterized specimens for testing, and practical relevance of the results to be achieved
26 through testing.
27

28 EPA's Office of Pollution Prevention and Toxics, NIEHS, NIOSH, and OSHA assembled
29 an expert panel a decade ago to consider major issues in animal model chronic inhalation
30 toxicity and carcinogenicity testing of thoracic-size elongate particles. Issues considered
31 included: the design of chronic inhalation exposure of animals to EMPs; preliminary
32 studies to guide them; parallel mechanistic studies to help interpret study results and to
33 extrapolate findings to potential for human health effects; and available screening tests
34 for identifying and assigning a priority for chronic inhalation study. There was general
35 agreement that: (1) chronic inhalation studies of EMPs in the rat are the most appropriate
36 tests for predicting inhalation hazard and risk of EMPs to humans; (2) no single assay and
37 battery of short-term assays could predict the outcome of a chronic inhalation bioassay
38 for carcinogenicity; and (3) several short-term *in vitro* and *in vivo* studies may be useful
39 to assess the relative potential of various EMPs to cause lung toxicity or carcinogenicity
40 [Vu et al. 1996].
41

42 Such short-term assays and strategies were considered by an expert working group
43 assembled by the International Life Sciences Institute's Risk Science Institute to arrive at
44 a consensus on current short-term assays useful for screening EMPs for potential toxicity

1 and carcinogenicity [ILSI 2005]. Dose, dimension, durability, and possibly surface
2 reactivities were identified as critical parameters for study, while it was noted that no
3 single physicochemical property or mechanism can now be used to predict
4 carcinogenicity of all EMPs. The strategy for short-term (i.e., 3 months or less) testing in
5 animal models included: sample preparation and characterization (composition,
6 crystallinity, habit, size-distribution); testing for biopersistence *in vivo* using a standard
7 protocol such as that of the European Union [European Commission 1999]; and a sub-
8 chronic inhalation or instillation challenge of the rat with evaluation of lung weight and
9 fiber burden, bronchoalveolar lavage profile, cell proliferation, fibrosis, and
10 histopathology. Additionally, other non-routine analyses for particle surface area and
11 surface reactivities and short-term *in vitro* cellular toxicological assays might be
12 evaluated. The use of *in vitro* tests should be tempered by the observations that standard
13 protocols fail to distinguish relative pathogenic potentials of even non-elongate silicates
14 (i.e., quartz versus clay dusts) and that treatment of particle surfaces (i.e., modeling their
15 conditioning upon deposition on the lipoprotein-rich aqueous hypophase surface of the
16 deep lung) can greatly affect their expression of toxicities [ATSDR 2003].
17

18 EMPs encountered in any particular work environment are frequently heterogeneous,
19 which limits the ability of epidemiological and other types of health assessment studies to
20 evaluate the influence of EMP dimensions (length and width), chemical composition,
21 biopersistence, and other characteristics on toxicity. Toxicological testing is needed to
22 address some of the fundamental questions about EMP toxicity that cannot be determined
23 through epidemiology or other types of health assessment studies. Irrespective of study
24 type or design, the full characterization of all particulate material in a test sample is an
25 essential step in understanding the mechanisms of EMP toxicity. The determination of
26 EMP dimensions is important and best expressed as bivariate size distributions (i.e.,
27 width and length). Such determinations should be made using both relatively simple
28 procedures (optical microscopy) and highly specialized techniques (e.g., TEM or SEM
29 with EDS) because size-specific fractions of EMP exposures have both biological and
30 regulatory significance.
31

32 The chemical composition (e.g., intrinsic chemical constituents and surface chemistry) of
33 mineral fibers and other EMPs has been shown to have a direct effect on their ability to
34 persist in the lung and to interact with surrounding tissue to cause DNA damage. For
35 example, ferric and ferrous cations are major components of the crystalline lattice of
36 amphibole asbestos fibers; iron may also be present as surface impurities on chrysotile
37 asbestos fibers and other EMPs. The availability of iron at the surface of asbestos fibers
38 and other EMPs has been shown to be a critical parameter in catalyzing the generation of
39 ROS which may indirectly cause genetic damage [Kane 1996]. Also, attempted
40 clearance of long asbestos fibers from the lung causes frustrated phagocytosis, which
41 stimulates the release of ROS [Mossman and Marsh 1989]. Individual adaptive
42 responses to oxidant stress and the body's ability to repair damaged DNA are dependent
43 on multiple exogenous and endogenous factors, but few experiments have been attempted
44 to evaluate these variables in animal or human model systems. Kane [1996] has

1 suggested that the mechanisms responsible for the genotoxic effects of asbestos fibers are
2 due to indirect DNA damage mediated by free radicals and to direct physical interference
3 with the mitotic apparatus by the fibers themselves. Research to address the following
4 questions would assist in validating these proposed mechanisms:

- 5 • Are *in vitro* genotoxicity assays relevant to carcinogenesis of asbestos fibers and
6 other EMPs?
- 7 • Are *in vitro* doses relevant for *in vivo* exposures?
- 8 • Can genotoxic effects of asbestos fibers and other EMPs be assessed *in vivo*?

9
10 Macrophages are the initial target cells of EMPs and other particulates deposited in the
11 lungs or pleural and peritoneal spaces. Phagocytosis of asbestos fibers has been shown to
12 be accompanied by the activation of macrophages, which results in the generation of
13 ROS as well as a variety of chemical mediators and cytokines [Kane 1996]. These
14 mediators amplify the local inflammatory reaction. Persistence of asbestos fibers in the
15 lung interstitium or in the sub-pleural connective tissue may lead to a sustained chronic
16 inflammatory reaction accompanied by fibrosis [Oberdorster 1994]. The unregulated or
17 persistent release of these inflammatory mediators may lead to tissue injury, scarring by
18 fibrosis, and proliferation of epithelial and mesenchymal cells. In the lungs and pleural
19 linings, chronic inflammation and fibrosis are common reactions following exposure to
20 asbestos fibers, but research is needed to understand the relationship between
21 inflammation, fibrosis, and cancer including the effects of fiber dimension and fiber
22 loading on the development of these disease endpoints.

23
24 It has been suggested that asbestos fibers and other EMPs may contribute to
25 carcinogenesis by multiple mechanisms and that EMPs may act at multiple stages in
26 neoplastic development depending on their physicochemical composition, surface
27 reactivity, and biopersistence in the lung [Barrett 1994]. Animal inhalation studies are
28 needed to investigate the biopersistence and toxicity of asbestos fibers and other EMPs
29 representing a range of chemical compositions and morphological characteristics
30 (including crystalline habits) and representing a range of discrete lengths and widths. An
31 additional factor which should be considered and evaluated is the influence of concurrent
32 exposure to other particles and contaminants on the biopersistence and toxicity of EMPs.
33 In a recently reported short-term (5-day) animal inhalation study to evaluate the
34 biopersistence of chrysotile fibers with and without concurrent exposure to joint
35 compound particles (1–4 μm MMAD), the clearance half-time of all fiber sizes was
36 approximately an order of magnitude less for the group exposed to chrysotile and joint-
37 compound particles [Bernstein et al. 2008]. Based on histopathological examination, the
38 combination of chrysotile and fine particles accelerated the recruitment of alveolar
39 macrophages, resulting in a ten-fold decrease in the number of fibers remaining in the
40 lung. Although no mention was made of any pathological changes in the lungs of the
41 chrysotile/particulate exposed group, other studies have shown that the recruitment of
42 macrophages then increases the production and recruitment of polymorphonuclear

1 leukocytes, which themselves can generate ROS [Driscoll et al. 2002; Donaldson and
2 Tran 2002].

3
4 Much research has been focused on lung cancer and mesothelioma. Even if it is
5 determined that EMPs from some minerals have low potency for causing cancer,
6 additional studies may be needed to investigate their potential for causing inflammation,
7 fibrosis, and other nonmalignant respiratory effects. Also, the relationship between EMP
8 dimension and fibrosis should be more fully investigated. The results of such research
9 may allow currently used standard exposure indices to be modified by specifying
10 different dimensional criteria (lengths and widths) relevant to each of the disease
11 outcomes associated with EMP exposures, and by determining whether biopersistence
12 should be included as an additional criterion. However, this research may be dependent
13 on the development of new aerosol technology that can generate mineral fibers and other
14 EMPs of specific dimensions in sufficient quantities to conduct animal inhalation
15 experiments. Consequently, the development of revised exposure indices based on EMP
16 dimension may not be possible in the short term.

17
18 This research strategy described above should conform with the general strategies and
19 tactics that have been recommended by several expert panels for clarifying the risks and
20 causes of asbestos exposure-associated diseases, and with the current effort of the U.S.
21 Federal Government Interagency Asbestos Working Group (IAWG), involving
22 participation of the EPA, USGS, NIOSH, ATSDR, CPSC, OSHA, MSHA, and the
23 NIEHS/NTP, to identify federal research needs and possible actions regarding asbestos
24 fibers and other durable EMPs of public health concern [Vu et al. 1996; ILSI 2005;
25 Schins 2002; Greim 2004; Mossman et al. 2007].

26
27 An ILSI Risk Science Institute Working Group supported by EPA published a tiered
28 testing strategy for fibrous particles in 2005 [ILSI 2005]. Consideration should be given
29 to the following slight modification of this published scheme. Noteworthy in the findings
30 of the ILSI Working Group report is the inadequacy of *in vitro* test models to predict the
31 *in vivo* toxicity of EMPs. Indeed, many man-made mineral fibers are positive in cell test
32 systems but do not to cause fibrosis or cancer in chronic animal models. The *in vitro* test
33 systems lack predictive ability because they do not incorporate biopersistence. For this
34 reason, *in vitro* tests, other than assays for durability, are not included in the tiered testing
35 strategy given below.

36
37 **Step 1. Preparation and characterization of test EMPs.**

38 This is the initial, required step for any toxicological evaluation. It should
39 include:

- 40 • full chemical and mineralogical characterization, including
- 41 crystallinity and EMP habit.
- 42 • size distribution of the EMPs found in the workplace (total
- 43 particulate sample), as well as dimensional characteristics of size-

1 selected fraction(s) to be used for hazard evaluation. A limiting step
2 for detailed toxicological evaluation is the availability of sufficient
3 quantities of size-selected EMPs of known chemistry and
4 mineralogy.
5

6 ***Step 2. Assessment of in vitro durability***

7 Evidence indicates that highly soluble fibrous particles do not exhibit fibrotic or
8 carcinogenic potential in animal studies. One should measure rate of dissolution
9 in simulated body fluids using a dynamic flow-through system as outlined by
10 Potter et al. [2000]. Briefly, EMPs are exposed by continuous flow to a modified
11 Gamble's solution, and fiber diameter is monitored optically over time.

12 Biopersistence would be an indication of concern and would indicate the need for
13 further testing of the pathogenic potential of the EMP. This step is optional, as
14 one could move directly to Step 3.
15

16 ***Step 3. Short-term in vivo biopersistence test***

17 Biopersistence of fibers longer than 20 μm has been found to be an excellent
18 predictor of collagen deposition in chronic inhalation studies [Bernstein et al.
19 2001]. Two alternative methods are accepted by the European Commission
20 [1997] — intratracheal instillation or 5-day inhalation of rats. It is recommended
21 that fiber burden be measured at time points up to 3 months post-exposure.

22 Biopersistence would be an indication of concern and would indicate the need for
23 further testing of the pathogenic potential of the EMP.
24

25 ***Step 4. Sub-chronic inhalation study***

26 Parameters that should be measured in such an inhalation study are noted by EPA
27 [2001]. The test should conduct inhalation exposure for 3 months and evaluate
28 pulmonary responses over 6 months post-exposure. Responses to be measured
29 should include: biopersistence, persistent inflammation, cell proliferation
30 (bromodeoxyuridine [BrdU] assay), fibrosis, epithelial cell hyperplasia, lung
31 weight, and fiber burden. Biopersistence and persistent inflammation are notable
32 markers of concern. If the sub-chronic study is positive, a long-term inhalation
33 study is necessary to conduct a full risk assessment.
34

35 ***Step 5. Long-term inhalation study***

36 The test would include a 2-year inhalation study in rats with life-long follow up.
37 Fibrosis, lung tumors, and mesothelioma should be measured following EPA
38 guidelines [EPA 2001] for long-term inhalation studies of fibers. Lung burden,
39 dose-related response, and time-course data would enable risk assessment.
40

41 Implicit in any new or revised occupational health policy for EMPs would be the need to
42 conduct appropriate assessments of risk. Risk assessments for lung cancer,
43 mesothelioma, and asbestosis have been conducted on worker populations exposed
44 to various asbestos minerals. These risks have been qualitatively confirmed in animals,

1 but no adequate quantitative multi-dose inhalation studies with asbestos have been
2 conducted in rodents that would permit direct comparisons to lung cancer and
3 mesothelioma risks determined from exposed human populations. Given the availability
4 of risk estimates for lung cancer in asbestos-exposed humans, chronic studies with rats
5 exposed to asbestos (e.g., chrysotile) fibers would provide an assessment of the rat as a
6 valid "predictor" for human lung cancer risks associated with exposure to asbestos fibers
7 and other EMPs.

8 9 **3.4.1 Conduct *In Vitro* Studies to Ascertain the Physical and Chemical Properties that** 10 **Influence the Toxicity of Asbestos Fibers and Other EMPs**

11
12 Although *in vitro* studies may not be appropriate for toxicology screening testing of
13 EMPs, they can help clarify the mechanisms by which some EMPs induce cancer,
14 mesothelioma, or fibrosis, and the properties of EMPs and conditions of exposure that
15 determine pathogenicity. *In vitro* studies allow specific biological and mechanistic
16 pathways to be isolated and tested under controlled conditions which are not feasible in
17 animal studies. *In vitro* studies can yield data rapidly and provide important insights and
18 confirmations of the mechanism which can be confirmed with specifically designed *in*
19 *vivo* studies.

20
21 With the exception of *in vitro* genotoxicity testing of asbestos fibers, little information is
22 available on the potential genotoxicity of other EMPs. In contrast to standard
23 genotoxicity testing of soluble substances, the results from testing EMPs can be
24 influenced by dimension, surface properties, and biopersistence. The mechanisms of
25 asbestos-induced genotoxicity are not clear, but direct interaction with the genetic
26 material and indirect effects via production of ROS have been proposed. A combination
27 of the micronucleus test and the comet assay using continuous treatment (without
28 exogenous metabolic activation) has been reported to detect genotoxic activity of
29 asbestos fibers [Speit 2002]. However, further research is needed to determine whether
30 this approach is applicable for genotoxicity testing of other EMPs. Before conducting
31 such studies, the following EMP interactions should be addressed:

- 32 • initial lesions evoking cell damage or response (e.g., direct or indirect cytotoxic
33 or genotoxic events or induction of toxic reactive intermediate materials);
- 34 • subsequent multi-stage cellular response (e.g., intracellular signaling through a
35 kinase cascade to nuclear transcription of factors for apoptosis, cell
36 transformation, and cell or cell system proliferation or remodeling and initiation
37 or promotion of neoplasia or fibrosis); and
- 38 • critical time-course events in those processes (e.g., cell-cycle-dependent EMP
39 interactions or EMP durability under different phagocytic conditions).

40
41 Capabilities for conducting these studies have improved in the last decade through:

1 of phagocytic activity of the cell or the stages in the cell cycle with collapse of the
2 nuclear membrane in mitosis). These again suggest care in the preparation of EMPs and
3 the manner of challenge with EMPs employed in *in vitro* experiments.

4
5 The two modes of primary damage, a release of reactive toxic agents induced by long
6 particulates or a surface-based membranolytic or genotoxic mechanism, may be involved
7 singly or jointly in primary cell responses to EMPs. These may be investigated by
8 comparing the effects of different types of EMPs (e.g., relative potencies of erionite
9 fibers and amphibole asbestos fibers in *in vitro* cell transformation studies are different
10 than their potencies in *in vivo* induction of mesothelioma).

11
12 In the second phase of cellular response to EMPs, the central dogma of intracellular
13 response is being intensively researched. The initial extracellular primary damage
14 induces intracellular signaling (e.g., by MAPK) which causes a cascade of kinase
15 activities that stimulate selective nuclear transcription of mRNAs leading to production
16 of TNF- α or other cytokines for extracellular signaling of target cells. Those other
17 cytokines may induce cell proliferation toward cancer or collagen synthesis toward
18 fibrosis. Further definition of signaling mechanisms and analyses of their induction by
19 different primary EMP-cellular interactions may better define the ultimate role of EMP
20 properties in the overall process. That research, again, may be facilitated by using
21 different specific types EMPs, each type with relatively homogeneous morphology and
22 surface properties.

23
24 While full investigation of biopersistence of EMPs may require long-term animal model
25 studies, *in vitro* systems coupled with advanced surface analytical tools (e.g., field
26 emission scanning electron microscopy-energy dispersive X-ray spectroscopy or
27 scanning Auger spectroscopy) may help guide *in vivo* studies. This could be done by
28 detailing specific surface properties of EMPs and their modifications under cell-free or *in*
29 *vitro* conditions representing the local pH and reactive species at the EMP surface under
30 conditions of extracellular, intra-phagolysosomal, or frustrated annular phagocytic
31 environments.

32 33 **3.4.2 Conduct Animal Studies to Ascertain the Physical and Chemical Properties that** 34 **Influence the Toxicity of Asbestos Fibers and Other EMPs**

35
36 A multi-species testing approach has been recommended for short-term assays [ILSI
37 2005] and chronic inhalation studies [EPA 2000] that would provide solid scientific
38 evidence on which to base human risk assessments for a variety of EMPs. To date, the
39 most substantial base of human health data for estimating lung cancer risk exists for
40 workers exposed to fibers from different varieties of asbestos minerals.

41
42 Interspecies differences have been identified in the clearance of inhaled particles.
43 Variations in deposition patterns and airway cell morphology and distribution account for
44 significant deposition and clearance differences among species. In addition, the efficacy

1 of pulmonary macrophage function differs among species. All these differences could
2 affect particle clearance and retention. It has been suggested that the following species
3 differences should be considered in the design of experimental animal inhalation studies
4 of elongate particles [Dai and Yu 1988; Warheit et al. 1988; Warheit 1989]:

- 5 • Due to differences in airway structure, airway size, and ventilation parameters, a
6 greater fraction of larger AED particles are deposited in humans than in rodents.
- 7 • Alveolar deposition fraction in humans varies with workload. An increase in the
8 workload reduces the deposition fraction in the alveolar region because more of
9 the inhaled particulate is deposited in the extra-thoracic and bronchial regions.
- 10 • Mouth breathing by humans results in a greater upper bronchial deposition and
11 enhanced particle penetration to the peripheral lung.
- 12 • For both animals and humans, the deposition rate of particles is greatest in the
13 AED range between 1 and 2 μm . Alveolar deposition of EPs decreases as their
14 aspect ratio increases when their width remains constant.
- 15 • For rats and hamsters, alveolar deposition becomes practically zero when particle
16 AED exceeds 3.0 μm and aspect ratio exceeds 10. In contrast, considerable
17 alveolar deposition is found for humans breathing at rest, even for EPs with
18 AEDs approaching 5 μm and aspect ratio exceeding 10.
- 19 • Rodents have smaller-diameter airways than humans, which increases the chance
20 for particle deposition via contact with airway surfaces.
- 21 • Turbulent air flow, which enhances particle deposition via impaction, is common
22 in human airways but rare in rodent airways.
- 23 • Variations in airway branching patterns may account for significant differences
24 in deposition between humans and rodents. Human airways are characterized by
25 symmetrical branching, wherein each bifurcation is located near the centerline of
26 the parent airway. This symmetry favors deposition "hotspots" on carinal ridges
27 at the bifurcations due to disrupted airstreams and local turbulence. Rodent
28 airways are characterized by asymmetric branching, which results in a more
29 diffuse deposition pattern because the bulk flow of inspired air follows the major
30 airways with little change in velocity or direction.
- 31 • Alveolar clearance is slower in humans than in rats. Human dosimetry models
32 predict that, at non-overloading exposure concentrations, a greater proportion of
33 particles deposited in the alveolar region will be interstitialized and sequestered
34 in humans than in rats.

35
36 An important consideration in the conduct and interpretation of animal studies is the
37 selection of well characterized (with respect to chemical and physical parameters) and
38 appropriately sized EMPs that take into account differences in deposition and clearance
39 characteristics between rodents and humans. EMPs that are capable of being deposited in
40 the bronchoalveolar region of humans cannot be completely evaluated in animal
41 inhalation studies because the maximum thoracic size for particles in rodents is
42 approximately 2 μm AED, which is less than the maximum thoracic size for humans of
43 about 3 μm AED [Timbrell 1982; Su and Cheng 2005].

1
2 3.4.2.1 Short-Term Animal Studies
3

4 There are advantages to conducting short-term animal studies in rats. The information
5 gained (e.g., regarding overload and maximum tolerated dose [MTD]) from these studies
6 can be used in designing chronic inhalation studies [ILSI 2005]. The objectives of these
7 studies would be to:

- 8 • Evaluate EMP deposition, translocation, and clearance mechanisms;
- 9 • Compare the biopersistence of EMPs retained in the lung with results from *in*
10 *vitro* durability assays;
- 11 • Compare *in vivo* pulmonary responses to *in vitro* bioactivity for EMPs of different
12 dimensions; and
- 13 • Compare cancer and noncancer toxicities of EMPs from asbestiform and
14 nonasbestiform amphibole mineral varieties of varying shapes as well as within
15 narrow ranges of length and width.

16
17 More fundamental studies should also be performed to:

- 18 • Identify biomarkers or tracer/imaging methods that could be used to predict or
19 monitor active pulmonary inflammation, pulmonary fibrosis, and malignant
20 transformation;
- 21 • Investigate mechanisms of EMP-induced pulmonary disease; and
- 22 • Determine whether cell proliferation in the lungs (terminal bronchioles and
23 alveolar ducts) can be a predictive measure of pathogenicity following brief
24 inhalation exposure using the BrdU assay [Cullen et al. 1997].

25
26 Exposure protocols for tracheal inhalation or instillation in an animal model for short-
27 term *in vivo* studies using field-collected or laboratory-generated EMPs should address
28 possible adulteration of EMP morphology (e.g., anomalous agglomeration of particles).
29 This might be addressed in part by pre-conditioning EMPs in a delivery vehicle
30 containing representative components of pulmonary hypophase fluids. Exposure
31 protocols using pharyngeal aspiration as a delivery system should be considered given the
32 observations in studies with single-walled carbon nanotubes that such a delivery system
33 closely mimics animal inhalation studies [Shvedova et al. 2005, 2008].
34

35 Studies evaluating the roles of biopersistence and dimension in the development of non-
36 cancer and cancer endpoints from exposure to EMPs are also needed. These studies
37 should attempt to elucidate the physicochemical parameters that might affect bio-
38 durability of EMPs of specific dimensions. While short-term animal inhalation studies
39 would be informative, companion *in vitro* assays should also be conducted to assess their
40 validity for screening EMPs.

1
2 Acellular assays could include measurement of the generation of ROS employing
3 electron spin resonance (ESR) or oxidant sensitive fluorescent dyes. Evaluation of the
4 mobilization of metal ions from EMPs could indicate cytotoxic potential.

5
6 The *in vitro* cellular tests could include the following:

- 7 • generation of reactive species measured by ESR or fluorescent dyes;
- 8 • generation of inflammatory, fibrogenic, and proliferative mediators, such as TNF-
9 alpha, IL-1, TGF, etc.;
- 10 • DNA damage by comet assay;
- 11 • effects on cell growth regulation by measuring cell proliferation;
- 12 • effects on mitosis and aneuploidy using confocal fluorescent microscopy; and
- 13 • signal transduction pathways, such as MAPkinase, and phosphoinositide-3 (PI3)
14 kinase pathways.

15
16 *In vivo* tests would measure markers of inflammation (e.g., BAL neutrophils,
17 inflammatory cytokines and chemokines), fibrosis (e.g., collagen, hydroxyproline), and
18 proliferation (e.g., BrdU assay, hyperplasia) which precede pathology. Knockout mice or
19 pathway inhibitors in rats may be used to confirm mechanistic pathways identified *in*
20 *vitro* and develop biomarkers for disease initiation and progression. Potential biomarkers
21 identified in *in vitro* and *in vivo* studies would be evaluated in human populations with
22 known exposure to EMPs, and the type and extent of the relationships between the
23 marker and clinical signs of disease could be determined.

24 25 26 **3.5 Develop Information and Knowledge on Occupational Exposures to Asbestos** 27 **Fibers and Other EMPs and Related Health Outcomes**

28
29 Many studies have been published concerning occupational exposures to asbestos fibers
30 and associated health effects. These studies have formed a knowledge base that has
31 supported increased regulation of occupational asbestos exposures and substantial
32 reductions in asbestos use and asbestos exposures in the United States over the past
33 several decades. But, as this *Roadmap* makes clear, much less is known about other
34 types of mineral fibers and EMPs in terms of occupational exposures and potential health
35 effects.

36
37 Research is needed to produce information on:

- 38 • current estimates and, where possible, future projections of numbers of U.S.
39 workers exposed to asbestos fibers;
 - 40 • levels of current exposures; and nature of the exposures (e.g., continuous, short-
41 term, or intermittent); and
 - 42 • the nature of any concomitant dust exposures.
- 43

1 Similar research is needed to produce analogous information about occupational
2 exposures to other EMPs. Research is needed to assess and quantify potential human
3 health risks associated with occupational exposures to other EMPs, as well as to better
4 understand and quantify the epidemiology of asbestos-related diseases using more refined
5 indices of exposure. Research is also needed to produce improved methods and clinical
6 guidance for screening, diagnosis, secondary prevention, and treatment of diseases
7 caused by asbestos fibers and other hazardous EMPs.

9 ***3.5.1 Assess Available Information on Occupational Exposures to Asbestos Fibers and*** 10 ***Other EMPs***

11
12 A fully informed strategy for prioritizing research on EMPs should be based on
13 preliminary systematic collection and evaluation of available information on: (1)
14 industries/occupations/job tasks/processes with exposure to various types of asbestos
15 fibers and other EMPs; (2) numbers of workers exposed; (3) characteristics and levels of
16 exposures; and (4) associated concomitant particulate exposures. Such information could
17 enable estimations of:

- 18 • the overall distribution and levels of occupational exposures and an estimate of
19 the total number of workers exposed to EMPs currently, in the past, and projected
20 in the future; and
- 21 • the specific distributions and levels of exposures to each particular type of EMP,
22 as well as numbers of workers exposed to each type of EMP currently, in the past,
23 and (projected) in the future.

24
25 Initial efforts should be made to collect, review, and summarize available occupational
26 exposure information and to collect and analyze representative air samples relating to
27 various types of EMPs. For example, systematic compilation of exposure data collected
28 by OSHA, MSHA, NIOSH, state agencies, and private industry could contribute to an
29 improved understanding of current occupational exposures to EMPs, particularly if there
30 are opportunities to (re)analyze collected samples using enhanced analytical methods to
31 better characterize the exposures (see Section 3.6). To help limit potential impact of
32 sampling bias that may be inherent in the available EMP exposure data, these initial
33 efforts should be supplemented with efforts to systematically identify, sample, and
34 characterize EMP exposures throughout U.S. industry. These exposure assessments
35 should include workplaces in which a fraction of the dust is comprised of EMPs (i.e.,
36 mixed-dust environments), and occupational environments in which EMPs may not meet
37 the current regulatory criteria to be counted (i.e., “short” fibers). With appropriate
38 planning and resources, such efforts could be designed and implemented as ongoing
39 surveillance of occupational exposures to EMPs, with periodic summary reporting of
40 findings. Representative EMP exposure data could help identify worker populations or
41 particular types of EMPs warranting further study (i.e., more in-depth exposure
42 assessment, medical surveillance; epidemiology studies of particular types of EMPs,
43 processes, job tasks, occupations, or industries; toxicity studies of particular EMPs).

1 Occupational exposure data should be collected and stored in a comprehensive database.
2 Information similar to that described in Marchant et al. [2002] should be incorporated
3 into the database to support these efforts. This could be accomplished in parallel with
4 efforts to develop an occupational exposure database for nanotechnology [Miller et al.
5 2007] or efforts to develop a national occupational exposure database [Middendorf et al.
6 2007].
7

8 ***3.5.2 Collect and Analyze Available Information on Health Outcomes Associated*** 9 ***with Exposures to Asbestos Fibers and Other EMPs***

10
11 The body of knowledge concerning human health effects from exposure to EMPs consists
12 primarily of epidemiological studies of workers exposed to asbestos fibers and several
13 other types of EMPs (e.g., wollastonite, attapulgite, erionite). Additional relevant
14 information may be gleaned from the epidemiological studies conducted on some SVFs
15 (e.g., glass and mineral wool fibers, ceramic fibers). There is general agreement that
16 workers exposed to fibers from any asbestiform mineral would be at risk of serious
17 adverse health outcomes of the type caused by exposure to fibers from the six
18 commercially exploited asbestos minerals. NIOSH commented on the recent MSHA
19 proposed rule on asbestos (subsequently promulgated as a final rule), stating that
20 "NIOSH remains concerned that the regulatory definition of asbestos should include
21 asbestiform mineral fibers such as winchite and richterite, which were of major
22 importance as contaminants in the Libby, MT vermiculite" [NIOSH 2005]. To ensure a
23 clear science base that might support a formal recommendation for control of
24 occupational exposures to all asbestiform amphibole fibers, it would be reasonable to
25 thoroughly review, assess, and summarize the available information on asbestiform
26 amphiboles that have not been commercially exploited as asbestos. Publication of such a
27 review could be done in the short term.
28

29 It will also be important to authoritatively and quantitatively determine health risks posed
30 by EMPs from nonasbestiform amphiboles and to compare them to those posed by fibers
31 from asbestiform amphiboles. Animal and *in vitro* studies have indicated a potential risk
32 for exposed humans, but available epidemiological studies have limitations that do not
33 allow them to definitively resolve this major area of current controversy. If
34 nonasbestiform amphibole EMPs are, in fact, associated with some risk, a quantitative
35 risk assessment would be needed to understand the risks relative to those associated with
36 exposures to asbestos fibers. A risk assessment of nonasbestiform amphibole EMPs
37 should be performed if new epidemiological and other evidence is sufficient to support
38 such a risk estimate that could, in turn, lead to development of risk management policy
39 for nonasbestiform amphibole EMPs that is distinct from risk management policy for
40 asbestos fibers. Separate risk management policies would motivate the development of
41 new analytical methods that differentiate asbestiform from nonasbestiform particles on
42 air sample filters and their routine use.
43

1 Surveillance and epidemiological studies generally have been circumscribed by the long
2 latency periods that characterize manifestations of either pulmonary fibrosis (e.g., as
3 detected by chest radiographs or pulmonary function tests) or cancer caused by asbestos
4 exposures. Modern medical pulmonary imaging techniques or bioassays of circulating
5 levels of cytokines or other biochemical factors associated with disease processes might
6 be adaptable to better define early stages of asbestosis, and might provide a new
7 paradigm for early detection of the active disease process. For example, positron
8 emission tomographic imaging using tracers indicative of active collagen synthesis can
9 detect fibrogenic response in a matter of weeks after quartz dust challenge in a rabbit
10 animal model [Jones et al. 1997; Wallace et al. 2002].

11 12 ***3.5.3 Conduct Selective Epidemiological Studies of Workers Exposed to Asbestos*** 13 ***Fibers and Other EMPs*** 14

15 Statistically powerful and well designed epidemiological studies are typically very
16 expensive and time consuming, but they have been invaluable for defining associations
17 between human health outcomes and occupational exposures. In fact, the strongest
18 human evidence indicating that, at a sufficient dose and with a sufficient latency, certain
19 EMPs of thoracic dimension and high durability pose risks for malignant and
20 nonmalignant respiratory disease has come from epidemiological studies of workers
21 exposed to asbestos fibers.

22
23 Outcomes from proposed research efforts outlined above in Section 3.5.2 may identify
24 additional opportunities for informative epidemiological studies following the example of
25 NIOSH researchers who have recently undertaken a reanalysis of data from a prior
26 epidemiological study of asbestos textile workers after having more thoroughly
27 characterized exposures using sample filters archived from that study [Kuempel et al.
28 2006]. Outcomes from the approaches outlined above in Section 3.3.2 might also
29 potentially identify opportunities for aggregate meta-analyses of data from multiple prior
30 epidemiological studies, allowing an assessment of risks across various types of EMPs.

31
32 Given the ongoing and widespread occupational and environmental exposure to Libby
33 vermiculite, a more complete understanding of the mortality experience of the Libby
34 occupational cohort could shed light on risks associated with exposure to the attic
35 insulation from Libby, such as exposures at the World Trade Center disaster, as well as
36 the health effects among the Libby community. Analyses of the Libby worker cohort
37 continue and future analyses are envisioned, with the following aims:

- 38 • complete exposure-response modeling and occupational risk assessment for
39 mesothelioma and asbestosis.
 - 40 • description of non-respiratory outcomes (e.g., mortality with rheumatoid arthritis;
41 mortality from extra-pulmonary cancers)
- 42

1 Other research relating to Libby amphibole also continues. EPA and ATSDR have been
2 engaged in a program of research involving several recent projects, including evaluation
3 of:

- 4 • the relationship between radiographic abnormalities and lung function in Libby
5 community residents, finding that diffuse pleural thickening on radiography was a
6 significant predictor of both restrictive and obstructive patterns on spirometry.
- 7 • the natural history of radiographic disease progression, observing an exposure-
8 response relationship between cumulative fiber exposure and small opacity profusion
9 level on chest radiographs among Libby workers.
- 10 • the effect of exposure to asbestos-containing Libby vermiculite at 28 processing sites
11 in the United States. Activities included conducting medical screening of former
12 workers and household contacts at 6 sites. A summary report is available at:
13 www.atsdr.cdc.gov/asbestos/sites/national_map.
- 14 • cases of mesothelioma, asbestosis, and lung cancer among former workers and others
15 with non-occupational exposure associated with a vermiculite processing facility in
16 northeast Minneapolis.
- 17 • disease progression in workers exposed to asbestos-containing vermiculite ore at a
18 fertilizer plant in Marysville, Ohio.
- 19 • autoimmune conditions not classically associated with asbestos exposure, and on
20 health effects associated with low-level exposure and childhood exposure.

21
22 In addition, ATSDR continues to update its Tremolite Asbestos Registry (TAR) of
23 individuals exposed to vermiculite-associated asbestiform amphibole in Libby.
24 Opportunities for additional informative epidemiological studies relating to Libby
25 amphibole could be pursued in the future, particularly if an EM-based job-exposure
26 matrix for workers exposed to the Libby amphiboles is developed, or if amphibole
27 exposures during commercial building and household construction renovation tasks were
28 well-characterized.

29
30 Large unstudied populations with sufficiently high exposure to commercial asbestos
31 fibers are unlikely to be identified in developed countries like the United States, where
32 asbestos use has been markedly curtailed and where occupational exposures have been
33 strictly regulated in recent decades. Nevertheless, some developing countries (where
34 asbestos use continues on a large scale and where exposures may be less regulated) may
35 offer opportunities for *de novo* epidemiological studies that could contribute to a more
36 refined understanding of the association of human health outcomes with occupational
37 exposures to asbestos and other EMPs.

38
39 Opportunities for epidemiological studies of exposed workers might be sought in other
40 countries where medical registry data and historical or current workplace sampling data
41 are available (e.g., in China, where epidemiological studies of another occupational dust
42 disease, silicosis, have been collaboratively conducted by Chinese and NIOSH
43 researchers [Chen et al. 2005]).

1
2 Opportunities may also exist in other countries for epidemiological studies of non-worker
3 populations exposed to asbestos in ways not encountered in more developed countries.
4 For example, regular whitewashing of the interiors of homes has, in more than one
5 country, been shown to be fraught with hazard. In parts of Greece and Turkey, and in
6 New Caledonia, the local earthen material traditionally used for whitewashing homes
7 was predominantly composed of tremolite asbestos, resulting in high rates of
8 nonmalignant pleural plaques [Constantopoulos et al. 1987], lung cancer [Luce et al
9 2000; Menvielle et al. 2003], and malignant mesothelioma [Sakellariou et al. 1996;
10 Senyigit et al. 2000]. The whitewashing work, including crushing of the dry material
11 before addition of water, was typically done by women with small children in tow,
12 placing both sexes at risk of intermittent heavy exposures very early in life [Sakellariou et
13 al. 1996]. This, along with the longer term and lower-level exposures associated with
14 inhabiting homes whitewashed with this asbestos-containing material, represents an
15 exposure pattern very different from the occupational exposures to asbestos studied in the
16 United States and other industrialized countries.

17
18 Results from epidemiological studies of workers exposed to EMPs from nonasbestiform
19 amphibole minerals have provided limited, if any, evidence in support of an association
20 between occupational exposure and lung cancer or mesothelioma. It will be important to
21 establish *a priori* criteria to enable results of epidemiological studies or meta-analyses to
22 be used to indicate whether or not occupational exposure to EMPs from nonasbestiform
23 amphibole minerals is associated with a risk level that warrants preventive intervention.
24 Clearly laying out these criteria and assessing the feasibility of conducting necessary
25 studies should be done by a panel of knowledgeable experts. Laboratory research will
26 undoubtedly shed much light on the issue of potential human health risks associated with
27 specific physicochemical characteristics of EMPs, including amphibole cleavage
28 fragments. Still, where not only feasible but also judged likely to be informative, there is
29 reason to consider:

- 30 • Epidemiological studies of worker populations exposed to amphibole cleavage
31 fragments (e.g., taconite miners in Minnesota, talc miners in New York, etc.)
32 conducted either *de novo* or through updating of prior studies for more complete
33 follow-up of health outcomes and/or through re-analyzing archived exposure
34 samples for development of more specific knowledge concerning etiologic
35 determinants and quantitative risk;
- 36 • Epidemiological studies of worker populations incidentally exposed to EMPs
37 from fibrous minerals, including asbestiform minerals (e.g., those associated with
38 Libby vermiculite);
- 39 • Epidemiological studies of populations exposed to other less-well-studied EMPs
40 (e.g., wollastonite, attapulgite, and erionite); and
- 41 • Meta-analyses of data from multiple epidemiological studies of various worker
42 populations, each exposed to EMPs with somewhat different attributes (e.g., EMP

1 type, dimensions, etc.), to better define specific determinants of EMP-associated
2 adverse health outcomes for purposes of risk assessment.

3
4 The following criteria should be considered in selecting and prioritizing possible
5 populations for epidemiological study: (1) type of EMP exposure (e.g., mineral source,
6 chemical composition, crystalline structure, surface characteristics, and durability); (2)
7 adequate exposure information (e.g., EMP concentrations and (bivariate) EMP
8 dimensions); (3) good work histories; (4) sufficient latency; (5) number of workers
9 needed to provide adequate statistical power for the health outcome(s) of interest; and (6)
10 availability of data on other potentially confounding risk factors. Priority should be
11 placed on epidemiological studies with potential to contribute to the understanding of
12 EMP characteristics that determine toxicity, including type of mineral source (e.g.,
13 asbestiform mineral habit vs. other fibrous mineral habit vs. blocky mineral habit) and
14 morphology and other aspects of the airborne EMPs (e.g., dimensions [length and width],
15 chemical composition, crystalline structure, surface characteristics, and durability).

16
17 In addition to epidemiological studies that address etiology and that quantify exposure-
18 related risk, epidemiological studies can be used to better understand the pathogenesis of
19 lung diseases caused by asbestos fibers and other EMPs. For example, appropriately
20 designed epidemiological studies could be used to assess the relationship between lung
21 fibrosis and lung cancer.

22 23 ***3.5.4 Improve Clinical Tools and Practices for Screening, Diagnosis, Treatment, and*** 24 ***Secondary Prevention of Diseases Caused by Asbestos Fibers and Other EMPs***

25
26 Given the huge human and economic impact of asbestos-related disease and litigation,
27 Congress has considered asbestos-related legislation on several occasions in recent years.
28 To date, bills with provisions to require private industry to fund an asbestos victims' trust
29 fund have not succeeded in passing Congress. Most recently, a "Ban Asbestos in
30 America Act," which passed the U.S. Senate in 2007 but was not acted on in the House of
31 Representatives would have authorized and funded a network of Asbestos-Related
32 Disease Research and Treatment Centers to conduct research, including clinical trials, on
33 effective treatment, early detection, and prevention [U.S. Senate 2007]. This bill also
34 called for the establishment of a mechanism for coordinating and providing data and
35 specimens relating to asbestos-caused diseases from cancer registries and other centers,
36 including a recently funded virtual biospecimen bank for mesothelioma [Mesothelioma
37 Virtual Bank 2007].

38
39 Various research objectives relevant to clinical aspects of asbestos-related diseases are
40 worthy of pursuit by NIOSH and other federal agencies along with their partners to
41 improve screening, diagnosis, secondary prevention, and treatment. These include, but
42 are not limited to:

- 43 • Continue to develop and validate technical standards for the assessment of digital
44 chest radiographs using the ILO classification system. The ILO system for

1 classifying chest radiographs of the pneumoconioses is widely used as a standard
2 throughout the world. While initially intended for use in epidemiological studies,
3 the ILO system is now also commonly used as a basis for describing severity of
4 disease in clinical care and for awarding compensation to individuals affected by
5 non-malignant diseases of the chest caused by asbestos and other airborne dusts.
6 To ensure that digital chest radiographic methods used in future clinical and
7 epidemiological studies can be compared with past studies based on conventional
8 film radiography, there is a critical need to continue ongoing research to validate
9 use of the ILO system for classification of digital chest images.

- 10 • Develop and promote standardized assessment of non-malignant dust-induced
11 diseases, including asbestos-related pleural and parenchymal disease, on
12 computed tomography (CT) images of the chest. Over the past several decades,
13 CT scanning of the chest has become increasingly used for assessing chest disease
14 and high-resolution CT scanning is often done in clinical settings. While
15 approaches for standardizing classifications of CT images for dust-related
16 diseases have been proposed, none have yet been widely adopted or
17 authoritatively promoted.
- 18 • Develop, validate, and promote standardization of approaches for assessment of
19 past asbestos exposures by measurement of asbestos bodies and uncoated fibers,
20 particularly in samples collected noninvasively (e.g., sputum). Various
21 approaches for quantifying fiber burden have been used for research and clinical
22 purposes, but results are often difficult or impossible to compare across different
23 studies due to lack of standardization and differential rates of biopersistence and
24 translocation of various types of asbestos fibers.
- 25 • Develop and validate biomarkers for asbestosis, lung cancer, and mesothelioma to
26 enable more specific identification of those at risk or early detection of disease in
27 those previously exposed to asbestos. For example, non-invasive bioassays for
28 mesothelioma warrant further research before they can be considered ready for
29 routine application in clinical practice.
- 30 • Develop and/or adapt emerging medical imaging techniques to better define
31 stages of asbestosis, or to provide a new paradigm for early detection or grading
32 of the active disease process. For example, positron emission tomographic (PET)
33 imaging using tracers indicative of active collagen synthesis can detect pulmonary
34 fibrogenic response in a matter of weeks after quartz dust challenge in a rabbit
35 animal model [Jones et al. 1997; Wallace et al. 2002]. This holds promise for
36 non-invasive approaches for earlier clinical detection and more sensitive
37 surveillance and epidemiological studies, that to date have been circumscribed by
38 the long latency periods that characterize pulmonary fibrosis associated with
39 asbestos exposure (e.g., as detected by conventional chest radiography).
- 40 • Develop new treatment options to reduce risk of malignant and nonmalignant
41 disease among those exposed to asbestos and to effectively treat established
42 asbestos-induced disease. For example, many widely used anti-inflammatory
43 drugs exert their effect by inhibiting cyclooxygenase-2 (COX-2), an enzyme that

1 is induced in inflammatory and malignant (including pre-malignant) processes.
2 Promising results of laboratory and case-control epidemiological studies have led
3 to clinical trials of COX-2 inhibitors as adjuvant therapy to enhance treatments for
4 various types of cancer. Research is warranted to determine whether these drugs
5 can reduce the risk of asbestos-related malignancies in exposed individuals.

- 6 • Clear clinical guidance for practitioners, based on expert synthesis of available
7 literature, should be regularly updated and disseminated in an authoritative
8 manner.

9 10 **3.6 Develop Improved Sampling and Analytical Methods for Asbestos Fibers and** 11 **Other EMPs**

12
13 There are important scientific gaps in understanding the health impacts of exposure to
14 EMPs. Changes in how EMPs are defined for regulatory purposes will likely have to be
15 accompanied by improvements to currently used analytical methods or development and
16 application of new analytical methods. An ability to differentiate between fibers from the
17 asbestos minerals and EMPs from their nonasbestiform analogs in air samples is an
18 important need, especially for recommendations (e.g., occupational exposure limits)
19 specific to type of mineral. However, overcoming this obstacle may be difficult because
20 of: (1) lack of standard criteria for the mineralogical identification of airborne EMPs; and
21 (2) technical difficulties in generating test aerosols of size-specific EMPs representative
22 of worker exposures so that sampling and analytical methods can be tested and validated.

23
24 Improvements in exposure assessment methods are needed to increase the accuracy of the
25 methods used to identify, differentiate, and count EMPs captured in air-sampling filter
26 media. Until new analytical methods are developed and validated, it will be necessary to
27 investigate the various proposals that have been made to modify current analytical
28 methods, such as those discussed in Section 3.6.2, and additional modifications to the
29 current analytical methods.

30
31 Manual microscopy methods are labor intensive and error prone. Automated analyses
32 would permit examination of larger sample fractions and improve the accuracy of particle
33 classification. Developing a practical method that accurately counts and sizes all EMPs
34 could improve risk assessments and exposure assessments done in support of risk
35 management. Automated methods will reduce operator bias and inter-laboratory
36 variability, providing more consistent results for risk assessments.

37
38 Some barriers to improving current analytical methods have been identified. Increasing
39 the optical resolution of PCM analysis may help to increase counts of thinner asbestos
40 fibers. However, any increases in optical microscopy resolution will not be sufficient to
41 detect all asbestos fibers. In addition, any improvements in counting EMPs (e.g.,
42 increase in the number of EMPs observed and counted) will need to be evaluated by
43 comparing them with counts made by the current PCM method. The use of electron

1 microscopy (EM) would improve the capability to detect thin fibers and also provide a
2 means to identify many types of minerals. However, the routine use of EM would:

- 3 • require the development of standardized analytical criteria for the identification of
4 various EMPs;
- 5 • require specialized experience in microscopy and mineral identification;
- 6 • increase analytical costs; and
- 7 • potentially increase the lag time between collecting the sample and obtaining
8 results.

9
10 In some workplace situations, such as in construction, increases in the time needed to
11 analyze samples and identify EMPs could potentially delay the implementation of
12 appropriate control measures to reduce exposures.

13
14 Several potential sampling and analytical improvements are currently under study. Some
15 of the studies are aimed at improving the accuracy of current techniques used for
16 monitoring exposures to asbestos. One such study is evaluating the use of thoracic
17 samplers for the collection of airborne EPs and another is studying the use of gridded
18 cover slips for PCM analyses. The proposed use of gridded cover slips for sample
19 evaluation can aid in the counting of asbestos and other EMPs and can provide a means
20 for "recounting" fibers at specific locations on the filter sample. Another study is
21 evaluating the proposed ASTM method to determine whether inter-operator variability of
22 differential counting (to distinguish fibers of asbestos minerals from other EMPs) is
23 within an acceptable range.

24
25 Research into new methods development is warranted. One such area would be the
26 development of methods that would permit an assessment of the potential biopersistence
27 (e.g., durability) of EMPs collected on air sampling filters prior to their evaluation by
28 PCM or other microscopic methods. If durability is deemed biologically relevant, then
29 an exposure assessment limited to only durable EMPs collected on a sample would help
30 to reduce possible analytical interferences caused by other non-durable EMPs and may
31 eliminate the need for mineral identification. Another such area would be improvement
32 in EM particle identification techniques, such as field emission SEM and the capability to
33 determine the elemental composition of EMPs using an SEM equipped with EDS.

34
35 Modifications of current analytical methods and development of new analytical methods
36 will require an assessment of their implications for worker health protection (e.g., how do
37 the results using improved or new methods relate to human risk estimates based on
38 counts of EMPs made by PCM?). To ensure that relevant toxicological parameters (e.g.,
39 dimension, durability, and physicochemical parameters) are incorporated in the analysis
40 and measurement, any changes in analytical methods should be made in concert with
41 changes in how asbestos fibers or other EMPs are defined.

1
2 **3.6.1 Reduce Inter-operator and Inter-laboratory Variability of the Current Analytical**
3 **Methods Used for Asbestos Fibers**
4

5 To ensure the validity of EMP counts made on air samples, it is important to ensure
6 consistency in EMP counts between and among analysts. Microscopy counts of EMPs on
7 air sample filters are made using only a small percentage of the surface area of the filter,
8 and the counting procedures require the analyst to make decisions on whether each
9 observed particle meets specified criteria for counting. Interlaboratory sample exchange
10 programs have been shown to be important for ensuring agreement in asbestos fiber
11 counts between laboratories [Crawford et al. 1982]. Unfortunately, microscopists from
12 different laboratories are unlikely to view exactly the same fields, and this alone accounts
13 for some of the observed variation in fiber counts between microscopists. A mechanism
14 to allow recounts of fibers from the exact same field areas would remove this variable
15 and allow a better assessment of the variation attributable to microscopists in analyzing
16 samples.

17
18 A technique is under development for improving the accuracy of PCM-based fiber-
19 counting by allowing the same sample fields to be examined by multiple microscopists or
20 by the same microscopist on different occasions [Pang et al. 1984, 1989; Pang 2000].
21 The method involves the deposition of an almost transparent TEM grid onto the sample.
22 Included with the grid are coordinates which allows relocation of each grid opening.
23 Photomicrographs of typical grid openings superimposed on chrysotile and amosite
24 samples have been published [Pang et al. 1989]. Slides prepared in this manner have
25 been used in a Canadian proficiency test program for many years. The main errors
26 affecting the counts of various types of fibers (e.g., chrysotile, amosite, and SVF) have
27 been evaluated by examining large numbers of slides by large numbers of participants in
28 this program. A recently developed scoring system for evaluating the performance of
29 microscopists is based on errors compared with a reference value defined for each slide
30 by the laboratory in which they were produced [Pang 2002]. A statistical analysis of the
31 intra-group precision in this study was able to identify those analysts who were outliers
32 [Harper and Bartolucci 2003]. In a pilot study, the pooled relative standard deviations,
33 without the outliers, met the requirements for an unbiased air sampling method. Further
34 study is needed to validate these findings and to identify other techniques that can reduce
35 inter-laboratory and inter-operator variability in counting asbestos and other EMPs by
36 PCM.

37
38 Reference slides made from proficiency test filters from the American Industrial Hygiene
39 Association (AIHA) have been created and circulated to laboratories and individual
40 microscopists recruited from AIHA laboratory quality programs [Pang and Harper 2008;
41 Harper et al. 2009]. The results illustrate an improved discrimination of fiber counts
42 when the proficiency test materials have a more controlled composition. These reference
43 slides have also been evaluated in Japan, the United Kingdom, and elsewhere in Europe.

1 Further research will be useful in determining the value of these slides for training
2 purposes.

3
4 **3.6.2 Develop Analytical Methods with Improved Sensitivity to Visualize Thinner**
5 **EMPs to Ensure a More Complete Evaluation of Airborne Exposures**

6
7 Most PCMs can visualize EMPs with widths $>0.25 \mu\text{m}$, which is the approximate lower
8 resolution limit when the microscope is operated at a magnification of 400X and
9 calibrated to NIOSH 7400 specifications [NIOSH 1994a]. However, higher-end optical
10 microscopes can resolve thinner widths, and, for crocidolite, they may resolve widths as
11 thin as $0.1 \mu\text{m}$.

12
13 Improvement in the optical resolution may be possible using an oil-immersion 100X
14 objective with a numerical aperture of 1.49. Also, the use of 15X eyepiece oculars would
15 help improve the visibility of small particles and thin EMPs on samples. However, using
16 oil immersion has several drawbacks. When exposed to air for more than a few hours,
17 the oil on the slide dries and its optical properties change. Also, the oil cannot be wiped
18 off because the cover slip is likely to be moved and ruin the sample. For these reasons,
19 using oil immersion does not permit recounts or further analysis for quality control
20 purposes and is not an attractive alternative.

21
22 Other methods may also allow for increased resolution using optical microscopes.
23 Anecdotal information on the use of PCM using dark-medium (DM) objectives,
24 presented at a meeting in November 2007, suggests that analysts using DM objectives
25 could resolve more blocks of the Health and Safety Executive/National Physical
26 Laboratory (HSL/ULO) test slide⁴ than are allowable for the method and produced higher
27 counts of chrysotile fibers than expected [Harper et al. 2009]. The implication is that
28 using DM objectives can resolve thinner chrysotile fibers than the accepted method. This
29 methodology should be explored further to determine its resolution and potential
30 application in asbestos exposure assessment.

31
32 As stated previously, because risk estimates for workers exposed to asbestos fibers have
33 been based on counts made by the current PCM method, counts made with improved
34 optical microscope resolution capabilities would not be directly comparable to current
35 occupational exposure limits for airborne asbestos fibers. Additionally, the findings that
36 asbestos fibers thinner than $0.1 \mu\text{m}$ are most associated with mesothelioma and that
37 optical microscopes cannot resolve fibers $<0.1 \mu\text{m}$ in width suggest that alternatives to
38 PCM should be researched.

⁴The HSE/NPL Mark II or HSL/ULO Mark III Phase Shift Test Slide checks or standardizes the visual detection limits of the PCM. The HSL/ULO Test Slide consists of a conventional glass microscope slide with seven sets of parallel line pairs of decreasing widths. The microscope must be able to resolve the blocks of lines in accordance with the certificate accompanying the slide. Only slides where at least one block of lines is intended to be invisible should be used. Microscopes which resolve fewer or greater numbers of blocks than stated on the certificate cannot be used in the NIOSH 7400 fiber counting method.

1
2 TEM can resolve asbestos fibers with widths $< \sim 0.01 \mu\text{m}$, which effectively detects the
3 presence of asbestos fibers and other EMPs collected on airborne samples. Both TEM
4 and SEM provide greater resolution for detecting and sizing EMPs. Both methods also
5 provide capability for mineral identification (TEM using selected area X-ray diffraction
6 [SAED], TEM and SEM using EDS or WDS for elemental analysis). The cost of using
7 TEM and/or SEM for routine analysis of all samples would be considerably higher than
8 PCM analysis and the turnaround time for analysis would be substantially longer. In
9 addition, any routine use of EM methods for counting and sizing asbestos fibers or other
10 EMPs would require formal evaluation of inter-operator and inter-laboratory variability.

11
12 SEM is now a generally available method which can routinely resolve features down to
13 $\sim 0.05 \mu\text{m}$, an order of magnitude better than optical microscopes. Field emission SEM
14 (FE-SEM) is now commercially available and further increases this resolution. *In vitro*
15 or short-term or long-term animal model studies can now utilize these EM imaging
16 technologies to characterize EMPs for studies of etiology and disease mechanism. EM
17 analyses of EMP size and composition can be supplemented with analysis of surface
18 elemental composition by scanning Auger spectroscopy or X-ray photoelectron
19 spectroscopy. Investigation is needed to determine whether SEM-backscatter electron
20 diffraction analysis can be adapted to EMP crystallographic analyses equivalent to TEM-
21 SAED capability. Ease of sample preparation and data collection for SEM analysis
22 compared to TEM, along with some SEM advantage in visualizing EMP and EMP
23 morphology (e.g., surface characteristics), provides reason to reevaluate SEM methods
24 for EMP characterization and mineral identification both for field and laboratory sample
25 analysis.

26 27 ***3.6.3 Develop a Practical Analytical Method for Air Samples to Differentiate Between*** 28 ***Asbestiform Fibers from the Asbestos Minerals and EMPs from Their*** 29 ***Nonasbestiform Analogs*** 30

31 A recently published ASTM method for distinguishing other EMPs from probable
32 asbestos fibers uses PCM-determined morphologic features to differentiate asbestos
33 fibers from other EMPs [ASTM 2006]. The proposed method has several points of
34 deviation from existing PCM methods. It uses a new graticule that has not been tested
35 for conformance with the traditional graticule used in standard PCM analysis of asbestos
36 air samples. It specifies additional counting rules to classify particles, and there are few
37 data to show these rules provide consistently achievable or meaningful results. Also,
38 only limited data are available to show inter- or intra-operator or inter-laboratory
39 variation. These issues must be addressed before the method can be considered
40 acceptable. NIOSH researchers are currently addressing these issues. Specific aims of
41 the project are:

- 42 • to determine the effect of using the traditional Walton-Beckett graticule and the
43 new RIB graticule on the precision of measuring fiber dimensions; and

- 1 • to determine the inter-laboratory variation of the proposed method for
2 determining particle identities by observing morphological features of individual
3 particles.
4

5 Anticipated outcomes of these ongoing research projects include a measure of method
6 precision, which will help to determine whether the method meets the requirements of
7 regulatory and other agencies.
8

9 While EM may currently not be suitable for routine analysis of samples of airborne
10 EMPs, EM techniques used to characterize and identify minerals (e.g., differentiating
11 between asbestos fibers and other EMPs) should be further investigated and evaluated to
12 determine whether results are reproducible by multiple microscopists and laboratories.
13

14 ***3.6.4 Develop Analytical Methods to Assess Durability of EMPs***

15
16 While some research has been conducted to determine the ability of biological assays to
17 evaluate the biopersistence of EMPs in the lung, there is a need to consider how the
18 assessment of EMP durability might be incorporated into the evaluation of air samples
19 containing a heterogeneous mix of EMPs. Research with several types of glass fibers and
20 some other SVFs indicate that they dissolve in media at different rates depending on the
21 pH and that they dissolve more rapidly than chrysotile and amphibole asbestos fibers
22 [Leineweber 1984]. Chrysotile fibers have been shown to dissolve at a rate which varies
23 not only with the strength of the acid, but also with the type of acid. Amphibole asbestos
24 fibers have been shown to be more resistant to dissolution than chrysotile fibers.
25 Research suggests that the rate of dissolution in the lungs for most EMPs appears to be
26 strongly dependent on their chemical composition, surface characteristics, and dimension.
27

28 The selective dissolution of EMPs might be a useful approach in eliminating specific
29 types of EMPs or other particles collected on air samples prior to analysis (e.g.,
30 microscopic counting). The removal of interfering EMPs prior to counting could
31 potentially eliminate the need for additional analysis to identify EMPs on the sample.
32 Selective dissolution of samples to remove interferences is well established in NIOSH
33 practice for other analytes. NIOSH Method 5040 for diesel exhaust has an option for
34 using acidification of the filter sample with hydrochloric acid to remove carbonate
35 interference [NIOSH 2003a]. Silicate interferences for quartz by infra-red spectroscopic
36 detection are removed by phosphoric acid digestion in NIOSH Method 7603 [NIOSH
37 2003b]. Although selective dissolution might be accomplished for some EMPs, research
38 will be necessary to develop and characterize a procedure that would correlate residual
39 EMP counts to the results of toxicity studies.
40

41 ***3.6.5 Develop and Validate Size-selective Sampling Methods for EMPs***

42
43 For measuring airborne concentrations of non-elongate particles in the workplace,
44 conventions have been developed for sampling the aerosol fractions that penetrate to

1 certain regions of the respiratory tract upon inhalation: the inhalable fraction of
2 particulate that enters into the nose or the mouth; the fraction that penetrates into the
3 thorax (i.e., beyond the larynx); and the respirable fraction that reaches the alveoli of the
4 lung. The thoracic convention is recognized by NIOSH and other organizations that
5 recommend exposure limits, and NIOSH has established precedence in applying it in
6 RELs (e.g., the REL for metalworking fluid aerosols [NIOSH 1998]).

7
8 Asbestos fibers currently are collected for measurement using standard sampling and
9 analytical methods (e.g., NIOSH Method 7400 [NIOSH 1994a], in OSHA ID-160
10 [OSHA 1998], in Methods for the Determination of Hazardous Substances (MDHS) 39/4
11 [HSE 1995], and in ISO 8672 [ISO 1993]). In these methods, air samples are taken using
12 a membrane filter housed in a cassette with a cowled sampling head. Early studies
13 [Walton 1954] showed that the vertical cowl excludes some very coarse particles due to
14 elutriation, but its selection characteristics should have little effect on the collection
15 efficiency for asbestos fibers. However, when Chen and Baron [1996] evaluated the
16 sampling cassette with a conductive cowl used in sampling for asbestos fibers, they found
17 inlet deposition was higher in field measurements than predicted by models.

18
19 Unlike the WHO [1997], NIOSH has not recommended an upper limit for width of
20 asbestos fibers to be counted because airborne asbestos fibers typically have widths <3
21 μm . The absence of an upper width criterion for the NIOSH Method 7400 A rules has
22 generated criticism that some EMPs counted by this method may not be thoracic-size.
23 Others have recommended NIOSH Method 7400 B rules for the sampling and analysis of
24 various types of fibers and EPs, including asbestos fibers [Baron 1996], because the B
25 rules specify an upper limit of 3 μm for EP width. However, Method 7400 B rules have
26 not been field-tested for occupational exposures to asbestos and many types of EPs.

27
28 Two separate but complementary investigations have examined the performance of
29 thoracic samplers for EMPs [Jones et al. 2005; Maynard 2002]. Thoracic samplers allow
30 the collection of airborne particles that meet the aerodynamic definition of thoracic-size
31 EMPs (i.e., with physical widths equal to or less than 3 μm for the typical length
32 distributions of fibers of silicate composition), collecting only those EMPs considered
33 most pathogenic. The results of studies have indicated that penetration of some thoracic
34 samplers is independent of EMP length, at least up to 60 μm , indicating that the
35 samplers' penetration characteristics for an EP aerosol should be no different than that of
36 an isometric aerosol. In the Jones et al. [2005] study, the relative ability of the thoracic
37 samplers to produce adequately uniform distributions of EPs on the surface of the
38 membrane filter was also tested. Based on results of these studies, two samplers
39 appeared to meet the criteria of minimal selection bias with respect to EP length and
40 uniform distribution on the collection filters. However, neither of these samplers has
41 been tested under conditions of field use. NIOSH is currently evaluating these two
42 thoracic samplers and the traditional cowled sampler in three different mining
43 environments. The results from the first of these environments have been published [Lee
44 et al. 2008]. In this study, one sampler provided results comparable to the standard 25-

1 mm cowed cassette, while the other did not. Additional results are required to clarify
2 this conclusion.

3 4 **3.7 From Research to Improved Public Health Policies for Asbestos Fibers and** 5 **Other EMPs**

6
7 Section 3 of this *Roadmap* proposes several strategic goals and associated objectives for a
8 multi-disciplinary research program on asbestos fibers and other EMPs. In summary,
9 accomplishing these goals is intended: (1) to further elucidate the physicochemical
10 properties that contribute to their pathogenicity; (2) to improve existing analytical tools
11 and develop new analytical tools for identifying and measuring exposures to EMPs using
12 metrics that reflect the important determinants of toxicity (e.g., dimension, composition,
13 etc.); (3) to better understand the nature and extent of occupational exposures to EMPs
14 and their relationships to EMP-related health outcomes among exposed worker
15 populations; and (4) to improve clinical tools for screening, diagnosis, secondary
16 prevention, and treatment of EMP-related diseases.

17
18 Results of much of the research to date (e.g., animal and human studies with asbestos and
19 other EMPs) are readily available and should be considered in developing the research
20 program, including the specification of minerals to be studied. Much of this evidence
21 supports the important role of particle dimension as a determinant of lung deposition and
22 retention and the concomitant role of particle composition and crystalline structure as a
23 determinant of durability and biopersistence. Despite this body of research, several
24 fundamental issues are not clearly understood and a broad systematic approach to further
25 toxicological and epidemiological research would help to reduce remaining uncertainties.
26 Although long, thin asbestos fibers clearly cause respiratory disease, the role of
27 unregulated short (i.e., $<5\mu\text{m}$) asbestos fibers is not entirely clear. It also remains unclear
28 to what extent each of the various physicochemical parameters of asbestos fibers is
29 responsible for respiratory disease outcomes (e.g., asbestosis, lung cancer, and
30 mesothelioma) observed in asbestos-exposed individuals. Limited evidence from studies
31 with other EMPs confirms the importance of particle dimension and biopersistence in
32 causing a biological response. However, uncertainty remains as to whether the
33 respiratory disease outcomes observed in workers exposed to asbestos fibers can be
34 anticipated for workers exposed to other EMPs of thoracic-size and with elemental
35 compositions similar to asbestos.

36
37 Results of much of the research to date, conducted on materials that are readily available
38 or of specific interest, should be considered in developing the research program,
39 including the specification of materials to be studied. Another important effort that can
40 inform development of the research program will involve a systematic collection and
41 review of available information on: (1) industries and occupations with exposure to
42 EMPs; (2) airborne exposure in these industries and occupations; and (3) numbers of
43 workers potentially exposed in these industries and occupations. Additional relevant
44 minerals and mineral habits identified should also be considered for study. The minerals

1 identified through these efforts should be carefully and comprehensively characterized
2 with respect to both structure and elemental composition. In the characterization of
3 minerals, consideration should also be given to: (1) purity of the mineral; (2) particle
4 morphology (range of dimensions and sizes); (3) surface area; (4) surface chemistry; and
5 (5) surface reactivity. Care must be taken to ensure that a sufficient amount of the
6 studied material is available, not only for current studies, but also as reference material
7 for possible future studies. The information developed from all of these efforts should be
8 entered into a database which can serve as a tool for selection of minerals for testing and
9 validation of toxicological tests, as well as to assist in identification of worker
10 populations for possible epidemiological studies.

11
12 An objective of the proposed research is to achieve a level of mechanistic understanding
13 that can provide a basis for developing biologically-based models for extrapolating
14 results of animal inhalation and other types of *in vivo* studies to predict risks to worker
15 health associated with exposure conditions typically encountered in workplaces.
16 Presently, little information exists on the mechanisms by which asbestos fibers and some
17 other EMPs produce lung cancer, mesothelioma, and non-malignant respiratory diseases.
18 As these mechanisms become understood, biologically based models can be developed to
19 extrapolate from exposure-dose-response relationships observed in animals to estimates
20 of disease risk in exposed humans. In addition, such studies would provide: (1) an
21 opportunity to measure molecular and cellular outcomes that can be used to determine
22 why one animal species responds differently from another; and (2) information on EMP
23 characteristics associated with eliciting or potentiating various biological effects. The
24 outcomes of these studies can then be evaluated in subsequent experiments to provide:
25 (1) risk assessors with a useful understanding of the various disease mechanisms by
26 which animals respond to EMP exposures; and (2) regulatory agencies and industrial
27 hygiene and occupational health professionals with information needed to implement
28 appropriate exposure limits and risk management programs for monitoring worker
29 exposure and health.

30
31 It is anticipated that it may be difficult to find populations of workers that are exposed to
32 EMPs with characteristics (e.g., dimension, composition) of interest that are sufficiently
33 large to provide adequate statistical power, and where exposures are unconfounded or
34 where confounding can be effectively controlled in the analysis. NIOSH retains exposure
35 information and, in some cases, personal air sample filters collected and archived from
36 past epidemiological studies of workers exposed to asbestos. Such existing data might be
37 used to update and extend findings from these studies. Where appropriately balanced
38 epidemiological studies can be identified, it may be possible to conduct meta-analyses to
39 investigate important EMP characteristics. The analysis of archived samples may help to
40 elucidate how more detailed characteristics of exposure (e.g., particle dimension) relate to
41 disease outcomes. New epidemiological (retrospective and prospective) studies should
42 not be undertaken unless feasibility studies (e.g., preliminary assessments of study
43 population size, exposure latencies, records of exposure, confounders, etc.) have been
44 appropriately considered.

1
2 Because the opportunities for informative epidemiological studies are likely to be limited,
3 it will be necessary to complement them with toxicological testing, and an integrated
4 approach to toxicological research will be needed to understand how various types of
5 EMPs induce disease. Where epidemiological studies of new cohorts are possible, or
6 where epidemiological studies of previously studied cohorts can be updated, attempts
7 should be made to link their results with those of toxicological studies to assess the
8 ability of various types of toxicological testing to predict health outcomes in humans.
9 Toxicological testing should be done with attention to collecting more specific
10 information, including: (1) physical characteristics (e.g., dimension); (2) chemical
11 composition; (3) *in vitro* acellular data (dissolution, durability); and (4) *in vitro/in vivo*
12 cellular data (e.g., cytotoxicity, phagocytosis, chromosomal damage, mediator release).
13

14 To help elucidate which physicochemical properties are important for inducing a
15 biological effect, it may be necessary to generate exposures to EMPs of specific
16 dimensions and composition. Several approaches are being pursued by NIOSH to
17 overcome technological difficulties in generating sufficient quantities of well-
18 characterized and dimensionally-restricted EMPs. Efforts to generate mineral samples of
19 appropriate particle size dimensions using grinding techniques have met with some
20 success, but have not consistently generated EMPs in restricted size ranges of interest or
21 in sufficient quantity to enable toxicity testing. Another approach has used a fiber size
22 classifier [Deye et al. 1999], but this has not provided large enough quantities of EMPs
23 for long-term inhalational exposure studies in animals. NIOSH researchers are currently
24 evaluating the possibility of developing a fiber size classifier with increased output to
25 generate much larger quantities of particles in restricted size-ranges for toxicological
26 testing.
27

28 An outcome of the proposed research programs should be an understanding of the
29 relationships between and among the results of human observational studies and *in vitro*,
30 short-term *in vivo*, and long-term *in vivo* experimental studies. Any research undertaken
31 should be designed to ensure that results can be interpreted and applied within the context
32 of other studies. For example, EMPs used in long-term animal inhalation studies should
33 also be tested in *in vitro/in vivo* assay systems so that findings can be compared. The
34 results of such experiments can help to develop and standardize *in vitro/in vivo* assay
35 systems for use in predicting the potential toxicity of various types of EMPs.
36

37 Government agencies, other organizations, and individual researchers have already
38 recommended similar research strategies for evaluating the toxicity of mineral and
39 synthetic fibers [Greim 2004; ILSI 2005; Mossman et al. 2007; Schins 2002; Vu et al.
40 1996]. These published strategies should be used as a foundation for developing a
41 research program.
42

43 Some research and improvements in sampling and analytical methods used to routinely
44 assess exposures to EMPs can be done in the short term, and as the results of the

1 toxicological studies provide a clearer understanding of EMP characteristics that
2 determine toxicity, it will be necessary to ensure that the measurement techniques used in
3 evaluating workplace exposures incorporate the exposure metrics used in determining the
4 dose-response effect found in animal studies. The development of such exposure
5 measurement techniques should: (1) reduce the subjectivity inherent in current methods
6 of particle identification and counting; (2) closely quantify EMPs based on characteristics
7 that are important to toxicity; and (3) reduce cost and shorten turnaround times compared
8 to current EM methods.

9
10 Toxicological, exposure assessment, and epidemiological research should be conducted
11 with the overarching goal of developing information necessary for risk assessments.
12 Improved risk assessments and analytical methodology are needed to inform the
13 development of new and revised occupational exposure limits for control of exposures
14 associated with the production of EMP-caused disease.

15
16 For those individuals who have an asbestos-related disease or are at a high risk of
17 developing an asbestos-related disease, research is needed to improve methods and
18 clinical guidance for screening, diagnosis, secondary prevention, and treatment of EMP-
19 caused diseases. The development and validation of biomarkers of disease and improved
20 lung imaging technologies can lead to earlier diagnosis of asbestos-related disease. It
21 will also be important to advance knowledge on how to effectively treat EMP-caused
22 diseases, especially malignant mesothelioma, which is currently a fatal disease in most
23 cases. Accomplishing the goals of early diagnosis and development of treatment options
24 can improve the quality and quantity of life for those who develop asbestos-related
25 disease.

26
27
28

4 THE PATH FORWARD

1
2
3 Developing an interdisciplinary research program and prioritizing research projects to
4 implement the research agenda envisioned in *Asbestos Fibers and Other Elongate*
5 *Mineral Particles: State of the Science and Roadmap for Research* will require a
6 substantial investment of time, scientific talent, and resources by NIOSH and its partners.
7 However, achieving the proposed goals will be well worth the investment because it will
8 improve the quality of life of U.S. workers by preventing workplace exposure to
9 potentially hazardous EMPs, and it will reduce future healthcare costs. As with any
10 strategic approach, unintended and unforeseen results and consequences will require
11 program adjustments as information is produced and time goes on.

4.1 Organization of the Research Program

12
13
14
15 To ensure that the scientific knowledge created from implementation of the *Roadmap* is
16 applied as broadly as possible, NIOSH plans to partner with other federal agencies,
17 including the Agency for Toxic Substances and Disease Registry (ATSDR), the
18 Consumer Product Safety Commission (CPSC), the Environmental Protection Agency
19 (EPA), the Mine Safety and Health Administration (MSHA), the National Institute of
20 Standards and Technology (NIST), the National Institute of Environmental Health
21 Sciences (NIEHS), the National Toxicology Program (NTP), the Occupational Safety and
22 Health Administration (OSHA), and the United States Geological Survey (USGS), as
23 well as with labor, industry, academia, practitioners, and other interested parties
24 including international groups. Partnerships and collaborations will be used to help focus
25 the scope of the research to be undertaken, enhance extramural research activities, and
26 assist in the development and dissemination of educational materials describing the
27 outcomes of the research and their implications for occupational and public health
28 policies and practices.

29
30 Some of the next steps in development will involve organizing study groups with
31 representatives from federal agencies, industry, academia, and workers' groups to
32 identify the specific priorities for the research programs developed within the overarching
33 research framework. Study groups should be assembled from among the partners to
34 identify specific research elements needed to address the information gaps and data needs
35 outlined in this *Roadmap*. Although it may be appropriate to organize separate study
36 groups around the scientific disciplines needed to conduct the research, such as
37 epidemiology, toxicology, exposure assessment, mineralogy, particle characterization and
38 analysis, and risk assessment, each of the study groups will need to include members
39 from other disciplines to ensure the multi-disciplinary nature of the research is considered
40 and addressed. Also important will be coordination between and among study groups to
41 ensure the efforts in the various research areas are complementary and move toward
42 common goals and the eventual development of sufficient information for risk
43 assessment. These study groups should be maintained over the lifetime of the research

1 program to oversee and help guide the research. An independent group could provide
2 oversight of the overall research effort, periodically reviewing the various discipline-
3 specific research programs to help ensure that the most appropriate research is
4 accomplished in a timely, and coordinated manner and to help maintain the scientific
5 quality of the research.

6 7 **4.2 Research Priorities**

8
9 The key issues discussed in Section 2.10 include several research needs: (1) for the
10 asbestos minerals, development of a clearer understanding of the important dimensional
11 and physicochemical determinants of pathogenicity; (2) for other EMPs, such as those
12 from nonasbestiform habits of the asbestos minerals and erionite, development of a
13 deeper understanding of the determinants of toxicity; and (3) development of analytical
14 methods that can differentiate EMPs and quantify airborne exposures to EMPs. To begin
15 addressing these issues, infrastructure projects should be developed and initiated with
16 input from the study groups.

17
18 One of the infrastructure projects to be initiated with input from the study groups is the
19 development of a standardized set of terms that can be used to clearly and precisely
20 describe minerals and other scientific concepts. This is needed to help with the planning
21 of research projects and to effectively communicate research results. This effort should
22 involve representatives from each of the relevant scientific disciplines.

23
24 Another infrastructure project that should be considered at the onset of prioritizing
25 research is the development of criteria and logistics for establishing a mineral reference
26 repository. Initially, representative samples from the known asbestos deposits should be
27 procured and carefully and comprehensively characterized. If samples of these repository
28 minerals are further processed in the course of conducting research, the processed
29 materials will need to be fully characterized as well. Concomitant with this
30 characterization effort should be the development of a mineralogical research effort
31 addressing issues pertaining to the identification of minerals that might be found on
32 airborne samples collected at various workplace environments and to develop further and
33 deeper understanding of mineralogical properties which may contribute to the toxicity of
34 particles.

35
36 One of the earliest research efforts will be preliminary systematic collection and
37 evaluation of available information on: (1) industries/occupations/job tasks/processes
38 with exposure to various types of asbestos fibers and other EMPs; (2) numbers of
39 workers exposed; (3) characteristics and levels of exposures; and (4) associated
40 particulate exposures. The knowledge generated from these efforts will be needed to
41 identify the EMPs that workers are exposed to and worker populations that have the
42 potential to be included in epidemiological studies. In addition to ascertaining EMP
43 exposures and EMP-exposed populations in the U.S., networking and other tools should
44 be used to identify potential international populations for epidemiological studies.

1 Representative samples of the EMPs identified through these efforts should be procured,
2 characterized, and included in the mineralogical reference repository. After thorough
3 characterization, these samples can be classified and prioritized for use in the
4 toxicological studies.

5
6 A part of this early effort should be the development of a comprehensive and integrated
7 public-use information management system to warehouse: (1) the mineral
8 characterization information generated on the reference samples; (2) data generated from
9 hazard and health surveillance activities; (3) information on the minerals tested and the
10 methods used as well as the results of toxicological studies; and (4) the data gathered
11 from epidemiological and other surveillance investigations. By having the results of
12 previous studies available in the information management system, it could be used to
13 promote the development of an efficient, non-duplicative research program. It could also
14 be a resource for data exploration and additional analyses of accumulated results.

15
16 After comprehensive review of current knowledge and the available data in the above-
17 described information management system, the study groups should identify specific
18 research aims and plan, prioritize, and conduct mineralogical, toxicological,
19 epidemiological, and clinical research within the general framework laid out in this
20 *Roadmap*. The results from early research will inform the need for later research and will
21 dictate changes in priorities and directions for the research needed to accomplish the
22 overall goals of the research program.

23
24 Ongoing research and study on improvements of the analytical methods currently used
25 for regulatory purposes should be independent of other research. However, as
26 surveillance and exposure assessment efforts proceed, research on analytical methods
27 should advance the capability to identify and characterize worker exposures and to
28 measure relevant exposure parameters identified by toxicological research. Eventually,
29 after determinants of EMP toxicity are more fully elucidated, research should
30 increasingly focus on sampling and analytical methods that can be routinely used in
31 compliance exposure assessment.

32 33 **4.3 Outcomes**

34
35 NIOSH will promote integration of the research goals set forth in the *Roadmap* into the
36 industry sector-based and research-to-practice-focused National Occupational Research
37 Agenda (NORA), an agenda for the Nation involving public and private sectors. The
38 goals and objectives of this *Roadmap* can be substantially advanced through robust
39 public-private sector partnership.

40
41 The ideal outcome of a comprehensive research program for asbestos fibers and other
42 EMPs would be to use the results of this research to develop recommendations to protect
43 workers' health that are based on unambiguous science. Optimally, such
44 recommendations may specify criteria, such as a range of chemical composition,

1 dimensional attributes (e.g., ranges of length, width, and aspect ratio), dissolution
2 rate/fragility parameters, and other factors that can be used to indirectly assess the
3 toxicity of EMPs. It would be particularly advantageous if the results of the research
4 could be used to devise a battery of validated *in vitro* or short-term *in vivo* assays with
5 sufficient predictive value to identify EMPs warranting concern based on their physical
6 and chemical properties, without the need for comprehensive toxicity testing and/or
7 epidemiological evaluation of each individual EMP. Newly identified EMPs could be
8 compared to the criteria to determine a likelihood of toxicity. Coherent risk management
9 approaches for EMPs that fully incorporate a clear understanding of the toxicity could
10 then be developed to minimize the potential for EMP-related disease outcomes among
11 exposed workers.

12
13 Although beyond the scope of this *Roadmap*, the extent to which a health-protective
14 policy for EMPs could be extended to SVFs and other manufactured materials, such as
15 engineered carbon nanotubes, warrants exploration. It has been noted that elongate
16 nanoscale particles (e.g., single- and multi-walled carbon nanotubes) cause interstitial
17 fibrosis in mice [Shvedova et al. 2005; Porter et al. 2009] and that peritoneal exposure of
18 mice to carbon nanotubes has been reported to induce pathological responses similar to
19 those caused by asbestos, suggesting potential for induction of mesothelioma [Poland et
20 al. 2008]. Recommendations have been made elsewhere to systematically investigate the
21 health effects of these manufactured nanomaterials within the next five years [Maynard et
22 al. 2006; NIOSH 2008b]. Integrating results of nanoparticle toxicity investigations with
23 the results of the research program developed as a result of this *Roadmap* may lead to a
24 broader and more fundamental understanding of the determinants of toxicity of EPs.

25
26 Working towards achieving the goals delineated in the *Roadmap* is consonant with
27 NIOSH's statutory mission to generate new knowledge in the field of occupational safety
28 and health and to transfer that knowledge into practice for the benefit of workers.
29 Advancing knowledge relevant for use in protecting workers from adverse health effects
30 arising from exposure to asbestos fibers and other EMPs is the ultimate goal. Though
31 further scientific research conducted by NIOSH researchers will continue to focus on the
32 *occupational* environment, NIOSH intends to pursue partnerships to ensure that scientific
33 research arising from the *Roadmap* will comprise an integrated approach to
34 understanding and limiting EMP hazards incurred not only in work settings, but also in
35 the general community and the general environment.

36
37 In addition to participation in the development of the research priorities and programs,
38 partnerships and collaborations will assist in the development and dissemination of
39 educational materials describing the outcomes of the research and their implications for
40 occupational and public health policies and practices.

41
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6 GLOSSARY

6.1 Definitions of New Terms Used in this Roadmap

Countable elongate mineral particle: A particle that meets specified dimensional criteria and is to be counted according to an established protocol. A countable elongate mineral particle under the NIOSH REL for *Airborne Asbestos Fibers and Related Elongate Mineral Particles* is any asbestiform fiber, acicular or prismatic crystal, or cleavage fragment of a *covered mineral* which is longer than 5 μm and has a minimum aspect ratio of 3:1 based on a microscopic analysis of an air sample using NIOSH Method 7400 or an equivalent method.

Covered mineral: Minerals encompassed by a specified regulation or recommended standard. Under the NIOSH REL for *Airborne Asbestos Fibers and Related Elongate Mineral Particles*, covered minerals include those minerals having the crystal structure and elemental composition of the asbestos varieties [chrysotile, riebeckite asbestos (crocidolite), cummingtonite-grunerite asbestos (amosite), anthophyllite asbestos, tremolite asbestos, and actinolite asbestos], or their nonasbestiform analogs (the serpentine minerals antigorite and lizardite, and the amphibole minerals contained in the cummingtonite-grunerite mineral series, the tremolite-ferroactinolite mineral series, and the glaucophane-riebeckite mineral series).

Elongate mineral particle (EMP): Any fragment or crystal of a mineral with a minimum aspect ratio of 3:1. The *Roadmap* is focused on EMPs that are of inhalable, thoracic, or respirable size as described below in Section 6.2.

Elongate particle (EP): Any particle with a minimum aspect ratio of 3:1. The research described in the *Roadmap* is focused on EPs that are of inhalable size, thoracic size, or respirable size as described below in Section 6.2.

6.2 Definitions of Inhalational Terms

Inhalable particulate matter: particles which deposit anywhere in the respiratory tract. This varies by species, but for humans can be approximated as those particles captured according to the following collection efficiency regardless of sampler orientation with respect to wind direction:

$$\text{IPM}(d_{\text{ae}}) = 0.5 (1 + \exp[-0.06 d_{\text{ae}}]) \pm 10; \text{ for } 0 < d_{\text{ae}} \leq 100 \mu\text{m}$$

Where: IPM(d_{ae}) = the collection efficiency and d_{ae} is the aerodynamic diameter in μm . [ACGIH 1999]

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Table 1. Definitions of General Mineralogical Terms and Specific Minerals

TERM	Dictionary of Mining, Mineral, and Related Terms [U.S. Bureau of Mines 1996] [Note: Footnotes identify the Primary Source Citation for the definition]	Glossary of Geology 5 th ed. [American Geological Institute 2005]	Leake et al. [1997]	NIOSH [1990a]
General Mineralogical Terms Acicular ⁵	1. A mineral consisting of fine needlelike crystals; e.g., natrolite. 2. Slender needlelike crystal. 3. Refers to needlelike crystals. ⁶	[crystal]: Said of a crystal that is needlelike in form.		
Amphibole	A mineral group; characterized by double chains of silica tetrahedra having the composition $A_0B_2Y_5Z_8O_{22}(OH,F,Cl)$, where (A=Ca, Na, K, Pb, B), (B=Ca, Fe, Li, Mg, Mn, Na), (Y=Al, Cr, Fe, Mg, Mn, Ti), and (Z=Al, Be, Si, Ti); in the orthorhombic or monoclinic crystal systems, including actinolite, anthophyllite, arfvedsonite, cummingtonite, hornblende, richterite, glaucophane, grunerite, anthophyllite, riebeckite, tremolite, and others. All display a diagnostic prismatic cleavage in two directions parallel to crystal	1. A group of dark [sic] rock-forming ferromagnesian silicate minerals, closely related in crystal form and composition and having the general formula: $A_{2-3}B_5(Si,Al)_8O_{22}(OH)_2$, where A = Mg, Fe ²⁺ , Ca, or Na, and B = Mg, Fe ³⁺ , Li, Mn, or Al. It is characterized by a cross-linked double chain of tetrahedral with silicon:oxygen ratio of 4:11, by columnar or fibrous prismatic crystals, and by good prismatic cleavage in two directions parallel to the crystal faces and intersecting at angles of 56° and 124°; colors range from white to	A mineral comprising a double silicate chain with the general formula $AB_2C_5T_8O_{22}(OH)_2$ with the components of the formula conventionally described as A, B, C, T and "OH" corresponding to the following crystallographic sites: A one site per formula unit; B two M4 sites per formula unit; C a composite of five sites made up of 2 M1, 2 M2 and 1 M3 sites per formula unit; T eight sites, in two sets of four, that need not be distinguished; "OH" two sites per formula unit. The ions considered normally to occupy these sites are in the	Minerals in the amphibole group are widely distributed in the earth's crust in many igneous or metamorphic rocks. In some instances, the mineral deposits contain sufficient quantities of the asbestiform minerals to be economically minable for commercial use. The minerals and mineral series of the amphibole group have variable compositions with extensive elemental substitutions. They are found in forms ranging from massive to fibrous. The most common commercially exploited asbestiform varieties of this

⁵ Additional definitions can be found at: Lowers H, Meeker G [2002]. Tabulation of Asbestos-Related Terminology Open-File Report 02-458, 70 pp. [<http://pubs.usgs.gov/of/2002/ofr-02-458/>]. Date accessed: December 21, 2009.

⁶ Nelson, A [1965] Dictionary of Mining. 523 pp. Philosophical Library, Inc., New York

TERM	<p>Dictionary of Mining, Mineral, and Related Terms [U.S. Bureau of Mines 1996] <i>[Note: Footnotes identify the Primary Source Citation for the definition]</i></p>	<p>Glossary of Geology 5th ed. [American Geological Institute 2005]</p>	<p>Leake et al. [1997]</p>	<p>NIOSH [1990a]</p>
<p>faces and intersecting at angles of about 54° and 124°. Some members may be asbestiform.</p>	<p>black. Most amphiboles crystallize in the monoclinic system, some in the orthorhombic. They constitute an abundant and widely distributed constituent in igneous and metamorphic rocks (some are wholly metamorphic), and they are analogous in chemical composition to the pyroxenes.</p> <p>2. A mineral of the amphibole group, such as hornblende, anthophyllite, cummingtonite, tremolite, actinolite, riebeckite, glaucophane, arfvedsonite, etc.</p> <p>3. A term sometimes used a synonym for hornblende. Etymol: Greek "amphibolos", "ambiguous, doubtful", in reference to its many varieties.</p>	<p>following categories: (empty site) and K at A only; Na at A or B; Ca at B only; L-type ions: Mg, Fe²⁺, Mn²⁺, Li and rarer ions of similar size, at C or B; M-type ions: Al at C or T, Fe³⁺, and, more rarely Mn³⁺, Cr³⁺ at C only; high-valency ions: Ti⁴⁺ at C or T, Zr⁴⁺ at C only, Si at T only; anions: OH, F, Cl, O at "OH". M-type ions normally occupy M2 sites and so are normally limited to two of the five C sites. Exceptions may occur to the above "normal" behavior. Four groups are classified depending on the occupancy of the B sites: Mg-Fe-Mn-Li group; calcic group; sodic-calcic group; and sodic group. Asbestiform amphiboles should be named according to their precise mineral name (when known) followed by the suffix -asbestos, e.g. anthophyllite-asbestos, tremolite-asbestos.</p>	<p>mineralogical group include crocidolite, amosite, anthophyllite, tremolite, and actinolite. Crocidolite, amosite, and anthophyllite are selectively mined for commercial use, whereas tremolite and actinolite are most often found as a contaminant in other mined commodities such as talc and vermiculite. The amphiboles have good thermal and electrical insulation properties, and they have moderate to good resistance to acids.</p>	<p>A specific type of mineral fibrosity in which the growth is primarily in one dimension and the crystals form naturally as long, flexible</p>
<p>Asbestiform⁷</p>	<p>1. Said of a mineral that is fibrous, i.e., like asbestos.</p>	<p>Said of a mineral that is composed of separable fibers.</p>		

⁷ See footnote #5

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TERM	<p>Dictionary of Mining, Mineral, and Related Terms [U.S. Bureau of Mines 1996] <i>[Note: Footnotes identify the Primary Source Citation for the definition]</i></p>	<p>Glossary of Geology 5th ed. [American Geological Institute 2005]</p>	<p>Leake et al. [1997]</p>	<p>NIOSH [1990a]</p>
Asbestos ⁸	<p>1. A commercial term applied to silicate minerals that separate readily into thin, strong fibers that are flexible, heat resistant, and chemically inert, thus making them suitable for uses (as in yarn, cloth, paper, paint, brake linings, tiles, insulation, cement, fillers, and filters) where incombustible, nonconducting, or chemically resistant material is required. Since the early 1970's, there have been serious environmental concerns about the potential health hazards of asbestos products, which has resulted in strong environmental regulations.</p> <p>2. Any asbestiform mineral of the serpentine group (chrysotile, best adapted for spinning and the principal variety in commerce) or amphibole group (esp. actinolite, anthophyllite, gedrite,</p>	<p>1. A commercial term applied to a group of silicate minerals that readily separate into thin, strong fibers that are flexible, heat resistant, and chemically inert, and are therefore suitable for uses (as in yarn, cloth, paper, paint, brake linings, tiles, insulation, cement, fillers, and filters) where incombustible, nonconducting, or chemically resistant material is required.</p> <p>2. A mineral of the asbestos group [sic], principally chrysotile (best adapted for spinning) and certain fibrous varieties of amphibole (esp. amosite, anthophyllite, and crocidolite).</p> <p>3. A term strictly applied to the fibrous variety of actinolite. Certain varieties are deleterious to health.</p>		<p>fibers. Fibers can be found in bundles that can be easily separated into smaller bundles or ultimately into fibrils.</p> <p>Asbestos is a generic term for a number of silicate minerals with a fibrous crystalline structure. The quality of commercially used asbestos depends on the mineralogy of the asbestiform variety, the degree of fiber development, the ratio of fibers to acicular crystals or other impurities, and the length and flexibility of the fibers. The asbestiform varieties of these minerals can be found in both the amphibole and serpentine mineral groups. The asbestiform varieties occur in veins or small veinlets within rock containing or composed of the common (nonasbestiform) variety of the same mineral. The major asbestiform varieties of minerals used commercially are chrysotile, tremolite-actinolite asbestos, cummingtonite-grunerite asbestos,</p>

⁸ See footnote #5

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Cleavage fragment ⁹	cumingtonite, grunerite, riebeckite, and tremolite). 3. A term strictly applied to asbestiform actinolite.	A fragment of a crystal that is bounded by cleavage faces.		anthophyllite asbestos, and crocidolite. Asbestos is marketed by its mineral name (e.g., anthophyllite asbestos), its variety name (e.g., chrysotile or crocidolite), or its trade name (e.g., Amosite). A fragment produced by the breaking of crystals in directions that are related to the crystal structure and are always parallel to possible crystal faces. Minerals with perfect cleavage can produce perfect regular fragments. Amphiboles with prismatic cleavage will produce prismatic fragments. <i>Note:</i> These fragments can be elongated and may meet the definition of a fiber upon microscopic examination.
Crystal habit	The forms typically appearing on specimens of a mineral species or group, rarely all the forms permitted by its point group. Crystal habits range from highly diverse, e.g. calcite, to almost	The general shape of crystals, e.g. cubic, prismatic, fibrous. For a given type of crystal, the habit may vary from locality to locality depending on environment of growth.		

⁹ See footnote #5

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<p>Fiber¹¹</p>	<p>never showing crystal faces, e.g. turquoise. In addition to describing mineral habits with form names, e.g. prismatic, pyramidal, or tetrahedral, other names for appearances are used, e.g. fibrous, columnar, platy, or botryoidal. Intergrowths are given by specific description.¹⁰</p> <p>The smallest single strand of asbestos or other fibrous material.¹²</p>	<p>A strengthening cell, usually elongated, tapering, and thick-walled, occurring in various parts of vascular plants. <i>[Note: The definition provided does not refer to mineral fibers.]</i></p>		<p>An acicular single crystal or similarly elongated polycrystalline aggregate particles. Such particles have macroscopic properties such as flexibility, high aspect ratio, silky luster, and axial lineation. These particles have attained their shape primarily because of manifold dislocation planes that are randomly oriented in two axes but parallel in the third. <i>Note:</i> Upon microscopic examination, only particles that have a 3:1 or greater aspect ratio are defined as fibers. Other macroscopic properties used to define fibers cannot be ascertained for individual particles</p>

¹⁰ Pryor, Edmund J. (1963) Dictionary of Mineral Technology. 437 pp. Mining Publications, Ltd., London

¹¹ See footnote #5

¹² Mersereau, Samuel Foster. (1947) Materials of Industry, 4th ed. 623pp. McGraw-Hill, NY

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Fibril ¹³	1. A single fiber, which cannot be separated into smaller components without losing its fibrous properties or appearance. ¹⁴			examined microscopically. A single fiber that cannot be separated into smaller components without losing its fibrous properties or appearances.
Fibrous ¹⁵	1. Applied to minerals that occur as fibers, such as asbestos. Syn: asbestiform 2. Consisting of fine threadlike strands, e.g., satin spar variety of gypsum.			
Fibrous habit		The tendency of certain minerals, e.g. asbestos, to crystallize in needlelike grains or fibers.		
Fibrous structure	If the crystals in a mineral aggregate are greatly elongated and have a relatively small cross-section, the structure or texture is fibrous. The fibers may be parallel, as in crocidolite and sometimes in calcite and cerussite. When the fibers are very fine, they may impart a silky luster to the aggregate, as in crocidolite or satin-spar gypsum. There is also a	Fibrous prismatic structure: A prismatic structure in which each first-order prism is like a simple prism in showing nonspherulitic prismatic and noncomposite prismatic substructure, but the prisms have much higher length/width ratios than typical simple prisms, occurring as long fibers.		

¹³ See footnote #5

¹⁴ Campbell, W.J., et al. Selected Silicate Minerals and their Asbestiform Varieties. USBM Circular 8751

¹⁵ See footnote #5

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Fibrous texture:	feltlike type. Fibrous crystals may radiate from a center, forming asteriated or starlike groups, either coarse or fine, as frequently observed in pyrolusite, wavelite, natrolite and tourmaline, and sometimes in stibnite and other minerals. Also called fibrous texture. ¹⁶	In mineral deposits, a pattern of finely acicular, rod-like crystals, e.g. in chrysotile and amphibole asbestos. ¹⁷		
Mineral	1. A naturally occurring inorganic element or compound having an orderly internal structure and characteristic chemical composition, crystal form, and physical properties. CF: metallic. 2. In miner's phraseology, ore. See also: ore. 3. See: mineral species; mineral	1. A naturally occurring inorganic element or compound having a periodically repeating arrangement of atoms and characteristic chemical composition, resulting in distinctive physical properties. 2. An element or chemical compound that is crystalline and formed as a result of geologic		A homogeneous, naturally occurring, inorganic crystalline substance. Minerals have distinct crystal structures and variation in chemical composition, and are given individual names.

¹⁶ Chemical Publishing Co. (1948) Chamber's Mineralogical Dictionary. 47 pp. New York

¹⁷ American Geological Institute. (1987) Glossary of geology, 3rd ed. 788 pp. AGI, Alexandria, VA; (1957) Glossary of Geology and Related Sciences. 325 pp. supplement, 1969, 72 pp.

¹⁸ American Geological Institute. (1987) Glossary of geology, 3rd ed. 788 pp. AGI, Alexandria, VA (1957) Glossary of Geology and Related Sciences. 325 pp. supplement, 1969, 72 pp.

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<p>TERM</p>	<p>Dictionary of Mining, Mineral, and Related Terms [U.S. Bureau of Mines 1996] [Note: Footnotes identify the Primary Source Citation for the definition]</p> <p>series; mineral group.</p> <p>4. Any natural resource extracted from the earth for human use; e.g. ores, salts, coal, or petroleum.</p> <p>5. In flotation, valuable mineral constituents of ore as opposed to gangue minerals.</p> <p>6. Any inorganic plant or animal nutrient.</p> <p>7. Any member of the mineral kingdom as opposed to the animal and plant kingdoms.¹⁸</p>	<p>Glossary of Geology 5th ed. [American Geological Institute 2005]</p> <p>processes. Materials formed by geological processes from artificial substances are no longer accepted (after 1995) as new minerals (Nickel, 1995). Mercury, a liquid, is a traditional exception to the crystallinity rule. Water is not a mineral (although ice is), and crystalline biological and artificial materials are not minerals (cf. mineraloid).</p> <p>3. Any naturally formed inorganic material, i.e. a member of the mineral kingdom as opposed to the plant or animal kingdom.</p>	<p>Leake et al. [1997]</p>	<p>NIOSH [1990a]</p>
<p>Mineral series</p>				<p>A mineral series includes two or more members of a mineral group in which the cations in secondary structural position are similar in chemical properties and can be present in variable but frequently limited ratios (e.g., cummingtonite-actinolite). The current trend in referring to a mineral series is to simplify long series names by using the mineral name of only one (end or intermediate) member (i.e., tremolite-actinolite-</p>

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Mineral variety				ferroactinolite). The variety distinguishes minerals that are conspicuously different from (1) those considered normal within the common crystallization habits, polytypes, and other structural variants, and (2) those with different physical properties such as color. Varieties are named by mineralogists, miners, gemologists, manufacturers of industrial products, and mineral collectors.
Needle	5. A needle-shaped or acicular mineral crystal.	[crystal]: A needle-shaped or acicular mineral crystal.		
Nonasbestiform habit				Each of the six commercially exploited asbestiform minerals also occurs in a nonasbestiform mineral habit. These minerals have the same chemical formula as the asbestiform variety, but they have crystal habits where growth proceeds in two or three dimensions instead of one dimension. When milled, these minerals do not break into fibrils but rather into fragments resulting from cleavage along the two or three growth planes. Particles thus formed are referred to as

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Prism	3. An open crystal form with faces and their intersecting edges parallel to the principle crystallographic axis. Prisms have three (trigonal), four (tetragonal), six (ditrigonal or hexagonal), eight (ditetragonal), or twelve (dihexagonal) faces. The nine-sided prisms of tourmaline are a combination of trigonal and hexagonal prisms.	[crystal] A crystal form having three, four, six, eight, or twelve faces, with parallel intersection edges, and which is open only at the two ends of the axis parallel to the intersection edges of the faces.		cleavage fragments and can meet the definition of a fiber for regulatory purposes.
Prismatic	3. Pertaining to a crystallographic prism. 4. Descriptive of a crystal with one dimension markedly longer than the other two. 5. Descriptive of two directions of cleavage.	[crystal] Said of a crystal that shows one dimension markedly longer than the other two.		
Serpentine Minerals		A rock consisting almost wholly of serpentine-group minerals, e.g., antigorite, chrysotile, or lizardite, derived from the hydration of ferromagnesian silicate minerals such as olivine and pyroxene. Accessory chlorite, talc, and magnetite may be present.		The serpentine minerals belong to the phyllosilicate group of minerals. The commercially important variety is chrysotile, which originates in the asbestiform habit. Antigorite and lizardite are two other types of serpentine minerals that are structurally

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Zeolite	<p>1. A generic term for class of hydrated silicates of aluminum and either sodium or calcium or both, of the type $\text{Na}_2\text{O} \cdot \text{Al}_2\text{O}_3 \cdot n\text{SiO}_2 \cdot x\text{H}_2\text{O}$. The term originally described a group of naturally occurring minerals. The natural zeolites are analcite, chabazite, heulandite, natrolite, stibite, and thomsonite. Artificial zeolites are made in a variety of forms, ranging from gelatinous to porous and sandlike, and are used as gas adsorbents and drying agents as well as water softeners. Both natural and artificial zeolites are used extensively for water softening. The term zeolite now includes such diverse groups of compounds as sulfonated organics or basic resins, which act in a similar manner to effect either cation or anion exchange.</p> <p>2. A group of hydrous aluminosilicates that are similar to the feldspars. They easily lose and</p>	<p>a generic term for a large group of white or colorless (sometimes tinted red or yellow by impurities) hydrous aluminosilicate minerals that have an open framework structure of interconnected $(\text{Si}, \text{Al})\text{O}_4$ tetrahedra with exchangeable cations and H_2O molecules in structural cavities. They have a ratio of $(\text{Al} + \text{Si})$ to nonhydrous oxygen of 1:2, and are characterized by their easy and reversible loss of water of hydration and by their ready fusion and swelling when strongly heated under the blowpipe. Zeolites have long been known to occur as well formed crystals in cavities in basalt. Of more significance is their occurrence as authigenic minerals in the sediments of saline lakes and the deep sea and esp. in beds of tuff. They form "during and after burial, generally by reaction of pore</p>		<p>distinct. The fibrous form of antigorite is called picrolite.</p>

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	regain their water of hydration and they fuse and swell when heated. Zeolites are frequently used in water softening, ion exchange and absorbent applications.	waters with solid aluminosilicate materials (e.g., volcanic glass, feldspar, biogenic silica, and clay minerals) ¹⁹ .		
Specific Mineral Terms				
Actinolite	A monoclinic mineral, $2[\text{Ca}_2(\text{Fe}, \text{Mg})\text{Si}_8\text{O}_{22}(\text{OH})_2]$; in the hornblende series $\text{Mg}/(\text{Mg}+\text{Fe}^{2+}) = 0.50$ to 0.89 of the amphibole group; forms a series with tremolite; green, bladed, acicular, fibrous (byssolite asbestos), or massive (nephrite jade); prismatic cleavage; in low-grade metamorphic rocks.	A bright-green or grayish-green monoclinic mineral of the amphibole group: $\text{Ca}_2(\text{Fe}, \text{Mg})_2(\text{OH})_2(\text{Si}_8\text{O}_{22})$. It may contain manganese. It sometimes occurs in the form of asbestos, and also in fibrous, radiated, or columnar forms in metamorphic rocks (such as schists) and in altered igneous rocks.	A monoclinic calcic amphibole intermediate between ferroactinolite and tremolite: $\text{Ca}_2(\text{Fe}, \text{Mg})_2\text{Si}_8\text{O}_{22}(\text{OH})_2$; with $\text{Mg}/(\text{Mg}+\text{Fe}^{2+})$ between 0.5 and 0.9 (otherwise if ≤ 0.5 it is ferroactinolite, and if ≥ 0.9 it is tremolite)	Actinolite can occur in both the asbestiform and nonasbestiform mineral habits and is in the mineral series tremolite-ferroactinolite. ²⁰ The asbestiform variety is often referred to as actinolite asbestos.
Amosite	1. A monoclinic mineral in the cummingtonite-grunerite series. ²¹ 2. A commercial asbestos composed of asbestiform gedrite, grunerite, or anthophyllite of the amphibole group; has typically long fibers.	A commercial term for an iron-rich, asbestiform variety of amphibole occurring in long fibers. It may consist of an orthorhombic amphibole (anthophyllite or gedrite) or of a monoclinic amphibole (cummingtonite or grunerite).		Amosite is the commercial term derived from the acronym "Asbestos Mines of South Africa." Amosite is in the mineral series cummingtonite-grunerite, ²² in which both asbestiform and nonasbestiform habits of the mineral can occur. This mineral type is commonly referred to as "brown asbestos."
Antigorite	A monoclinic mineral, $(\text{Mg}, \text{Fe})_3\text{Si}_2\text{O}_7(\text{OH})_4$; kaolinite-serpentine group; polymorphous	A macroscopically lamellar brown to green monoclinic serpentine mineral, which consists		

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Anthophyllite	An orthorhombic mineral, 4[Mg,Fe] ₇ Si ₈ O ₂₂ (OH) ₂ ; amphibole group; commonly lamellar or fibrous, green to clove-brown; in schists from metamorphosed ultramafic rocks; a nonspinning grade of asbestos.	A clove-brown to colorless orthorhombic mineral of the amphibole group: (Mg, Fe ²⁺) ₂ (Mg,Fe ²⁺) ₃ Si ₈ O ₂₂ (OH) ₂ . It is dimorphous with cummingtonite; with increase in aluminum it grades into gedrite. Anthophyllite occurs in metamorphosed ultrabasic rocks, typically with olivine or talc or in monomineralic aggregates of parallel or radiating asbestiform fibers. It has been mined for asbestos.	An orthorhombic Mg-Fe-Mn-Li amphibole: Mg ₃ Si ₈ O ₂₂ (OH) ₂ ; may also contain divalent iron but with Mg/(Mg+Fe ²⁺) ≥ 0.50 (otherwise ferro-anthophyllite), and with Si > 7.00 (otherwise it is gedrite).	Anthophyllite can occur in both the asbestiform and nonasbestiform mineral habits. The asbestiform variety is often referred to as anthophyllite asbestos.
Attapulgite	A light-green, magnesium-rich clay mineral, named from its occurrence at Attapulgis, GA, where it is quarried as fuller's earth. Crystallizes in the monoclinic system.	An olive-green asbestiform variety of tremolite-actinolite.		
Byssolite	An olive-green asbestiform variety of tremolite-actinolite.	A group name for a monoclinic		
Clinoptilolite	A monoclinic mineral,			

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Chrysotile	(Na,K,Ca) ₂ Al ₃ (Al,Si) ₂ Si ₁₃ O ₃₆ ·12H ₂ O; of the zeolite group. A monoclinic mineral (clinochrysotile), or orthorhombic mineral (orthochrysotile, parachrysotile), [Mg ₆ (OH) ₈ Si ₄ O ₁₀]; serpentine group; forms soft, silky white, yellow, green, or gray flexible fibers as veins in altered ultramafic rocks; the chief asbestos minerals. (Not to be confused with chrysotile.)	zeolite mineral with the general formula A ₂₋₃ (Si,Al) ₁₈ O ₃₆ ·11H ₂ O, where A=Na, K, or Ca A white, gray, or greenish orthorhombic or monoclinic mineral of the serpentine group: Mg ₃ (OH) ₄ Si ₂ O ₅ . It is a highly fibrous, silky variety of serpentine, and constitutes the most important type of asbestos. Not to be confused chrysotile.		Chrysotile generally occurs segregated as parallel fibers in veins or veinlets and can easily separate into individual fibers or bundles. Often referred to as "white asbestos," it is used commercially for its good spinnability in the making of textile products, and as an additive in cement or friction products.
Crocidolite	An asbestiform variety of riebeckite; forms lavender-blue, or indigo-blue, or leek-green silky fibers and massive and earthy forms; suited for spinning and weaving. Also spelled krokitolit.	An asbestiform variety of riebeckite; forms lavender-blue, or indigo-blue, or leek-green silky fibers and massive and earthy forms. Also spelled krokidolit.		Crocidolite is from the fibrous habit of the mineral riebeckite and is in the mineral series glaucophane-riebeckite, in which both asbestiform and nonasbestiform habits can occur. This mineral type is commonly referred to as "blue asbestos."
Cummingtonite	A monoclinic mineral, (Fe,Mg) ₇ Si ₈ O ₂₂ (OH) ₂ ; amphibole group; has Mg/(Mg+Fe ²⁺) = 0.30 to 0.69; prismatic cleavage; may be dactylic; fibrous varieties (amosite, magnesium rich, and montasite, iron rich) are used as asbestos.	A dark green, brown, gray, or beige monoclinic member of the amphibole group: (Mg,Fe ²⁺) ₇ Si ₈ O ₂₂ (OH) ₂ . It is dimorphous with anthophyllite, and typically contains calcium and manganese. Cummingtonite occurs in metamorphosed ironstone, mafic and ultrabasic	A monoclinic Mg-Fe-Mn-Li amphibole: Mg ₇ Si ₈ O ₂₂ (OH) ₂ ; may also contain divalent iron but with Mg/(Mg+Fe ²⁺) ≥ 0.50 (otherwise it is grunerite)	

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Erionite		rocks, some dacites and rhyolites, and as a component of uraltite. Its iron-rich variety is grunerite.		
Ferroactinolite	A monoclinic mineral, $\text{Ca}_2(\text{Fe}^{2+}, \text{Mg})_5\text{Si}_8\text{O}_{22}(\text{OH})_2$; amphibole group; has $\text{Mg}/(\text{Mg}+\text{Fe}^{2+}) = 0$ to 0.50; forms a series with tremolite and actinolite. Formerly called ferrotremolite.	A white hexagonal zeolite mineral. [Ed. Note: Designated as Erionite (Ca, K, Na) depending on the dominant cation substitution.	A monoclinic calcic amphibole: $\text{Ca}_2\text{Fe}^{2+}_5\text{Si}_8\text{O}_{22}(\text{OH})_2$; may also contain magnesium but with $\text{Mg}/(\text{Mg}+\text{Fe}^{2+}) \leq 0.5$ (otherwise it is actinolite).	
Fluoro-edenite		A green-black monoclinic mineral component representing a theoretical end-member of the amphibole group: $\text{Ca}_2\text{Fe}^{2+}_5\text{Si}_8\text{O}_{22}(\text{OH})_2$. Syn: ferrotremolite.		
Grunerite	A monoclinic mineral, $(\text{Fe}, \text{Mg})_7\text{Si}_8\text{O}_{22}(\text{OH})_2$; amphibole group; with $\text{Mg}/(\text{Mg}+\text{Fe}^{2+}) = 0-0.30$; forms series with cummingtonite and magnesio-cummingtonite; fibrous or needlelike, commonly in radial aggregates; characteristic of iron formations in the Lake Superior and Labrador Trough regions. Also spelled grunerite.	A vitreous dark brown monoclinic mineral of the amphibole group: $(\text{Na}, \text{K})\text{Ca}_2(\text{Mg}, \text{Fe}^{2+})_5(\text{Si}_7\text{-Al})\text{O}_{22}(\text{F}, \text{O}, \text{H})$. It represents edenite with $\text{F} > \text{OH}$.	A monoclinic Mg-Fe-Mn-Li amphibole: $\text{Fe}^{2+}_7\text{Si}_8\text{O}_{22}(\text{OH})_2$; may also contain magnesium but with $\text{Mg}/(\text{Mg}+\text{Fe}^{2+}) < 0.50$ (otherwise it is cummingtonite).	

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Halloysite	<p>1. A monoclinic mineral, $2[\text{Al}_2\text{Si}_4(\text{OH})_8\text{O}_{10}]$; kaolinite-serpentine group; made up of slender tubes as shown by electron microscopy; a gangue mineral in veins.</p> <p>2. Used as a group name to include natural "halloysite minerals" with different levels of hydration, as well as those formed artificially.</p>	<p>A 1:1 aluminosilicate clay mineral $\text{Al}_2\text{Si}_2\text{O}_5(\text{OH})_4 \cdot \text{X}(\text{H}_2\text{O})$ similar to kaolinite but perhaps with some Al(IV) and interlayer cations to compensate for the Al(IV). Probably because of this it is able to incorporate water in the interlayer space [Bailey 1989]. The terms "halloysite (7Å)" and halloysite (10Å)" were recommended for the anhydrous and dihydrate forms, respectively [Brindley and Pegro 1976]²³; the term "endellite" should not be used [Bailey et al. 1980]²⁴</p>		
Lizardite	<p>A trigonal and hexagonal mineral, $\text{Mg}_3\text{Si}_2\text{O}_5(\text{OH})_4$; kaolinite-serpentine group; polymorphous with antigorite, clinochrysotile, orthochrysotile, and parachrysotile; forms a series with nepouite; in platy masses as an alteration product of ultramafic rocks; the most abundant serpentine mineral.</p>	<p>The most abundant form of the trioctahedral serpentine minerals. It crystallizes as flat platelets. Variable amounts of Al substitute for both Mg and Si in the ideal serpentine formula of $\text{Mg}_3\text{Si}_2\text{O}_5(\text{OH})_4$ to create a better lateral fit between the component octahedral and tetrahedral sheets than found in antigorite and chrysotile. Several polytypes exist: rhombohedral, trigonal, hexagonal, or monoclinic.</p>		
Mordenite	<p>A white, yellowish, or pinkish member of the zeolite group of minerals with the formula</p>	<p>A white, yellowish, or pinkish orthorhombic zeolite mineral: $(\text{Na}_2, \text{Ca}, \text{K})_2[\text{Al}_2\text{Si}_{10}\text{O}_{28} \cdot 7\text{H}_2\text{O}]$.</p>		

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Palygorskite	(Ca, Na ₂ K ₂)Al ₂ Si ₁₀ O ₂₄ ·7H ₂ O. 1. A monoclinic and orthorhombic mineral, (OH) ₂ (Mg,Al) ₄ (Si,Al) ₈ O ₂₀ ·8H ₂ O; fibrous; in desert soils. 2. A general name for lightweight fibrous clay minerals showing significant substitution of aluminum for magnesium; characterized by distinctive rodlike shapes under an electron microscope.	(a) White, grayish, yellowish, or grayish-green chain-structure clay mineral: (Mg,Al) ₂ Si ₄ O ₁₀ (OH)·4H ₂ O. It crystallizes in several monoclinic and orthorhombic polytypes. (b) A group name for monoclinic minerals with an analogous composition; but with Mg ²⁺ replaced by Mn or Na, and Al replaced by Fe ³⁺ or Mn ³⁺ .		
Phillipsite	A monoclinic mineral, (K,Na,Ca) _{1-x} (Si,Al) ₈ O ₁₆ ·6H ₂ O; zeolite group; commonly occurs in complex twinned crystals; in basalt amydules, in pelagic red clays, in palagonite tuffs, in alkaline saline lakes from silicic vitric volcanic ash, in alkaline soils, and around hot springs in Roman baths.	A colorless or white monoclinic zeolite mineral. Usually designated as phillipsite - (Ca, K, or Na) depending on which is the dominant exchangeable cation: (Ca,K,Na) ₂ (Si,Al) ₈ O ₁₆ ·6H ₂ O.		
Richterite		A brown, yellow, or rose-red monoclinic member of the amphibole group: Na ₂ CaMg ₅ Si ₈ O ₂₂ (OH) ₂ . Cf: soda tremolite	A monoclinic sodic-calcic amphibole: Na(CaNa)Mg ₅ Si ₈ O ₂₂ (OH) ₂ ; may also contain divalent iron but with Mg/(Mg+Fe ²⁺) ≥ 0.5 (otherwise it is ferrosichterite)	
Riebeckite	A monoclinic mineral, Na ₂ Ca(Mg,Fe ²⁺) ₅ Si ₈ O ₂₂ (OH) ₂ [sic]; amphibole group with Mg/(Mg+Fe ²⁺) = 0 to 0.49 and	A dark blue or black monoclinic mineral of the amphibole group: Na ₂ Fe ²⁺ ₃ Fe ³⁺ ₂ Si ₈ O ₂₂ (OH) ₂ . It occurs as a primary constituent in	A monoclinic sodic amphibole: Na ₂ (Fe ²⁺ ₃ Fe ³⁺ ₂)Si ₈ O ₂₂ (OH) ₂ ; may also contain aluminum in place of trivalent iron but with ^{VI} Al < Fe ³⁺	

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Serpiolite	A monoclinic mineral, $Mg_4Si_6O_{15}(OH)_2 \cdot 6H_2O$; soft; sp gr, 2, but fibrous dry masses float on water; occurs in veins in calcite and in alluvial deposits formed from weathering of serpentine masses, chiefly in Asia Minor, as meerschau; may be used in making pipes, ornamental carvings.	An orthorhombic chain-structure clay mineral: $Mg_4Si_6O_{15}(OH)_2 \cdot 6H_2O$. It is a white to light gray or light yellow material, extremely lightweight, absorbent, and compact, that is found chiefly in Asia Minor and is used for making tobacco pipes, cigar and cigarette holders and ornamental carvings. Serpiolite occurs in veins with calcite, and in alluvial deposits formed from weathering of serpentine masses.	otherwise it is ferroglaucophane, and may also contain sodium and potassium in the A position but with $(Na+K)_A < 0.50$ otherwise it is arvedsonite, and may also contain magnesium in place of divalent iron but with $Mg/(Mg+Fe^{2+}) < 0.5$ otherwise it is magnesioriebeckite	
Tremolite	A monoclinic mineral, $2[Ca_2Mg_5Si_8O_{22}(OH)_2]$; amphibole group with magnesium replaced by iron, and silicon by aluminum toward actinolite; white to green, long-bladed or stout prismatic crystals, may show columnar, fibrous, or granular masses or compact aggregates; in low-grade metamorphic rocks such as	A white to dark-gray monoclinic mineral of the amphibole group: $Ca_2Mg_5Si_8O_{22}(OH)_2$. It has varying amounts of iron, and may contain manganese and chromium. Tremolite occurs in long blade-shaped or short stout prismatic crystals and also in columnar, fibrous, or granular masses or compact aggregates, generally in	A monoclinic calcic amphibole: $Ca_2Mg_5Si_8O_{22}(OH)_2$; may also contain divalent iron but with $Mg/(Mg+Fe^{2+}) \geq 0.9$ (otherwise it is actinolite)	Tremolite can occur in both the asbestiform and nonasbestiform mineral habits and is in the mineral series tremolite-ferroactinolite ²⁵ . The asbestiform variety is often referred to as tremolite asbestos.

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Winchite	dolomitic limestones and talc schists; the nephrite variety is the gemstone jade; the asbestiform variety is byssolite.	metamorphic rocks such as crystalline dolomitic limestones and talc schists. It is a constituent of much commercial talc. A blue or gray monoclinic member of the amphibole group: NaCa(Mg ₄ Al)Si ₈ O ₂₂ (OH) ₂	A monoclinic sodic-calcic amphibole: (CaNa)Mg ₄ (Al,Fe ³⁺)Si ₈ O ₂₂ (OH) ₂ ; may also contain divalent iron but with Mg/(Mg+Fe ²⁺) ≥ 0.5 (otherwise it is ferrichterite)	
Wollastonite	A triclinic mineral of the pyroxenoid group: CaSiO ₃ . It is dimorphous with parawollastonite. Wollastonite is found in contact-metamorphosed limestones, and occurs usually in cleavable masses or sometimes in tabular twinned crystals; it may be white, gray, brown, red, or yellow. It is not a pyroxene. Symbol, Wo.	A triclinic or monoclinic chain silicate mineral of the pyroxenoid type: CaSiO ₃ . It [Note: missing word?] dimorphous with parawollastonite. Wollastonite is found in contact-metamorphosed limestones, and occurs usually in cleavable masses or sometimes in tabular twinned crystals; it may be white, gray, brown, red, or yellow. It is not a pyroxene. Several polytypes have been characterized. Symbol: Wo.		

1 **6.4 References for Definitions of General Mineralogical Terms, Specific Minerals,**
2 **and Inhalational Terms**
3

4 ACGIH (American Conference of Governmental Industrial Hygienists) [1999]. Particle
5 Size-selective Sampling for Particulate Air Contaminants. JH Vincent, ed. ACGIH®,
6 Cincinnati, OH.

7
8 American Geological Institute [2005]. Glossary of Geology 5th Edition. KKE
9 Neuendorf, JP Mehl, and JA Jackson, eds. American Geological Institute, Alexandria,
10 VA.

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