Asbestos and Other Mineral Fibers: A Roadmap for Scientific Research

By

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February 2007

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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 and other mineral fibers and it is now well documented that fibers of asbestos minerals, when inhaled, can cause serious diseases in exposed workers. Yet, as we enter the 21st century, many questions and areas of scientific uncertainty remain. For instance, because of the complexity of the mineralogy, 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 21st century reappraisal of the areas of research needed to pursue on its own, and in collaboration with others. New scientific knowledge will be generated to serve as the basis for evidence-based public health policies for asbestos and other mineral fibers. As a first step in a science reappraisal effort, NIOSH convened an internal work group to develop a roadmap for future scientific research and policy development. The NIOSH Mineral Fibers Work Group authored *Asbestos and Other Mineral Fibers: A Roadmap for Scientific Research* which summarizes NIOSH's current understanding of occupational exposure and toxicity issues concerning asbestos and other mineral fibers. Most importantly, the *Roadmap* outlines a research program that will provide answers to current scientific questions, reduce scientific uncertainties, and provide a sound scientific foundation for future policy development.

NIOSH invites comments on the occupational health issues identified and the fiber research strategy suggested in the *Roadmap*. NIOSH seeks other views about additional key issues that need to be identified, additional research that needs to be conducted, and suggested methods to conduct the research. In particular, NIOSH is seeking input from stakeholders concerning study designs, techniques for generating size-selected fibers, analytic approaches, sources of particular types of fibers suitable for experimental studies, and worker populations suitable for epidemiological study. NIOSH is interested in available and forthcoming research results that can help answer the questions set forth in the *Roadmap*. Information also is requested on existing workplace exposure data, health effects, and control technologies.

NIOSH recognizes that results from fiber toxicity research may impact both occupational as well as environmental 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 intends to pursue partnerships with 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 Standards and Technology (NIST), the National Institute of Environmental Health Sciences (NIEHS), the National Toxicology Program (NTP), the Occupational Safety and Health Administration (OSHA), and the United States Geological Survey (USGS), as well as with labor, industry, academia, practitioners and other interested parties. These partnerships will help to focus the scope of the research that can contribute to the scientific understanding of asbestos and other mineral fibers, to fund and conduct the research activities, and to develop and disseminate educational materials describing results from the mineral fiber research and their implications for occupational and public health policies and practices.

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Executive Summary

Prior to the 1970s, attention concerning the health effects of fibers was focused on six commercially exploited minerals termed "asbestos:" the serpentine mineral chrysotile, and the amphibole minerals amosite, crocidolite, actinolite asbestos, anthophyllite asbestos, and tremolite asbestos. The realization that fiber shape might be more important than chemical composition in explaining the health effects of asbestos broadened interest to man-made fibers (e.g., synthetic vitreous fibers [SVF]) and to other naturally occurring mineral fibers. To date, interest in the latter has emphasized the importance of fibrous minerals exploited commercially (e.g., wollastonite, sepiolite, and attapulgite) or found as contaminants in certain mined commodities (e.g., richterite and winchite in vermiculite). Production and use of asbestos in the US and worldwide has been steadily declining, but there is still keen interest in determining the biological significance of occupational exposure to many of these minerals.

The term "mineral fibers" has included fibers that have grown naturally in an asbestiform habit as well as fibers that grow as needle-like (acicular) single crystals and fiber-like particles that result from the fracture of a mineral along cleavage planes. Mineral fibers that grow in asbestiform habits are clearly of health concern. Despite considerable research, it remains uncertain, as well as controversial, whether particles with similar dimensions from similar minerals, but with nonasbestiform habit, represent a similar health concern.

Regulatory definitions of asbestos used the best available information at the time they were developed and dealt with the uncertainties in identifying minerals covered, as well as limitations in the analytical methods commonly used.

For over a decade, the NIOSH Recommended Exposure Limit (REL) has defined airborne asbestos fibers as those particles that, when examined using phase contrast microscopy, have: (1) an aspect ratio of 3:1 or greater and a length greater than 5 µm; and (2) the mineralogic characteristics (i.e., the crystal structure and elemental composition) of the asbestos minerals (chrysotile, crocidolite, 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).

Several issues have been raised about the minerals covered by this definition. The first issue is whether other fibrous minerals, amphiboles and zeolites, should also be included; the second is whether the inclusion of fiber-like cleavage fragments of nonasbestiform amphiboles is appropriate; and the third issue is whether the specified dimensional criteria for fibers are appropriate.

Phase contrast microscopy (PCM) is the primary method used for analysis of air samples, but it has several limitations including: resolution is limited to fibers greater than about 0.25 µm in diameter and it cannot differentiate between different minerals. The analytical methods used for asbestos take on substantial significance because the current REL is set considering the limit of quantification of the PCM method rather than solely on estimates of risk. With a lower limit of quantification, a lower REL may have been proposed to reduce the risk of occupational cancer among asbestos-exposed workers. In applying the asbestos definition, it is important to have an analytical method and protocol that is practical and reliable and able to discriminate between types of fibers.

To reduce the uncertainty and controversy concerning exposure assessment and health effects of asbestos and other mineral fibers, strategic research endeavors are needed in toxicology, epidemiology, exposure assessment, and analytical methods. The resulting science can contribute to the potential development of new policies for asbestos and other mineral fibers with recommendations for exposure indices that more effectively protect workers' health. To bridge the uncertainty gaps, this *Roadmap* proposes to address the following three strategic goals: (1) to develop improved sampling and analytical methods for fibers; (2) to develop information on occupational exposures to fibers and health outcomes; and (3) to develop a broader understanding of the important determinants of toxicity for fibers and fiber-like cleavage fragments.

Developing improved sampling and analytical methods for fibers will involve: (a) reducing inter-operator and inter-laboratory variability of the current fiber analytical methods; (b) developing fiber analytical methods with improved resolution to visualize smaller diameter fibers to assure more complete fiber counts; (c) developing a practical analytical method to differentiate between airborne exposures to asbestiform fibers from the asbestos minerals and fiber-like cleavage fragments from their non-asbestiform analogs; (d) developing analytical methods to assess fiber durability; and (e) developing and validating thoracic-size methods for fibers.

Developing information and knowledge on occupational exposures to fibers and health outcomes will involve (a) collecting and analyzing available occupational exposure information to ascertain the characteristics and extent of exposure to various types of fibers and to fiber-like cleavage fragments; (b) collecting and analyzing available information on health outcomes associated with exposures to various types of fibers and fiber-like cleavage fragments, and (c) conducting epidemiologic studies of workers exposed to various types of fibers and fiber-like cleavage fragments to better define the association between fiber exposure and health effects..

Developing a broader understanding of the important determinants of toxicity for fibers and fiber-like cleavage fragments will involve conducting *in vitro* and animal studies to ascertain what physical and chemical properties influence the toxicity of fibers and fiber-like cleavage fragments.

As the *Roadmap* makes clear, the ideal outcome of a comprehensive research program for asbestos and other mineral fibers would be the development of a unified theory of toxicity for thoracic-sized mineral fibers. A unified approach would specify criteria, such as a range of chemical composition, dimensional attributes (e.g., length range, diameter range, aspect ratio), and dissolution rate/fragility (biopersistence), for inclusion of fibers as potentially toxic. It would be particularly advantageous if these criteria could be based primarily on results from *in vitro* or short-term *in vivo* studies. This would reduce the need for comprehensive toxicity testing and/or epidemiological evaluation of each material. Such an approach would have the advantage of identifying the pertinent qualities and attributes of fibers, and newly identified or manufactured fibers could be compared to the criteria to determine a likelihood of health effects. A unified theory of fiber toxicity would clearly identify the potency of fibers for causing specific diseases and how that potency varies, depending on the particular combination of fiber characteristics and dose. A unified, coherent risk management approach that fully incorporates this understanding of the toxicity of fibers could then be developed to minimize the potential for disease.

Achievement of the research goals proposed in *Asbestos and Other Mineral Fibers: A Roadmap for Scientific Research* will require a significant investment of time, scientific talent, and resources by NIOSH and its partners. Achieving the goals of the *Roadmap*, though, will be well worth the investment because the occupational health protection policies that NIOSH recommends for asbestos and other mineral fibers must be based on the results of sound scientific research.

Acknowledgements

The NIOSH Mineral Fibers Work Group wishes to acknowledge the contributions of Jimmy Stephens, PhD, to the early development of *Asbestos and Other Mineral Fibers: A Roadmap for Scientific Research*. Dr. Stephens initiated NIOSH's work on the *Roadmap* and was the first one to articulate many of its most critical issues. The Work Group would also like to acknowledge the many internal NIOSH reviewers who provided critical feedback important to the preparation of the *Roadmap* for external review by interested stakeholders.

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Abbreviations

A/C	asbestos-cement
ASTM	ASTM International
EDS	energy dispersive x-ray spectroscopy
EM	electron microscopy
EPA	US Environmental Protection Agency
EU	European Union
IMIS	Integrated Management Information System
ISO	International Standardization Organization
MSHA	Mine Safety and Health Administration
MTD	maximum tolerated dose
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIST	National Institute of Standards and Technology
NORA	National Occupational Research Agenda
NTP	National Toxicology Program
OSHA	Occupational Safety and Health Administration
PCM	phase contrast microscopy
PLM	polarized light microscopy
REL	recommended exposure limit
SEM	scanning electron microscope
STEM	scanning transmission electron microscope
SVF	synthetic vitreous fibers
SWCNT	single wall carbon nanotube
TEM	transmission electron microscope
TWA	time-weighted average
USGS	United States Geological Survey

1 INTRODUCTION

Prior to the 1970s, attention concerning the health effects of fibers was focused on six commercially exploited minerals termed “asbestos:” the serpentine mineral chrysotile, and the amphibole minerals amosite, crocidolite, actinolite asbestos, anthophyllite asbestos, and tremolite asbestos. The realization that fiber shape might be more important than chemical composition in explaining the health effects of asbestos broadened interest to man-made fibers (e.g., synthetic vitreous fibers [SVF]) and to other naturally occurring mineral fibers [Stanton et al. 1981]. To date, interest in the latter has emphasized the importance of fibrous minerals exploited commercially (e.g., wollastonite, sepiolite, and attapulgite) or found as contaminants in certain mined commodities (e.g., richterite and winchite in vermiculite). Many of the asbestos and other fibrous minerals typically occur in trace amounts or in veins with other minerals in geologic formations throughout the United States. The biological significance of occupational exposure to many of these minerals remains unknown and difficult to ascertain given the mixed and sporadic nature of exposure in many work environments and the general lack of good exposure characterization information.

This document considers naturally occurring minerals that are the source of particulates meeting the definition of fiber (see Glossary). The varying terminology used to name and describe these naturally occurring minerals has led to uncertainty and confusion. In an attempt to minimize uncertainty and confusion, key terms are defined in the Glossary (Section 5).

Although this document focuses on the naturally occurring minerals, a substantial effort has gone into investigating exposures to, and health effects of, some of the synthetic vitreous fibers. The observed similarities and differences among various fiber types may be instructive in developing an overall policy for asbestos and other mineral fibers.

To reduce the uncertainty and controversy concerning exposure assessment and health effects of asbestos and other mineral fibers, strategic research endeavors are needed in toxicology, epidemiology, exposure assessment, and analytical methods. The resulting science can inform the potential development of new policies for asbestos and other mineral fibers with recommendations for exposure indices that more effectively protect workers’ health. What follows is an overview of the current understanding and uncertainties associated with asbestos and other minerals.

1.1 Minerals, Mineral Fibers, and Asbestos

Minerals are typically crystalline substances comprised of inorganic elements and compounds, and are defined by their distinct structure and elemental composition. Asbestos is a term applied to silicate minerals from the serpentine and amphibole groups that grow in a fibrous habit and have properties that have been commercially valuable.

The crystals of asbestos minerals form long, thin, flexible fibers when separated. Minerals in the serpentine group are sheet silicates; amphiboles are double chain silicates. Chrysotile is the only asbestos mineral in the serpentine group. Five asbestos minerals – crocidolite, amosite, anthophyllite asbestos, tremolite asbestos, and actinolite asbestos – are in the amphibole group.

Although a large amount of information has been generated on asbestos, considerable confusion surrounds the identification of asbestos for a variety of reasons. Several systems for naming amphiboles have been used, and the nomenclature has not been unified under a single system until recently [Leake et al 1997]. The lack of consistency in nomenclature has led to uncertainty in the scientific literature, regulatory agencies, and regulated communities about the identity of specific minerals and, more importantly, about the identity of elongated particles in air samples and whether they are subject to regulation under asbestos standards.

Trade names for mined asbestos minerals predated the development of rigorous scientific nomenclature. For example, amosite is the trade name for fibrous grunerite, and crocidolite is the trade name for fibrous riebeckite. Adding to the complexity of the nomenclature, serpentine and amphibole minerals typically develop through metamorphism of pre-existing minerals, or may be in the process of metamorphosing into other forms. Thus transitional forms are often found. For example, an exchange of cations along the axis of a single fiber can result in a fiber having elemental characteristics of an asbestos mineral at some locations along its length, but not at others.

Finally, minerals with the same name may occur in a variety of forms called “habits.” The habit of a mineral is a result of the local environment during formation. The mineralogical terms applied to habits are generally descriptive; some of the habits important to asbestos and related minerals include fibrous, massive, prismatic, acicular, asbestiform, tabular, and platy. It is possible for both asbestiform and non-asbestiform versions of the same mineral to occur together, even to the extent that a single mineral vein is asbestiform in some parts and non-asbestiform in others.

In the scientific literature, the term “mineral fibers” has embraced not only fibers that have grown naturally in an asbestiform habit (in which bundles of fibers can be separated longitudinally into individual fibrils), but also fibers that grow as needle-like (acicular) single crystals and fiber-like particles that result from the fracture of a mineral along cleavage planes. There is controversy about whether cleavage fragments and acicular crystals are as hazardous as asbestos fibers. Mineral fibers that grow in asbestiform habits are clearly of health concern; it remains uncertain whether particles with similar dimensions from similar minerals, but with nonasbestiform habit, represent a similar health concern.

1.1.1 Asbestos Use and Occupational Exposures

Production and use of asbestos have been steadily declining in the U.S. In 2003 through 2005, there was no domestic production of asbestos and no employment in mining and milling of asbestos in the U.S. In 2003, 5000 metric tons of asbestos were imported, compared with an estimated 2000 metric tons in 2005 (see Figure 1). The primary current uses for asbestos materials are in roofing (80%), gaskets (8%), and friction products (4%) [Virta 2006]. Although the importation of raw asbestos has declined, information is not available on the importation of asbestos already contained in finished, manufactured products.

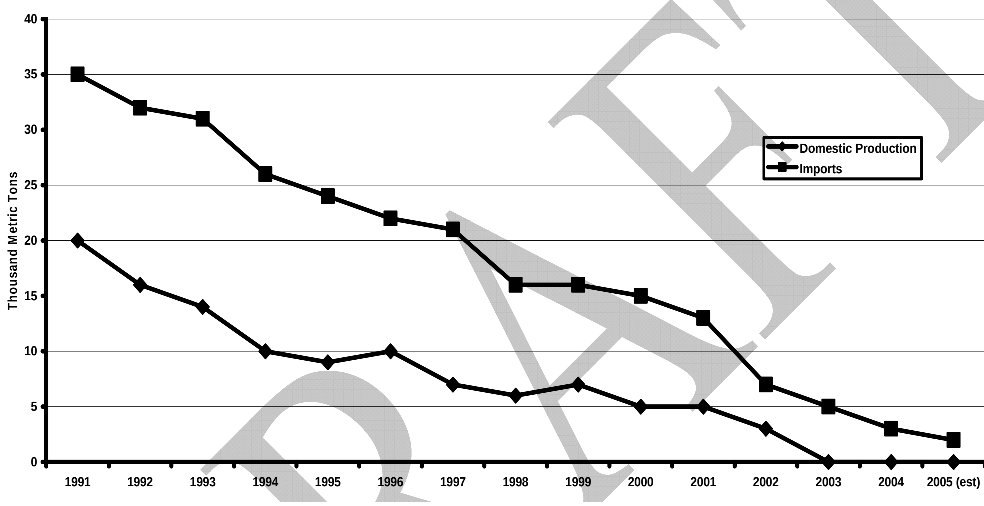

Figure 1. US Asbestos Production and Imports 1991-2005. [Virta 2006]. Data are also found at: http://minerals.usgs.gov/minerals/pubs/commodity/asbestos/asbesmcs04.pdf.

The annual geometric means of exposures to asbestos reported in the Occupational Safety and Health Administration's (OSHA) Integrated Management Information System (IMIS) and the Mine Safety and Health Administration's (MSHA) database have been consistently below the NIOSH Recommended Exposure Limit (REL) since 1986. The number of workers whose asbestos exposures were measured and reported in OSHA's database system during the 8-year period of 1987-1994 dropped from an average of 890 per year to 241 per year during the 5-year period of 1995-1999. The percentage exceeding the NIOSH REL dropped from 6.3% in 1987-1994 to 0.9% in 1995-1999. During the same two periods the number of exposures measured and reported in MSHA's database system dropped from an average of 47 exposures per year during 1987-1994 to an average of 23 exposures per year during 1995-1999. The percentage exceeding the NIOSH REL dropped from 11.1% in 1987-1994 to 2.6% in 1995-1999 [NIOSH 2002a].

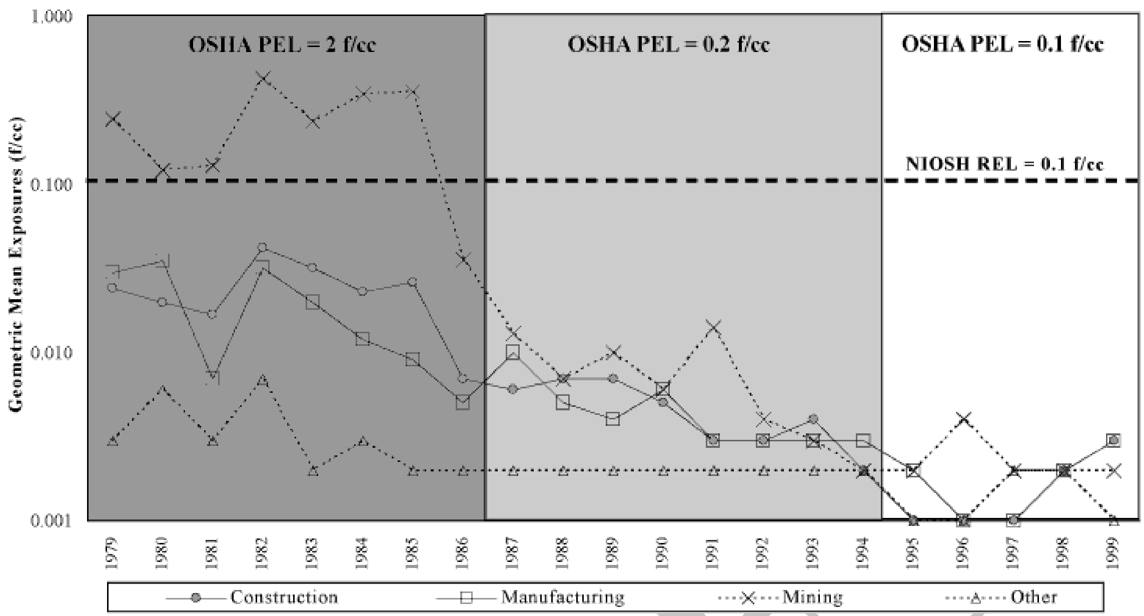

Figure 2. Asbestos: Annual geometric mean exposures by major industry division, MSHA and OSHA samples, 1979–1999. NIOSH [2002a]. Data are also found at: http://www2a.cdc.gov/drds/WorldReportData/SectionDetails.asp?SectionTitleID=1.

These numbers reported for asbestos use are based on the regulatory definition of asbestos, and do not include the cleavage fragments encompassed by the NIOSH REL for asbestos. Based on MSHA [2002] mine employment data, an estimated 44,000 miners and other mine workers may be exposed to asbestos fibers and/or cleavage fragments that contaminate mine commodities [NIOSH 2002b].

Worldwide, the use of asbestos has declined, particularly in Western Europe. Using asbestos production as a surrogate for consumption, worldwide use has declined from 5.09 million metric tons (Mt) in 1975 to about 1.93 Mt in 1999, although 2000-2004 production is estimated at 1.9 Mt to 2.4 Mt [Taylor et al. 2006]. Several Western European countries have banned some or all asbestos products. In other regions of the world, there is a continued demand for inexpensive, durable construction materials. Consequently, markets remain strong for asbestos-cement (A/C) products, such as A/C panels for construction of buildings and A/C pipe for water-supply lines. Currently over 70% of the world production is used in Eastern Europe and Asia [Tossavainen 2005].

Historically, chrysotile has accounted for more than 90 percent of the world's asbestos production, and it presently accounts for over 99 percent of the world production [Ross and Virta 2001; Virta 2002]. Mining of crocidolite (asbestiform riebeckite) and amosite (asbestiform cummingtonite-grunerite) deposits accounts for most of the other asbestos production, and small amounts of anthophyllite asbestos have been mined in Finland [Ross and Virta 2001].

1.2 Asbestos-related Disease Trends

Epidemiological studies of workers who have been occupationally exposed to asbestos fibers have clearly documented such exposure as etiologic for several respiratory diseases, including lung cancer, malignant mesothelioma, diffuse fibrosis of the lung, and non-malignant pleural abnormalities including acute pleuritis and diffuse and localized thickening of the pleura. Results of some studies suggest that other diseases (e.g., laryngeal cancer, digestive system cancers, and immune disorders) are also associated with exposure to asbestos fibers [ATSDR [2001].

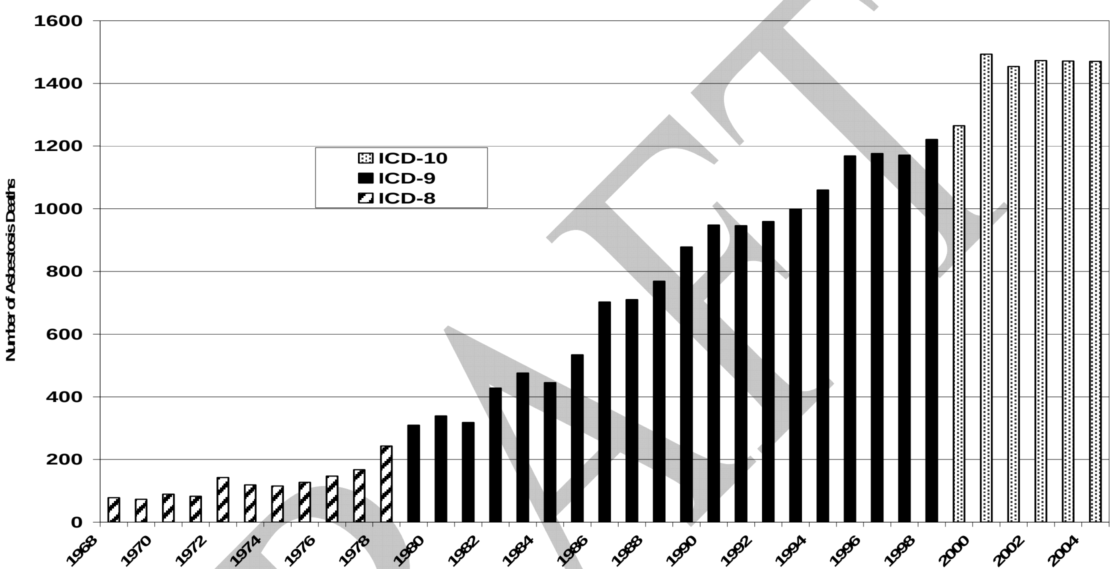

Figure 3. Number of asbestosis deaths, U.S. residents age 15 and over, 1968-2004. [NIOSH 2007]. Source: National Occupational Respiratory Mortality System (NORMS), found at: http://webappa.cdc.gov/ords/norms.html.

NIOSH tracks annual U.S. asbestosis deaths since 1968 and malignant mesothelioma deaths since 1999 using death certificate data in the National Occupational Respiratory Mortality System (NORMS). Data from NORMS show that despite the reduced exposures described above, asbestosis deaths increased almost 20-fold from the late 1960s to the late 1990s, and have apparently plateaued at nearly 1,500 per year only since 2000 (Figure 3) [NIOSH 2007]. A delayed impact of exposure reduction on asbestosis mortality is expected for two primary reasons: 1) the latency between exposure and disease onset is long, commonly one or two decades; and 2) asbestosis is a chronic disease and affected individuals typically live for many years with the disease before succumbing). Ultimately, it is anticipated that the annual number of deaths will decrease substantially as a result of documented reduced exposures. However, asbestos usage has not been completely eliminated and asbestos-containing materials remain in place in structural materials and machinery, so hazardous exposures remain a potential risk, so some asbestosis is anticipated to continue to occur for decades to come.

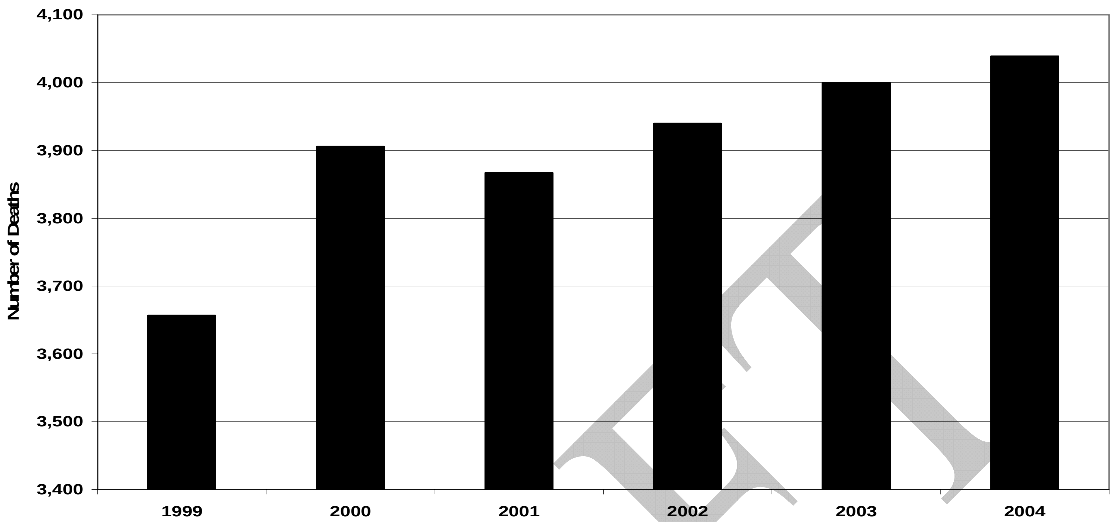

Figure 4. Number of malignant mesolthelioma deaths, U.S. residents age 15 and over, 1968-2004. [NIOSH 2007]. Source: National Occupational Respiratory Mortality System (NORMS), found at: http://webappa.cdc.gov/ords/norms.html.

A specific code for malignant mesothelioma, known to be caused by exposure to asbestos and some other mineral fibers [Pinheiro et al. 2004], was not designated until the most recent revision of the International Classification of Diseases. While only 6 years of NORMS data are available, the annual number of malignant mesothelioma deaths has apparently not yet plateaued, increasing from 2,485 deaths in 1999 to 2,657 in 2004 (Figure 4) [NIOSH 2007]. A later peak for mesothelioma deaths than for asbestos deaths is not entirely unexpected, given the typically longer latencies typical of mesothelioma [Järvholm et al. 1999]. The association of mesothelioma deaths with industries and occupations known to involve asbestos exposures is apparent from proportionate mortality analyses [Bang et al. 2006].

National surveillance data showing trends over time are not available for other asbestos-related diseases.

1.3 Components of Asbestos Definitions for Health Protective Regulations

Regulatory definitions of asbestos consist of both policy and analytical components. The policy component consists of a broad statement of agency intent about what should and should not be considered as asbestos. The analytical component describes the sampling and analytical methods to be used for collecting, characterizing, and counting fibers.

Ideally, an agency's asbestos definition will have analytical components that are closely aligned with the policy components.

Asbestos is a human carcinogen [HHS 2005a]. Based on asbestos' carcinogenicity, NIOSH established a REL of 100,000 fibers per cubic meter of air (100,000 fibers/m^3), which is equal to 0.1 fiber per cubic centimeter of air (0.1 fiber/cm^3) measured as an 8 hour time-weighted average (TWA) [NIOSH 1976]. The averaging time for the REL was changed to 100 minutes in accordance with NIOSH Analytical Method #7400 [NIOSH 1994a]. The change was first noted in testimony presented by NIOSH to OSHA [NIOSH 1990], 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 2002b]. This recommendation was set at the limit of quantification for the phase contrast microscopy (PCM) analytical method, but exposure at the REL is associated with a residual risk for lung cancer. A risk-free level of exposure to asbestos fibers has not been established.

For over a decade, NIOSH has defined airborne asbestos fibers as those particles that, when examined using PCM, have: (1) an aspect ratio of 3:1 or greater and a length greater than 5 µm; and (2) the mineralogic characteristics (i.e., the crystal structure and elemental composition) of the asbestos minerals (chrysotile, crocidolite, 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).

1.2.1 Policy Components of the NIOSH Asbestos Definition

NIOSH does not base its definition of asbestos on all the physical and chemical parameters (e.g., tensile strength, fibrous growth habit) typically used by mineralogists for identifying an asbestos mineral. Rather, NIOSH uses only specific physical criteria (i.e., particles that meet specific dimensional criteria) and compositional criteria (chemistry) to define asbestos.

The NIOSH REL applies to asbestos particles which have an aspect ratio of at least 3:1 and a length greater than 5 µm. Thus, the NIOSH asbestos REL applies to particles meeting the dimensional criteria of a fiber from chrysotile, crocidolite, amosite, anthophyllite asbestos, tremolite asbestos, and actinolite asbestos. It also applies to particles meeting the dimensional criteria of a fiber from other minerals contained in the cummingtonite-grunerite series (which includes amosite), the tremolite-ferroactinolite series (which includes tremolite and actinolite), the glaucophane-riebeckite series, and the serpentine minerals antigorite and lizardite.

Several issues have been raised about the minerals covered by this definition. The first issue is whether other amphiboles, fibrous minerals, and zeolites, should be included. Second is whether the inclusion of cleavage fragments of nonasbestiform amphiboles is appropriate. A third issue is whether the specified dimensional criteria for fibers are appropriate.

1.2.1.1 Fibrous Minerals

An asbestos definition restricted to the six commercially important asbestos minerals provides no protection from exposure to fibers from other fibrous silicate minerals with structures and chemical compositions similar to fibers from asbestos minerals, and which have either demonstrated health effects in exposed workers or can reasonably be predicted to produce health effects. This situation is illustrated by the now-closed vermiculite mine in Libby, MT. Vermiculite ore mined near Libby was contaminated with amphibole fibers mineralogically identified predominantly as winchite, richterite, as well as tremolite asbestos [Meeker et al. 2003]. Winchite and richterite are not covered by any of the OSHA, MSHA or NIOSH definitions of asbestos. Exposure to these fibers has resulted in high rates of lung diseases similar to the occurrence of asbestos-related diseases among asbestos-exposed workers in other industries [Sullivan 2007]. Inhalational exposure to other fibrous minerals, such as erionite which is a fibrous zeolite, also causes similar respiratory diseases [HHS 2005b].

In addition to health effects observed in human populations, findings from animal studies indicate that fiber dimension and biopersistence are the major factors in determining the pulmonary pathogenicity of fibers. Thus, in the absence of evidence to the contrary, NIOSH has historically maintained there is a science basis to assume that, regardless of other differences, various fibers with dimensions and biopersistence similar to fibers from the traditional six asbestos minerals will have similar potential for causing respiratory diseases (e.g., cancer and fibrosis).

1.2.1.2 Cleavage Fragments

The role of cleavage fragments in Federal regulatory and science asbestos policies has been the subject of a long-standing debate. Since 1990, NIOSH policy has included within its asbestos fiber definition cleavage fragments of nonasbestiform analogs of asbestos minerals if the particles meet the dimensional criteria of a fiber as determined microscopically (fiber-like cleavage fragments).

The basis for NIOSH's recommendation to regulate cleavage fragments as asbestos was first articulated in NIOSH testimony to OSHA in 1990. In that testimony, NIOSH based its recommendation on four elements:

- The first element was based on results of experimental animal carcinogenicity studies of various minerals demonstrating that carcinogenic potential depends on particle length, diameter, and biopersistence. The testimony characterized the evidence as suggesting that neither mineralogic identity nor origin of the particle are critical factors in carcinogenic potential.

- The second element was based on results of epidemiologic studies of worker populations with mixed exposures to asbestos fibers and nonasbestiform cleavage fragments or with exposures to cleavage fragments alone. The testimony characterized the evidence for excess lung cancer risk attributable to fiber-like cleavage fragment exposure as "equivocal."

- The third element was that asbestiform and nonasbestiform minerals can occur in the same area. Thus, determining the location and identification of asbestiform tremolite, actinolite, and anthophyllite within deposits of their nonasbestiform mineral analogs can be difficult, leading to inadvertent contamination of some mined/quarried commodities by tremolite asbestos, actinolite asbestos, and/or anthophyllite asbestos.

- The last element was the lack of routine analytical methods for airborne exposures that can be used to accurately differentiate nonasbestiform cleavage fragments from regulated asbestos fibers that meet the dimensional criteria of a fiber when examined microscopically.

NIOSH used these four elements, taken together, to support its historical recommendation that no regulatory distinction be made to exclude airborne fiber-like cleavage fragments from counts of airborne asbestos fibers. In the face of scientifically inconclusive epidemiological evidence for lung cancer risk associated with exposure to fiber-like cleavage fragments, NIOSH has relied upon the other three elements to explicitly recommend that fiber-like cleavage fragments of nonasbestiform analogs of asbestos minerals be included in counts of airborne asbestos fibers.

The NIOSH position on cleavage fragments has been criticized. Others allege that the scientific evidence from human studies and animal toxicity studies does not definitively demonstrate carcinogenic health effects from exposure to fiber-like cleavage fragments. Critics of the NIOSH policy argue that cleavage fragments do not cause cancer, and that defining fiber-like cleavage fragments as asbestos fibers does not provide any additional protection for the health of workers but increases costs and liability exposure. However, a conclusion that exposure to fiber-like cleavage fragments does not cause cancer lacks certainty due to the limited quality of relevant human health and animal data.

Much of the evidence comes from studies of a cohort of workers from a talc mine in New York. Industrial talc is a mixture of talc, tremolite, anthophyllite, serpentine and dolomite. During an exposure survey NIOSH identified airborne fibers of asbestos, but the mining company maintained that the material is not asbestiform. The initial study had a number of self-identified limitations, including its size (388 workers), lack of information on prior employment, and short duration of employment for some lung cancer cases. [NIOSH 1980]. Since 1980, the New York Talc Study has been updated and reanalyzed in five additional publications [Stille 1982; Lamm 1988; Brown 1990; Gamble 1993; Honda 2002]. Each publication examined the population differently including: extending the observation period, expanding the size of the cohort, evaluating potential confounders, or adding statistical analyses. Among these different studies, the mortality patterns reported were similar, showing an increased mortality from lung cancer and non-malignant respiratory disease in the cohort of talc workers. However, it is not clear whether the excess cancer deaths were work-related. The most recent and most thorough analysis [Honda et al. 2002] is based on an estimate of cumulative exposure to respirable dust for all job categories and years [Oestenstad et al. 2002]. Honda et al. [2002] conclude that the reason for increased lung cancer mortality remains unclear but is not well correlated with talc ore dust exposure. They also conclude that the increased mortality from non-malignant respiratory disease (NMRD) is probably related to exposure to the talc ore dust at the facility. While other evaluations of the cohort provide additional insight into the mortality experience of these workers, the same inherent limitations constrain the ability to draw definitive conclusions on the work-relatedness for some causes of death. The cohort is small, fewer than 800 workers, and has very limited information on potential confounders such as smoking and prior occupational exposures.

Several animal studies have attempted to address the toxicity of fiber-like cleavage fragments. In one study using rats [Davis et al. 1991], equal weights of the respirable fractions from six tremolite specimens were injected intraperitoneally and assessed for production of mesotheliomas. Three of the specimens were identified as asbestiform; the habits of the other three were different, and were not identified as asbestiform. The study reported that all samples possessed some potential to produce mesotheliomas, and that carcinogenicity was related to the number of long, thin fibers, but the relationship was not exact. However, it is not clear whether the toxicity was caused by the fiber-like cleavage fragments or by long, thin particles which were not identified as either fiber-like cleavage fragments or asbestiform fibers. The group exposed to the shortest fiber-like cleavage fragments had the lowest incidence of mesothelioma; however, it is not certain whether the low rate of disease in this group exceeded background rates.

It has been observed that only a small proportion of the cleavage fragments formed when nonasbestiform materials are fractured meet the NIOSH fiber definition, and those that do typically have shorter lengths and wider diameters than asbestiform fibers [Siegrist and Wylie 1980; Wylie 1988]. These and other differences between asbestiform fibers and fiber-like cleavage fragments might contribute to a shorter biopersistence in the lung for cleavage fragments. Asbestiform fibers tend to break longitudinally so that a deposited fiber can break into a multitude of fibrils as long as the originally deposited fiber [NRC 1984] and therefore can be just as difficult to clear from the lung. In contrast, fiber-like cleavage fragments tend to break transversely, resulting in several shorter particles that may be more easily cleared by macrophages. As a result of differences in surface structure, fiber-like cleavage fragments are weak and brittle in comparison to asbestiform fibers [Zoltai 1981]. Dissolution of cleavage fragments proceeds along cleavage planes and results in smaller cleavage fragments. However, dissolution of fibers from asbestiform amphiboles begins at the ends of the fiber and proceeds inward from the ends before the surface layer is dissolved [Zoltai 1981]. Magnesium leaching from the surface of chrysotile fibers in the lung is highly variable, and more is leached from thin fibers. However, the gross structure of the fiber is not changed early in the dissolution process [Morgan and Holmes 1986]. While fibers from asbestiform amphiboles have strong surfaces, cleavage fragments are expected to be weaker because of various types and sizes of defects introduced in the fracturing process [Zoltai 1981]. The impact of these structural differences on solubility in lung fluids is not known, but if there are substantial differences in the solubility in lung fluids between fibers from asbestiform minerals and fiber-like cleavage fragments, toxicity could differ.

In 1986, the Occupational Safety and Health Administration (OSHA) revised its asbestos standard and included non-asbestiform anthophyllite, tremolite, and actinolite (ATA) within the scope of the revised standard. OSHA's decision to include non-asbestiform ATA was controversial. In a proposal to further revised its asbestos standard, OSHA in 1990 noted that there were "a number of studies which raise serious questions about the potential health hazard from occupational exposure to non-asbestiform tremolite, anthophyllite and actinolite," but stated that the "current evidence is not sufficiently adequate for OSHA to conclude that these mineral types pose a health risk similar in magnitude or type to asbestos."

In 1992, OSHA stated in the preamble to the final rule revision removing non-asbestiform ATA from the asbestos standard that, "various uncertainties in the data[1] and a body of data showing no carcinogenic effect, do not allow the Agency to perform qualitative or quantitative risk assessments concerning occupational exposures. Further, the subpopulations of non-asbestiform ATA which, based on mechanistic and toxicological data, may be associated with a carcinogenic effect, do not appear to present an occupational risk. Their presence in the workplace is not apparent from the record evidence" [OSHA 1992].

In 2005, the Mine Safety and Health Administration (MSHA) followed in OSHA's analysis when it proposed revising its asbestos standard [MSHA 2005].

A U.S. Environmental Protection Agency (EPA) peer consultation workshop in 2003, convened to discuss a proposed protocol to assess asbestos-related disease risk, knew of little data to directly address the question of whether cleavage fragments with durability

[1] OSHA was making reference to the scientific data on which NIOSH based its own carcinogenic health effect recommendation to OSHA.

and dimension equal to fibers from the asbestos minerals would have similar or dissimilar potency for lung cancer, although their general view was that durability and dimension are critical to pulmonary pathogenesis. They thought that, "it is prudent to assume equivalent potency for cancer in the absence of other information to the contrary" and recommended that a rat inhalation study using tremolite cleavage fragments be considered to address the issue [EPA 2003].

There continues to be uncertainty at the Federal level about whether exposure to fiber-like cleavage fragments from non-asbestiform analogs of asbestos minerals cause cancer and other health effects similar to those caused by fibers from the six asbestos minerals.

1.2.1.3 Fiber Size Criteria and Biopersistence

Data gathered from epidemiologic and animal studies of mineral fibers indicate that the health risk posed by fiber exposures are largely determined by the fibers' dimensional characteristics (length and diameter), the fiber's ability to resist removal from the lung (biopersistence), and dose. Fibers deposit in different regions of the lung depending on their aerodynamic diameter which is a function of their diameter and length. Once fibers are deposited in the lung, the length of time they remain in the lung appears important for the initiation and progression of disease.

Fiber diameter is a major factor in defining the aerodynamic diameter of fibers, and aerodynamic diameter, in turn, determines which fibers are likely to be deposited in deep regions of the lung. In addition, some evidence indicates that thinner fibers have a greater potential than thicker fibers to migrate from the lung to pleural and peritoneal spaces. Fibers and particles with diameters less than 0.5 µm are more likely to cross membranes and translocate to pleural and peritoneal spaces and are more likely to enter the lymphatic and circulatory systems. Other than these factors, there is little evidence on the role of fiber diameter with regards to fiber pathogenicity. Overall, based on considerations of patterns of regional deposition in the respiratory tract in relation to disease development, all fibers deemed to be in the thoracic size fraction [Soderholm 1989] (e.g., capable of depositing in the bronchoalveolar regions) warrant concern.

NIOSH, OSHA, and MSHA asbestos definitions all specify that only fibers greater than 5 µm in length and having an aspect ratio (i.e., length:diameter) of at least 3:1 should be counted to assess compliance with exposure limits for asbestos. However, beyond the roles played by length and diameter, no data exist to demonstrate that fiber aspect ratio plays a role in determining the pathogenicity of fibers.

Clearance of fibers deposited in the lung is an important physiological defense mechanism that influences the risk associated with fiber exposure. The role of fiber length in pathogenicity has been the subject of considerable study and has recently been reviewed [Dodson et al. 2003]. Evidence from *in vitro* and *in vivo* studies in rodents indicate that fibers with a length equal to or greater than the diameter of rodent lung macrophages (about 15 µm) are most closely linked to biological effects observed in the lung [Blake et al. 1998]. Alveolar macrophages appear to be capable of phagocytizing and removing fibers shorter than approximately 15 µm in length, either by transport to the mucociliary system or to local lymph channels. Above this length, the alveolar macrophage appears to be ineffective at physical removal, although there is some evidence that longer fibers are partially engulfed by one or more macrophages, resulting in differential removal rates for fibers of different lengths. While fiber lengths greater than 15 µm appear to be associated with toxicity in experimental studies, a "critical" length for toxicity in humans has been shown to be probably greater than 15 µm [Zeidler-Erdely et al. 2006]. Because longer fibers cannot be easily cleared by macrophage removal, the ease with which long fibers can break into shorter lengths influences their biopersistence in the lung. When the alveolar macrophages are unsuccessful in removing these longer fibers (sometimes referred to as "frustrated phagocytosis"), enzymes, inflammatory mediators, oxidants and other contents of the macrophages are released into the lung where they can be toxic.

Stanton et al. [1981] found that lung cancer in rats was best predicted by the number of asbestos fibers longer than 8 µm and with a diameter less than 0.25 µm. However, fibers in other size categories having lengths greater than 4 µm and diameters up to 1.5 µm were also highly correlated with lung cancer. Lippmann [1988, 1990] reviewed the literature and suggested that lung cancer is most associated with asbestos fibers longer than 10 µm with diameters greater than 0.15 µm, while mesothelioma is most associated with fibers longer than 5 µm with diameters less than 0.1 µm. Evidence from animal and some *in vitro* studies suggests that short fibers (e.g., less than 5 µm long) may have some role in fibrosis but are of a lesser concern than longer fibers for cancer development. However, Dodson et al. [2003] noted that it is difficult to rule out the involvement of these shorter fibers in causing disease because exposures to asbestos fibers are overwhelmingly composed of fibers less than 5 µm long and that fibers observed in the lung and in extrapulmonary locations are also overwhelmingly less than 5 µm long. Suzuki and Yuen [2002] studied tissues from cases of malignant mesothelioma to characterize the asbestos fibers contributing to the induction of human malignant mesothelioma. They found that the majority of asbestos fibers in lung and mesothelial tissues were shorter than 5 µm in length. Although the presence of the short fibers does not substantiate causality, the authors concluded that short, thin asbestos fibers should be included in the list of fiber types contributing to the induction of human malignant mesothelioma.

NIOSH is currently attempting to ascertain the relationship between fiber dimensions (length and diameter) and the risk for developing lung cancer or asbestosis by updating the cohort of chrysotile exposed textile workers studied by Dement et al. [1994] and Stayner et al. [1997]. Archived samples collected by NIOSH at this textile plant were analyzed by TEM to obtain the bivariate fiber size distribution. Fiber-size specific exposure matrices (length and diameter) were determined and assigned to specific jobs within the plant. Analyses are underway to determine the influence of fiber dimension on lung disease risk [Kuempel et al. 2006].

Berman and Crump [1995] statistically analyzed data from 13 inhalation studies in which rats were exposed to asbestos dust to determine if a measure of asbestos exposure could be identified that satisfactorily predicts the observed lung tumor or mesothelioma incidence in the experiments. Samples of the original dusts used in the studies were regenerated and reanalyzed to provide detailed information on the mineralogy (i.e., chrysotile, amosite, crocidolite or tremolite), type (i.e., fiber, bundle, cluster, or matrix), size (length and width) and complexity (i.e., number of identifiable components of a cluster or matrix) of each individual structure. The investigators did not find a univariate measure of exposure that adequately described the lung tumor responses observed among the inhalation studies. However, bivariate measures of exposure were identified that adequately describe the lung tumor responses. Structures longer than 5 µm and thinner than 0.4 µm fibers and bundles contribute to lung tumor risk, with a possible contribution by long and very thick (>5 µm) complex clusters and matrices. Potency appears to increase with increasing length. Structures longer than 40 µm were found to be about 500 times more potent than structures between 5 and 40 µm in length. Structures <5 µm in length did not appear to contribute to lung tumor risk. Their analysis did not find a difference in the potency of chrysotile and amphibole for inducing lung tumors. However, mineralogy appeared to be important in the induction of mesothelioma with chrysotile being less potent than amphibole.

The characteristics of fibers that determine their retention in the lung include not only their length, but also their diameter, fragility, and dissolution rate in lung fluids (durability). Some fibers, such as certain types of glass fibers, are fairly soluble in lung fluid and disappear from the lung in a matter of days or months, while others, such as amphibole asbestos, can remain in the lung for decades. While some evidence indicates that fiber durability may be a determinant of toxicity for some fiber types, additional fibers need to be evaluated to determine whether they conform to this paradigm [ILSI 2005].

Biopersistence of fibers in the lung is a function of the site and rate of deposition, their rates of clearance by alveolar macrophages and mucociliary transport, their solubility in lung fluids, their breakage rate and breakage pattern (longitudinal or transverse), and their rates of translocation across membranes. It is plausible that a change in the rate of one of these processes could affect the rates of other processes. For example, the rate of deposition in the alveolar region could potentially overwhelm macrophage clearance mechanisms and increase the rate of translocation to the lung interstitium. Surface chemistry and diameter are important factors in the solubility of fibers. Fibers deposited in the lung are subjected to extracellular fluid (approximately pH 7) and lysosomal fluid (approximately pH 5); thus the solubility of a particular fiber at each of these pH levels is relevant to its biopersistence. Fibers that are more soluble will be less biopersistent, and fibers with larger diameters will take longer to dissolve than thinner fibers, all else being equal. The effect of high dust exposures on translocation and clearance mechanisms may also alter fiber clearance rates. A better understanding of the biological fate of fibers deposited in the lung is critical to understanding the mechanisms underlying differences in toxic potential of various fibers of different dimensions and compositions. Since fiber biopersistence is thought to play an important role in the development of disease, it may prove to be an important characteristic to incorporate into occupational safety and health policy concerning exposures to fibers.

1.2.2 Analytical Components of the NIOSH Asbestos Definition

The analytical components of the asbestos definition take on substantial significance because the current REL is set considering the limit of quantification of the PCM method rather than solely on estimates of risk. Had a lower limit of quantification been possible, a lower REL may have been proposed to reduce the risk of occupational cancer among asbestos-exposed workers. In applying the asbestos definition, it is important to have an analytical method and protocol that is practical and reliable and able to discriminate between types of fibers. The fiber counting rules used in PCM analysis of air samples result in an index of exposure which has been correlated with existing human health data and risk assessments. However, any PCM-based index of exposure for asbestos is not based upon a complete count of sampled fibers because very thin fibers are not visible by PCM.

There are two analytical components of the NIOSH asbestos fiber definition applied to air samples:

- *Phase contrast microscopy* (PCM) [NIOSH 1994a – Analytical Method 7400 – Asbestos and Other Fibers by PCM] is used to count all fibers that are longer than 5 µm and have a length-to-diameter ratio equal to or greater than 3:1.

- *Transmission electron microscopy* (TEM) [NIOSH 1994b – Analytical Method 7402 – Asbestos by TEM] is used to quantify the asbestos fiber fraction of fibers in air samples when there is uncertainty about whether the fibers present in an air sample are all asbestos fibers. The asbestos fiber fractions from TEM analysis are used to proportionally reduce fiber counts obtained by PCM Method 7400, yielding corrected counts of asbestos fibers.

  The method is currently annotated as follows: “Other amphibole particles that have aspect ratios greater than 3:1 and elemental compositions similar to the asbestos minerals may interfere in the TEM analysis. Some non-amphibole minerals may give electron diffraction patterns similar to amphiboles. High concentrations of background dust interfere with fiber identification.” This annotation might be inferred to mean that fiber-like cleavage fragments of the non-asbestiform analogs of the asbestos minerals are to be considered interferences; however, such an inference about the NIOSH asbestos fiber definition would not meet the intent of the current NIOSH definition.

In addition to the use of PCM (sometimes with TEM) for monitoring airborne fiber exposures, one other microscopic technique is commonly applied to the analysis of asbestos:

- *Polarized light microscopy* (PLM) [NIOSH 1994c – Analytical Method 9002] is used to identify asbestos in bulk materials.

Each of the microscopy methods used for asbestos analysis has limitations which have implications for accurate measurement of occupational exposures. Particles with diameters less than about 0.25 µm cannot be counted using Method 7400 because they are below the resolution limits of the optical microscopes routinely used. PCM does not differentiate between asbestos and other fibers, such as non-asbestos minerals fibers, glass fibers, cellulose fibers, hair, and organic synthetic fibers like nylon**.** When fiber identification is required, TEM analysis (i.e., Method 7402) is used to characterize and identify individual fibers by determining its crystalline structure and chemical composition; thus, TEM characterization is used to help improve the accuracy of the asbestos fiber counts obtained by PCM, as the latter could otherwise include various fibers not specified as asbestos fibers under the NIOSH definition. PLM analysis is often used for identifying asbestos in bulk samples; however, the method rarely is used for analyzing airborne samples because of difficulties in sample preparation. Like PCM, PLM cannot resolve fibers with diameters less than about 0.25 µm.

Another aspect of the NIOSH analytical method is the counting rules. The rules for counting that are commonly used, referred to as the "A" rules, instruct the microscopist to count fibers of any diameter that have a 3:1 or larger aspect ratio. However, fibers with a diameter greater than 3 µm are not likely to reach the thoracic region of the lung when inhaled. The "B" counting rules specify that only fibers less than 3 µm in diameter should be counted. Other differences between the counting rules are provided in Method 7400 [NIOSH 1994a]. The European Union is moving toward a standardized method that counts fibers using the method recommended by the World Health Organization (WHO) [WHO 1997] which specifies counting only particles less than 3 µm in diameter with a 3:1 or larger aspect ratio [European Parliament and Council 2003].

1.2.3 Analytical Components of the OSHA and MSHA Asbestos Definitions

The use of PCM in determining asbestos fiber concentrations, as required by OSHA and MSHA, cannot assure that fiber-like cleavage fragments are excluded from determinations of asbestos fiber concentrations. While there are ample ways to distinguish asbestiform materials from nonasbestiform materials in bulk samples, reliable and reproducible analytic methods are not available to distinguish individual fibers in air samples as nonasbestiform or asbestiform. The lack of reliable and validated analytical methods that can distinguish between fibers from the asbestos minerals and fiber-like cleavage fragments of their nonasbestiform analogs in air samples is clearly a major limitation in applying asbestos definitions intended to exclude fiber-like cleavage fragments. The challenge is especially great for environments with mixed (i.e., asbestiform fiber and fiber-like cleavage fragment) exposures. It is critically important that an analytical method that is able to clearly discriminate between fibers and fiber-like cleavage fragments be developed and validated.

A technique referred to as “differential counting” and suggested to differentiate between asbestiform fibers of the asbestos minerals and fiber-like cleavage fragments, is mentioned in a non-mandatory appendix to the OSHA asbestos standard. The appendix to that standard points out that the differential counting technique requires “a great deal of experience” and is “discouraged unless legally necessary. It relies heavily on subjective judgment and does not appear to be commonly used except for mine samples. In this technique, fibers that the microscopist judges as non-asbestiform (e.g., having the appearance of cleavage fragments) are not counted. However, any fibers not clearly distinguishable as either asbestos or non-asbestos using differential counting are to be counted as asbestos fibers. One effect of using differential counting is to introduce a source of variability in the fiber counts because of different “readings” between different microscopists. The technique has not been formally validated and is not used or recommended by NIOSH.

For counting asbestos fibers in mines and quarries, ASTM has proposed a “discriminatory counting” that incorporates the concepts of differential counting, but refers to the technique as “discriminatory counting.” The proposed method uses PCM and TEM in a tiered scheme. Air samples are first analyzed by PCM and, if fiber concentrations are greater than one-half the PEL but less than the PEL, discriminatory counting is then performed. Discriminatory counts are restricted to fiber bundles, fibers greater than 10 µm in length, and fibers less than 1.0 µm in diameter. If the discriminatory count is at least 50% of the initial fiber count, TEM is then performed to determine an equivalent PCM count of regulated asbestos fibers only. If the initial PCM count is greater than the PEL, then TEM is performed to determine an equivalent PCM count of regulated asbestos fibers only. These results are then used to compare to regulatory limits [ASTM 2006]. NIOSH has begun a validation evaluation of the ASTM method.

More powerful than PCM for distinguishing fiber types, electron microscopy can determine electron diffraction patterns that might reveal a particle’s crystal form to be more representative of a cleavage fragment than an asbestiform fiber, and can also be used to better visualize fine morphological structures that can be used to distinguish the two. Using scanning transmission electron microscopy (STEM), it is also possible to determine elemental composition, which can be used to identify mineral fibers from commonly encountered interfering fibers of fabrics (e.g., cellulose, nylon, cotton) and of glass and ceramics, which cannot be identified under PCM.

Other procedures have been suggested with the intent of ensuring that the fiber counts on air samples do not include cleavage fragments [IMA-NA 2005; NSSGA 2005]. These procedures include reviewing available geological information and/or results from analysis of bulk materials to establish that asbestos is present in the sampled environment, or specifying dimensional criteria to establish that airborne particulates have population characteristics typical of asbestos fibers (e.g., mean fiber aspect ratios exceeding 20:1). Whether these suggested procedures would assure adequate health protection for exposed workers is unclear, and the practical issues associated with implementing these supplemental procedures are also undetermined.

1.3 Summary

The above discussion identifies the major known areas of uncertainty about the toxicities of fibers from the asbestos minerals, of fiber-like cleavage fragments from non-asbestiform analogs of the asbestos minerals, and of other mineral fibers, as well as the short-comings of current analytical techniques. As a result of these scientific uncertainties, NIOSH proposes to address three strategic goals:

I. Develop improved sampling and analytical methods for fibers and fiber-like cleavage fragments.

II. Develop information and knowledge on occupational exposures to fibers and fiber-like cleavage fragments and health outcomes.

III. Develop a broader understanding of the important determinants of toxicity for fibers and fiber-like cleavage fragments.

To address the scientific issues and inform future NIOSH policies, a proposed research agenda is presented and discussed in Section 2.

2 FIBER RESEARCH

2.1 Strategic Research Goals and Objectives

The strategic goals for a fiber research program and the related objectives 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 improved sampling and analytical methods for fibers [2.2].

- Reduce inter-operator and inter-laboratory variability of the current fiber analytical methods [2.2.1];
- Develop fiber analytical methods with improved resolution to visualize smaller diameter fibers to assure more complete fiber counts [2.2.2];
- Develop a practical analytical method for air samples to differentiate between exposures to asbestiform fibers from the asbestos minerals and exposures to fiber-like cleavage fragments from their non-asbestiform analogs [2.2.3];
- Develop analytical methods to assess fiber durability [2.2.4]; and
- Develop and validate thoracic-size selective sampling methods for fibers [2.2.5].

II. Develop information and knowledge on occupational exposures to fibers and fiber-like cleavage fragments and health outcomes [2.3].

- Collect and analyze available occupational exposure information to ascertain the characteristics and extent of exposure to various types of fibers and to fiber-like cleavage fragments[2.3.1];
- Collect and analyze available information on health outcomes associated with exposures to various types of fibers and to fiber-like cleavage fragments [2.3.2]; and
- Conduct epidemiologic studies of workers exposed to various types of fibers and fiber-like cleavage fragments to better define the association between fiber exposure and health effects [2.3.3].

III. Develop a broader understanding of the important determinants of toxicity for fibers and fiber-like cleavage fragments [2.4].

- Conduct *in vitro* studies to ascertain what physical and chemical properties influence the toxicity of fibers and fiber-like cleavage fragments leading to a better understanding of how fibers induce disease [2.4.1]; and

- Conduct animal studies to ascertain what physical and chemical properties influence the toxicity of fibers and fiber-like cleavage fragments leading to a better understanding of how fibers induce disease [2.4.2].

Research conducted to support these three research goals should be integrated to optimize resources and facilitate the simultaneous collection of data. Much of this research may be accomplished by or in partnership with our Federal partners or stakeholders in the private sector. Any research that is undertaken should ensure that the results can be interpreted and applied within the context of other studies and lead to outcomes useful for decision-making and policy-setting.

2.2 Develop improved sampling and analytical methods for fibers.

There are important scientific gaps in understanding the health impacts of exposure to mineral fibers. Any changes in the scope of minerals and the characteristics of their fibers included in an updated fiber definition will likely have to be accompanied by improvements to currently used analytical methods or development and application of new analytical methods. These methods will need to provide accurate information about exposures to the fibers explicitly encompassed by the policy component of the definition. The ability to differentiate between fiber types, including between asbestiform fibers of the asbestos minerals and fiber-like cleavage fragments of their nonasbestiform analogs, is important especially if recommendations (e.g., RELs) are specific to the type of mineral. However, this could be a significant obstacle because validated analytical methods are not available that can effectively distinguish between fibers from the asbestos minerals and fiber-like cleavage fragments from their nonasbestiform analogs.

Until new analytical methods are developed and applied, it will be necessary to investigate the various proposals that have been made to adjust the current analytical methods, such as those discussed in Section 1.2.3, and additional modifications to the current analytical methods will have to be explored. Improvements in exposure assessment methods are important to increase the accuracy of the methods used to identify, differentiate, and count fibers.

Some barriers to improving the current methods have been identified. Requiring optical microscopes to have objective lenses with higher resolution to resolve thinner fibers in samples may not be sufficient to improve risk assessments. Requiring the use of electron microscopy (EM) would improve capability to detect small fibers, but it would also increase analytical costs and the lag time between sampling and obtaining results. In some workplace situations, such as in construction, this would eliminate the small window of time available to apply appropriate controls to reduce exposures.

Several potential improvements are currently under study. Some of the studies are aimed at improving the accuracy of current techniques, such as the evaluation of thoracic samplers for the collection of airborne fibers and the use of gridded cover slips when performing PCM analysis. Another study is intended to evaluate the ASTM method and determine whether inter-operator variability when performing differential counting between asbestos fibers and fiber-like cleavage fragments is within an acceptable range.

Areas of research for new methods development includes the development of methods that would permit an assessment of the potential biopersistence (e.g., durability) of fibers collected on air samples prior to their evaluation by PCM or other microscopic methods. In addition to the research described here, improvements in EM identification (EDS, energy dispersive x-ray spectroscopy) are needed, and other EM techniques for fiber identification need to be investigated.

Modifications to the current methods will require an assessment of worker health implications. Any changes in the analytical methods will necessarily be made in concert with an understanding of the types of fibers included in a new definition and their chemical and physical properties. Whether these changes would be effective and provide consistent results across the full range of occupational environments would also need to be explored.

2.2.1 Reduce inter-operator and inter-laboratory variability of the current fiber analytical methods.

To ensure the validity of fiber counts made on asbestos air samples, it is important to ensure consistency between analysts. Microscopic counts of asbestos fibers on air samples are made using only a small percentage of the surface area of the filter, and the counting procedures require the analysts to make decisions on whether a particle meets the definition of a fiber. Interlaboratory sample exchange programs have been shown to be important in ensuring agreement in fiber counts between laboratories [Crawford et al. 1982]. Unfortunately, microscopists from different laboratories are unlikely to view exactly the same fields, resulting in an uncontrollable component of the variation that exists in fiber counts between microscopists. A mechanism to allow recounts of fibers from the same field areas would remove this additional variation component and allow a better assessment of the variation between microscopists in analyzing samples.

A technique is under development for improving the accuracy of PCM fiber-counting by allowing exactly the same fields of view to be examined by multiple microscopists or the same microscopist on different occasions [Pang et al., 1984; Pang et al. 1989; and Pang 2000]. The method involves the deposition of an almost transparent TEM grid onto the sample. Included with the grid are coordinates allowing each grid opening to be relocatable. Photomicrographs of typical grid openings superimposed on chrysotile and amosite samples have been published [Pang et al. 1989]. Slides prepared in this manner have been used in a Canadian proficiency test program for many years. The main errors affecting the counts of each fiber type (chrysotile, amosite, and SVF) have been evaluated by examining large numbers of slides by large numbers of participants in this program. A scoring system for identifying the performance of microscopists has been developed [Pang 2002] based on errors compared with a reference value defined for each slide by the laboratory in which they were produced. A statistical analysis of the intragroup precision in this study was able to identify those analysts who were outliers [Harper and Bartolucci 2003]. In a pilot study, the pooled relative standard deviations, without the outliers, met the requirements for an unbiased air sampling method. Further study is needed to validate these findings and to identify other techniques that can reduce inter-laboratory and inter-operator variability in counting fibers by PCM.

2.2.2 Develop fiber analytical methods with improved resolution to visualize smaller diameter fibers to ensure more complete fiber counts.

Both optical and electron microscopes are available that can visualize fibers with diameters <0.25 µm which is the approximate lower resolution limit of PCM. To improve the optical resolution to about 0.1 µm, an oil immersion 100X objective with a numerical aperture of 1.49 would be required. Also, the use of 15X eyepiece oculars would help improve the visibility of particles and fibers on the sample. However, because risk estimates for workers occupationally exposed to asbestos have been determined based on fiber counts made by the current PCM methods, fiber counts made with improved microscope resolution capabilities would not be directly comparable to current occupational exposure limits for asbestos.

While improvements in optical microscopy resolution might be useful in establishing new criteria for counting fibers, studies would need to be conducted to evaluate inter-operator and inter-laboratory differences similar to that which has been conducted for the current PCM method. Results from experimental animal studies and the evaluation of fiber lung burdens in exposed asbestos workers suggest that fibers thinner than 0.1 µm are most associated with mesothelioma and fibers < 0.15 µm in diameter with lung cancer and asbestosis [Lippman 1988], so even improvement in the resolution of optical microscopy may not provide the information needed to completely assess the risks for mesothelioma, lung cancer, or lung fibrosis.

Transmission electron microscopy (TEM) can resolve fibers with diameters < 0.01 µm which is adequate for detecting the presence of asbestos and other mineral fibers collected in airborne samples. TEM, as well as scanning electron microscopy (SEM), provide improved resolution for detecting and sizing fibers. Both methods also provide the capability for mineral identification using selected area x-ray diffraction and/or elemental analysis (e.g., energy dispersive x-ray analysis). The cost of using TEM and/or SEM for routine sample analysis would be considerably higher than PCM analysis and the turnaround time for sample analysis would be increased substantially. In addition, any routine use of electron microscopy (EM) methods for counting and sizing fibers would require an analysis of inter-operator and inter-laboratory variability.

2.2.3 Develop a practical analytical method for air samples to differentiate between exposures to asbestiform fibers from the asbestos minerals and exposures to fiber-like cleavage fragments from their non-asbestiform analogs.

A recently published ASTM International Standard "Method for Sampling and Counting Airborne Fibers, Including Asbestos Fibers, In Mines and Quarries, by Phase Contrast Microscopy" (D7200-06) [ASTM 2006] contains a proposed methodology for separating fiber-like particles from probable asbestos fibers. The new ASTM procedure, which uses PCM-determined morphologic features to differentiate fiber-like cleavage fragments from other fibers, has several points of deviation from existing PCM methodologies. The proposed procedure uses a new graticule that has not been tested for conformance with the traditional graticule used in PCM asbestos analysis. It specifies additional counting rules to classify particles, and there are few data to show these rules provide a consistently achievable or meaningful result. Also, only limited data are available to show inter- or intra-operator or inter-laboratory variation. These issues must be addressed before the standard can be considered acceptable. NIOSH currently has a project addressing these issues. The specific aims of the project include:

a. To determine the effect on traditional PCM fiber counting of exchanging the Walton-Beckett graticule with the new RIB graticule.

b. To determine inter- and intra- operator and inter-laboratory variation of the technique of allocating particles to different morphological "bins" using standard slides.

c. To determine inter- and intra- operator and inter-laboratory variation of the technique of allocating particles to different morphological "bins" using real-world mining and ore-processing samples.

The outcomes of aims (b) and (c) would include a measure of method accuracy and a determination as to whether the method meets the accuracy requirements of regulatory and other agencies.

While electron microscopy (EM) may not be suitable for routine analysis of samples, EM techniques used to identify minerals (e.g., differentiate asbestiform fibers from fiber-like cleavage fragments) need to be further investigated and evaluated to determine whether the results can be reproduced by multiple microscopists and laboratories.

2.2.4 Develop analytical methods to assess fiber durability.

While research is being conducted to determine the ability of biological assays to evaluate the biopersistence (e.g., durability) of fibers in the lung, there is a need to consider how fiber "durability" might be incorporated into the analysis of an air sample containing a heterogeneous mix of fibers/particulates. Research with several types of glass fibers and some other synthetic vitreous fibers indicate that they dissolve in media at different rates depending on the pH and dissolve more rapidly than chrysotile and amphibole asbestos [Leineweber 1984]. Chrysotile fibers have been shown to dissolve readily in acidic pH, although the solubility varies with the type of acid rather than with acid strength. Amphibole asbestos fibers have been shown to be relatively resistant to dissolution. Research suggests that the rate of dissolution for most fibers appears to be strongly dependent on chemical composition and dimension.

The selective dissolution of fibers might be a useful approach in eliminating specific types of fibers/particulates collected on air samples prior to counting fibers. The removal of interfering fibers/particulates prior to determining fiber concentrations could eliminate the need for additional analysis to identify fibers and thereby reduce analytical time. Selective dissolution of samples to remove interferences is well established in NIOSH practice. Method 5040 for diesel exhaust has an option for using acidification of the filter sample with hydrochloric acid to remove carbonate interference [NIOSH 2003a]. Silicate interferences for quartz by infra-red spectroscopic detection are removed by phosphoric acid digestion in Method 7603 [NIOSH 2003b]. Although selective dissolution might be accomplished, research will be necessary to develop and characterize a procedure that would correlate residual fiber count to toxicity.

2.2.5 Develop and validate thoracic-size selective sampling methods for fibers

For measuring concentrations of non-fibrous dust in workplaces, conventions have been developed for sampling the aerosol fractions that penetrate to certain regions of the respiratory tract upon inhalation: the inhalable fraction of dust that enters into the nose or the mouth; the thoracic fraction of dust that penetrates into the thorax (i.e., beyond the wind pipe); and the respirable fraction of dust that reaches the alveolar lung. The thoracic convention is recognized by NIOSH and other organizations that recommend exposure limits, and NIOSH has begun to apply it in the derivation of RELs (e.g., metalworking fluids).

Fibers currently are collected for measurement using a standard sampling method, which is described in Method 7400 [NIOSH 1994a], in MDHS 39/4 [HSE 1995], and in ISO 8672 [ISO1993]. In these methods, air samples are taken using a membrane filter housed in a cassette with a cowled sampling head. Early studies [Walton 1954] showed that some exclusion of very coarse particles occurs due to elutriation in the vertical cowl, but its selection characteristics should have little effect on the collection efficiency for fibers. However, when Chen and Baron [1996] evaluated the sampling cassette with a conductive cowl used in sampling for asbestos fibers, they found inlet deposition was higher in field measurements than predicted by models.

Currently, NIOSH does not recommend an upper limit for asbestos fiber diameter, which has generated some criticism that some fibers counted by NIOSH Method 7400 (A rules) may not be inhalable. NIOSH and others have recommended NIOSH Method 7400 (B rules) for the sampling and analysis of various types of fibers, including asbestos [Baron 1996]. However, this method has not been field-tested for the collection and analysis of occupational exposures to many types of mineral and organic synthetic fibers. Samples analyzed by this method would presumably count only fibers in the thoracic size range. Thoracic samplers would allow the collection of airborne fibers that meet the aerodynamic definition of thoracic-sized fibers (i.e., fibers with diameters equal to or less than 3 µm), eliminating the deposition of large particles on the sample filter and limit collection of fibers to those considered most pathogenic.

Two separate but complementary projects have examined the performance of thoracic samplers for fibers [Jones et al. 2005; Maynard 2002]. The results of the studies indicated that the fiber penetration of some thoracic samplers was independent of fiber length at least up to 60 µm, indicating that the samplers' penetration characteristics for a fibrous aerosol should be no different than that of an isometric aerosol. In the Jones et al. study [2005], the relative ability of the thoracic samplers to produce adequately uniform distributions of fibers on the membrane filter's surface was also tested. Based on the results of these studies, two samplers appear to meet the criteria of minimal fiber length selection bias and even distribution on the collection filters. However, neither of these samplers has been tested under field use conditions. NIOSH is currently evaluating the two thoracic samplers and the traditional cowled sampler in two different mining environments.

2.3 Develop information and knowledge on occupational exposures to fibers and fiber-like cleavage fragments and health outcomes.

There is a need to ascertain and document the number of workers and the types of job tasks in which workers are potentially exposed to asbestos, fiber-like cleavage fragments, or other mineral fibers. Commensurate with this assessment is the need to measure and characterize worker exposures that could be used for conducting an analysis of risk. Health surveillance of workplaces where exposure to asbestos, fiber-like cleavage fragments, or other mineral fibers might occur could provide information on preclinical indicators of disease or sentinel health problems. This information will be beneficial in prioritizing research and identifying populations for potential epidemiological studies.

2.3.1 Collect and analyze available occupational exposure information to ascertain the characteristics and extent of exposures to various types of fibers and fiber-like cleavage fragments.

A strategy for prioritizing fiber research should include the systematic collection and evaluation of information on:

- Industries/occupations with exposure to various types of mineral fibers;
- Levels of worker exposure to airborne fibers in these industries/occupations; and
- Numbers of workers exposed in these industries/occupations.

The selection of industries and worker populations for study should be based on their ability to contribute to understanding the core issues associated with fiber toxicity, such as: type of mineral, dimensional characteristics (including length and diameter) of the airborne mineral, chemical identity, morphology (e.g., asbestiform fiber vs. fiber-like cleavage fragment), and information on its potential biopersistence.

As an initial step, efforts should be made to collect and analyze available occupational exposure information (e.g., industry data, OSHA/MSHA exposure measurement data, and NIOSH exposure measurement data) to ascertain the characteristics and extent of exposure to various types of fibers. Collection of such data is important to determine the need for possible toxicity studies, medical surveillance, and epidemiology studies (retrospective and prospective).

Worker exposure assessment studies should be supported by improvements in the currently used analytical methods or development of new methods that allow for the identification and quantification of biologically relevant fibers in air samples. Research on exposure assessment and analytical methods are discussed in Section 2.2.

2.3.2 Collect and analyze available information on health outcomes associated with exposures to various types of fibers and to fiber-like cleavage fragments.

The body of knowledge concerning human health effects from exposure to fibers consists primarily of epidemiologic studies of workers exposed to asbestos, some synthetic vitreous fibers (e.g., glass fibers, glass and mineral wool, ceramic fibers), and several other mineral fibers (e.g., wollastonite, attapulgite, erionite). There is general agreement on the interpretation of human health effects data of workers exposed to fibers from the asbestiform minerals. For example, NIOSH recently commented on the MSHA proposed rulemaking on asbestos, stating that "NIOSH remains concerned that the regulatory definition of asbestos should include asbestiform mineral fibers such as winchite and richterite, which were of major importance as contaminants in the Libby, MT vermiculite" [NIOSH 2005].

The results from epidemiologic studies of workers exposed to other types of mineral fibers and to fiber-like cleavage fragments are less clear and often equivocal. It is also important to determine whether other mineral fibers pose the same potential health risks as those observed in workers exposed to fibers from the asbestiform minerals. In the short term, it may be possible to review, analyze, and summarize the available information on a select group of amphibole minerals that grow in fibrous habits, such as winchite and richterite.

In addition to existing information from epidemiologic studies, relevant information on health outcomes in human populations exposed to various types of fibers may also be available from existing public health, occupational, and environmental surveillance systems and registries in the U.S. and other countries. Information from existing surveillance systems or registries, particularly those for strongly fiber-associated diseases such as mesothelioma, might prove useful for advancing the understanding of risks associated with specific fiber types if the data are accompanied with sufficient information to distinguish exposures to various fibers.

2.3.3 Conduct epidemiologic studies of workers exposed to various types of fibers and fiber-like cleavage fragments to better define the association between fiber exposure and health effects.

Studies that analyze mortality and cancer incidence data can be used to assess the association between various mineral fibers and respiratory and other diseases in exposed populations.

The human database on the health effects from exposure to fibers consists primarily of epidemiologic studies of workers exposed to asbestos, some synthetic vitreous fibers (e.g., glass fibers, glass and mineral wool, ceramic fibers), and several other mineral fibers (e.g. wollastonite, attapulgite, erionite). The results from epidemiologic studies of workers exposed to fibers from asbestos minerals provide the strongest human evidence indicating that fibers of thoracic dimension and high durability (at a sufficient dose and latency period) pose risks for malignant and nonmalignant respiratory disease. Results from epidemiologic studies of workers exposed to other fiber types have provided limited supporting evidence and additional epidemiologic studies should be considered for worker populations exposed to various types of synthetic (organic and inorganic) fibers and naturally occurring mineral fibers. Studies of populations exposed to different fibers of similar dimension could contribute to a better understanding of fiber durability.

The following criteria should be considered in selecting and prioritizing possible worker populations for study: 1) adequate exposure information (e.g., fiber concentrations, fiber dimension and durability characteristics, other confounding workplace exposures); 2) good work histories; and 3) sufficient latency and number of workers to provide adequate statistical power to detect the health outcome(s) of interest; and 4) availability of data on other potentially confounding risk factors.

In addition to epidemiologic studies that address etiology, epidemiologic studies can be used to better understand the pathogenesis of fiber-induced lung diseases. For example, appropriately designed epidemiological studies could be used to assess the relationship between lung fibrosis and lung cancer. Epidemiologic studies also provide an opportunity to determine whether a fiber-related increase in disease, including cancer, occurs in other organ systems among workers occupationally exposed to fibers.

Further epidemiological investigations based on a recently published study on asbestos-related disease in the Sierra foothills [Pan et al. 2005] may help clarify the potential toxicity of fiber-like cleavage fragments. In one specific location, El Dorado Hills, CA, EPA has identified asbestos fibers, mainly actinolite and tremolite. However, others have disputed the identification of asbestos fibers stating that the particles are fiber-like cleavage fragments. If the nature of the study population's exposure can be conclusively determined to be to fiber-like cleavage fragments, additional studies of this population and other similarly exposed populations may provide additional information on the toxicity of these particles.

For any epidemiology studies that are warranted, several fiber characterization efforts will need to be undertaken to develop possible exposure-response relationships. These exposure assessment efforts should include:

- Estimation of historical exposures;

- Examination of existing exposure data to develop process-specific conversion factors between diverse exposure measurements and biologically based exposure indices; and

- Development of sampling and analytical strategies for prospective studies including collection of bivariate (i.e., length and width) fiber distributions and a variety of exposure indices. Exposure-effect analysis based on bivariate data for all fibers, including those shorter than the traditional length cut-off of 5 µm, could contribute to an understanding of where a health-based exposure index cut-off for fiber length should be set.

2.4 Develop a broader understanding of the important determinants of toxicity for fibers and fiber-like cleavage fragments.

Fibers encountered in the work environment are frequently heterogeneous which limits the ability of epidemiological and other types of health assessment studies to evaluate the influence of fiber size (length and diameter), chemical composition, biopersistence, and other morphologic characteristics on toxicity. Toxicological testing is needed to address some of the fundamental questions about fiber toxicity that cannot be determined through epidemiology or other types of health assessment studies.

Animal inhalation studies are needed to investigate the biopersistence and toxicity of fibers with a range of chemical compositions and morphological characteristics (including crystalline habits) and representing a range of discrete lengths and uniform diameters.

Much research has been focused on lung cancer and mesothelioma. If it is determined that some minerals have low potency for causing cancer, then additional studies may be needed to investigate their potential for causing asbestosis and other nonmalignant respiratory diseases. Also, the relationship between fiber length and asbestosis should be more fully investigated. The results of such research may allow NIOSH to update current exposure indices by specifying different dimensional criteria (lengths and diameters) relevant to each of the disease outcomes associated with fiber exposures, and by determining whether biopersistence can be included as an additional criterion. However, this research is dependent on developing new technology and will take considerable time to conduct, so new recommendations on exposure indices cannot be developed in the short term.

Implicit in any new policy for mineral fibers may be new risk assessments. Risk assessments for lung cancer and asbestosis have been conducted on worker populations exposed to fibers from various asbestos minerals. These risks have been qualitatively confirmed in animals, but no adequate quantitative dose-response inhalation studies with asbestos have been conducted in rats which would allow for comparisons between minerals.

2.4.1 Conduct in vitro studies to ascertain what physical and chemical properties influence the toxicity of fibers and fiber-like cleavage fragments.

Within the context of answering the key questions on fiber dimension, chemistry, morphology, and durability, the selection of fibers to be tested should be prioritized based on existing knowledge that workers are (potentially) exposed and on existing exposure information (e.g., measurement data, fiber characterization).

The toxicological testing should involve both *in vitro* methods and experimental animals. Some of the testing can be accomplished using currently available techniques, but some of the needed tests, particularly the *in vitro* tests, must be developed and validated.

An important technological barrier to toxicological testing is the inability to generate large quantities of fibers or fiber-like cleavage fragments in narrow length- and diameter-classified size ranges. Although inhalation studies with size-selected refractory ceramic fibers and glass fibers have been conducted by the Research Consulting Company (Geneva, Switzerland) using a "water-based cyclone procedure" [Bernstein et al. 1994; Bernstein et al. 1995], it has not been determined whether the method can be adapted for naturally occurring minerals. Also, the technique is considered proprietary. NIOSH researchers have developed a dielectrophoresis technique for generating size-selected fractions of fibers by length; however, the technique is only capable of generating small quantities of fibers (i.e., 1 mg/day) suitable for short-term *in vivo* and *in vitro* studies [Baron et al. 1994]. Investigations are underway to identify appropriate materials and methods for generating the large quantities needed for chronic exposure studies.

A number of *in vitro* cellular assays are used to assess specific biological properties of fibers, including cytotoxicity, phagocytosis, mediator release, and chromosomal damage. *In vitro* assays provide an opportunity to:

- Evaluate the biological effects of fibers in a short time frame (1 to 2 weeks);
- Conduct studies at a low cost compared to long-term animal studies; and
- Control several variables in cell culture environments (e.g., culture conditions, homogeneous populations of cells, fiber dose).

In addition, *in vitro* assays can be used to study more fundamental issues of fiber toxicity, such as to evaluate critical changes in gene activation (oncogenes) or inactivation (cancer-suppressor genes) using molecular biology techniques.

A current hypothesis is that the relative toxicity of fibers increases with increasing durability (which influences biopersistence in the lung). This needs to be tested through the assessment of many types of fibers. Several studies have been conducted with various types of synthetic vitreous fibers (SVFs) and asbestos fibers to evaluate differences in durability. Although a variety of different acellular *in vitro* assays were used in these studies, all studies observed faster dissolution of SVFs compared to various asbestos fibers in the same assay. The rate of dissolution appeared to be dependent on chemical composition and dimension; thinner fibers tend to dissolve sooner than thicker ones of the same fiber type. Acellular *in vitro* assays of durability need to be validated against *in vivo* studies of biopersistence in animals.

The European Union has already adopted criteria for the hazard classification of synthetic fibers using assay systems for determining fiber durability and short-term animal studies for fiber biopersistence [European Commission 1997; European Commission 1999a; European Commission 1999b]. Studies should be initiated to validate the ability of these test criteria to screen for potential toxicity of other fiber types (including fiber-like cleavage fragments). Research to validate the durability assay system and conduct short-term biopersistence studies will require fibers (and fiber-like cleavage fragments) of uniform dimension and/or material that is representative of occupational exposure.

Research in the following areas would help to address issues related to fiber durability:

- Apply and validate acellular *in vitro* assays to measure fiber durability;
- Conduct studies to determine the effect of surface area and chemical composition on the durability of various fibers.

Another hypothesis is that fiber dimension determines relative toxicity. The existence of critical fiber dimensions can be tested by exposing lung cells in culture to fiber samples of various discrete lengths and/or diameters. Issues such as frustrated phagocytosis and/or the contribution of aspect ratio or surface area to bioactivity can be tested.

Research in the following areas would help address issues related to fiber dimension:

- Isolate fiber samples of identical composition but different lengths and diameters;
- Conduct cell toxicity, bioactivation, and genotoxicity studies to determine critical dimensions associated with fiber activity; and
- Address whether generation of reactive oxidant species by fibers is a critical factor in toxicity.

2.4.2 Conduct animal studies to ascertain what physical and chemical properties influence the toxicity of fibers and fiber-like cleavage fragments.

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

An important consideration in the conduct and interpretation of animal studies is the selection of appropriately sized fibers that accounts for differences that exist between the rodent and humans in fiber deposition characteristics. Fibers that are capable of being deposited in the bronchoalveolar region of humans cannot be completely evaluated in animal inhalation studies because the maximum thoracic fiber size for a rodent is a fiber with an aerodynamic diameter of approximately 2 µm, whereas in humans the maximum size is about 3 µm [Timbrell 1982; Su and Cheng 2006].

2.4.2.1 Short-Term Animal Studies

Short-term animal studies should primarily be conducted with rats so that information gained (e.g., regarding overload and maximum tolerated dose [MTD]) from these studies can be used in designing chronic inhalation studies [ILSI 2005]. The objectives of these studies would be to:

- Evaluate fiber deposition, translocation, and clearance mechanisms;
- Compare the biopersistence of fibers retained in the lung with results from *in vitro* durability experiments; and
- Compare *in vivo* pulmonary responses to *in vitro* bioactivity for fibers of different dimensions.

More fundamental studies could also be performed to:

- Identify biomarkers that could be used to predict pulmonary inflammation, pulmonary fibrosis, and malignant transformation; and
- Investigate mechanisms of fiber-induced pulmonary disease.

2.4.2.2 Long-term Animal Studies

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. The U.S. Environmental Protection Agency's proposed testing guidelines (SAP report 2001-01) should be used as the criteria for establishing the testing parameters for chronic studies [EPA 2000].

To date, chronic inhalation studies have been conducted with different animal species using different types of fibers. However, it is still uncertain which species of animal(s) best predict(s) the risk of respiratory disease(s) for workers exposed to different fiber types. Chronic inhalation studies should be initiated to establish exposure/dose-response relationships for at least two animal species. The rat has historically been the animal of choice for chronic inhalation studies with fibers; however, the low incidence of lung tumors and mesotheliomas occurring in rats exposed to fibers (e.g., asbestos) suggest that rats may be less sensitive than humans. Therefore, any future consideration for conducting long-term animal inhalation studies should address the need for using a multi-animal testing approach to help provide solid scientific evidence on which to base human risk assessments for a variety of fibers of different durabilities and dimensions. (For example, the hamster has been proven to be a more sensitive model for mesothelioma than the rat). Validation of an appropriate animal model could reduce the resources needed to perform long-term experimental studies on other fiber types [EPA 2000].

Multi-dose animal inhalation studies with asbestos (probably chrysotile, because estimates of human risk have been established from epidemiologic studies of chrysotile-exposed workers) are needed to provide an improved basis for comparing the potential cancer and non-cancer risks associated with other types of mineral fibers and various types of synthetic fibers. The asbestos fibers administered in these animal studies should be comparable in size dimension to those fibers found in the occupational environment. The results from these studies with asbestos (e.g., chrysotile) would provide a "gold standard" that could be used to validate the utility of long-term inhalation studies (in rats or other species) as predictors of human disease and establish relative differences between the human and animal dose-response relationships.

Studies evaluating the role of fiber biopersistence and fiber dimension in the development of non-cancer and cancer endpoints are also needed.

2.4.2.3 Statistical Analyses

The statistical analysis by Berman and Crump [1995] of the potency of bivariate size distributions of asbestos in rat toxicity studies is currently being documented and updated by the EPA. The results of this update will be of great interest and will be potentially valuable for assessing the contribution of length and diameter to disease, as well as differentiating the effects of fibers from various minerals. Of additional interest is whether these statistical techniques can be adapted for use with minerals beyond the asbestos minerals.

3 THE PATH FORWARD

Achievement of the research goals proposed in *Asbestos and Other Mineral Fibers: A Roadmap for Scientific Research* will require a significant investment of time, scientific talent, and resources by NIOSH and its partners. Achieving the goals will be well worth the investment because the occupational health protection policies that NIOSH recommends for asbestos and other mineral fibers must be based on the results of sound scientific research. As with any strategic approach, there may be unintended and unforeseen consequences that will require program adjustments as time goes on.

As the *Roadmap* makes clear, the ideal outcome of a comprehensive research program for asbestos and other mineral fibers would be the development of a unified theory of toxicity for thoracic-sized mineral fibers. A unified approach would specify criteria, such as a range of chemical composition, dimensional attributes (e.g., length range, diameter range, aspect ratio), and dissolution rate/fragility (biopersistence), for considering fibers as potentially toxic. It would be particularly advantageous if criteria for inclusion could be based primarily on results from validated *in vitro* or short-term *in vivo* assays. This would reduce the need for comprehensive toxicity testing and/or epidemiological evaluation of each material. Such an approach would have the advantage of identifying fibers warranting concern based on their qualities and attributes, and even new fibers identified or manufactured could be compared to the criteria to determine a likelihood of health effects. A unified theory of fiber toxicity would clearly identify the potency of fibers for causing specific diseases and how that potency varies, depending on the particular combination of fiber characteristics and dose. A unified, coherent risk management approach for fibers that fully incorporates this understanding of the toxicity of fibers would then be developed to minimize the potential for disease.

The extent to which a policy concerning thoracic-size fibers could be extended beyond mineral fibers to synthetic vitreous fibers and even to other manufactured materials such as engineered nanomaterials, needs to be explored. Although engineered nanomaterials are well beyond the scope of the *Roadmap*, it has been noted that fiber-shaped nanoscale particles (e.g., single-walled carbon nanotubes or SWCNTs) have been shown to cause interstitial fibrosis in mice beginning within 7 days from the onset of exposure and progressing over a 60 day post-exposure period [Shvedova et al. 2005]. Recommendations have been made to systematically investigate their health effects within the next five years [Maynard et al. 2006]. Integrating the results of these nanoparticle toxicity investigations into the *Roadmap* may further the development of a unified theory of fiber toxicity.

Achieving the goals delineated in *Asbestos and Other Mineral Fibers: A Roadmap for Scientific Research* is consonant with NIOSH's statutory mission to generate new knowledge in the field of occupational safety and health and to transfer that knowledge into practice for the benefit of the American worker. Advancing knowledge relevant for

use in protecting workers from adverse health effects arising from exposure to asbestos and other mineral fibers is the ultimate goal.
Though further scientific research conducted and applied by NIOSH will continue to focus on the *occupational* environment, NIOSH intends to pursue partnerships to ensure that the results of any scientific research arising from the *Roadmap* can be extended to communities and the general environment.

To ensure that the science arising from execution of the Roadmap is applied as broadly as possible, NIOSH plans to partner with other 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 Standards and Technology (NIST), the National Institute of Environmental Health Sciences (NIEHS), the National Toxicology Program (NTP), the Occupational Safety and Health Administration (OSHA), and the United States Geological Survey (USGS), as well as with labor, industry, academia, practitioners and other interested parties. Partnerships and collaborations will be used to help focus the scope of the research to be undertaken, enhance extramural research activities, and assist in the development and dissemination of educational materials describing the outcomes of fiber research and their implications for occupational and public health policies and practices.

NIOSH looks forward to integrating the research goals set forth in the *Roadmap* into the industry sector-based, research-to-practice-focused National Occupational Research Agenda (NORA). NORA is an agenda for the Nation and the goals and objectives of this *Roadmap* can be substantially advanced through robust public-private sector partnership.

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5 GLOSSARY

Acicular: Having the shape of a needle.

Actinolite: An amphibole mineral in the tremolite-ferroactinolite series. Actinolite can occur in both asbestiform and nonasbestiform mineral habits. The asbestiform variety is often referred to as actinolite asbestos.

Amphibole: A group of generally dark-colored rock-forming minerals, composed of double chain SiO_4 tetrahedra, linked at the vertices and generally containing ions of iron and/or magnesium in their structures. Amphibole minerals are of either igneous or metamorphic origin.

Amosite: An amphibole mineral in the cummingtonite-grunerite series. It occurs in the asbestiform habit. The name amosite is a commercial term derived from the acronym for "Asbestos Mines of South Africa." Amosite is commonly referred to as "brown asbestos."

Anthophyllite: An amphibole mineral that can occur in both the asbestiform and nonasbestiform mineral habits. The asbestiform variety is often referred to as anthophyllite asbestos.

Asbestiform: A specific type of mineral fibrosity in which the growth is primarily in one dimension and the crystals form naturally as long, flexible fibers. In minerals occurring in asbestiform habit, fibers form in bundles that can be separated into smaller bundles and ultimately into fibrils. All asbestos minerals occur in the asbestiform habit, but not all minerals having asbestiform habit are asbestos minerals.

Asbestos: A generic commercial term for a number of silicate minerals occurring in the asbestiform habit. The six asbestos minerals are chrysotile, in the serpentine mineral group; and tremolite asbestos, actinolite asbestos, anthophyllite asbestos, cummingtonite-grunerite asbestos (amosite), and riebeckite asbestos (crocidolite), in the amphibole mineral group.

Aspect ratio: The ratio of the length of a particle to its diameter.

Biopersistence: The ability to continue to exist in the lung or other tissue after deposition. Biopersistence of mineral fibers is a function of their fragility, durability, and clearance.

Chrysotile: A mineral in the serpentine mineral group that occurs in the asbestiform habit. Chrysotile generally occurs segregated as parallel fibers in veins or veinlets and can easily separate into individual fibers or bundles. Often referred to as "white asbestos," chrysotile is used commercially for its good spinnability in the making of textile products and as an additive in cement or friction products.

Cleavage fragment: A particle, formed by comminution of minerals (i.e., crushing, grinding or breaking) which often is characterized by parallel sides and a moderate aspect ratio (usually less than 20:1). At any level of examination, a population of cleavage fragments does not exhibit fibrillar bundling of any of the fragments.

Crocidolite*:* An amphibole mineral in the glaucophane-riebeckite series, in which both asbestiform and nonasbestiform habits can occur. Crocidolite is a varietal name for the asbestiform habit of the mineral riebeckite, and is commonly referred to as "blue asbestos."

Durability: The resistance to degradation in lung fluids.

Fiber: An elongated particle which is longer than 5 µm, with a minimum aspect ratio of 3:1, and sometimes also classified as having a maximum diameter of 3 µm (as this may equate to the size of fiber capable of depositing in the lung when inhaled). The determination is made based on a microscopic analysis of an airborne sample using NIOSH Method 7400 or an equivalent method.

Fiber-like cleavage fragment: A cleavage fragment which meets the criteria specified above for a fiber. In contrast to a population of asbestos fibers, a population of fiber-like cleavage fragments does not exhibit fibrillar bundling of any of the particles at any level of examination.

Fibril: A single fiber of asbestos which cannot be further separated longitudinally into thinner components without losing its fibrous properties or appearances.

Fibrous: A descriptive characteristic of a mineral composed of parallel, radiating, or interlaced aggregates of fibers, from which the fibers are sometimes separable. A crystalline aggregate that has a distinct fibrous appearance may be referred to as fibrous even if it is not composed of separable fibrils.

Fragility: The tendency of particles to break into smaller particles**.**

Mineral series: A grouping of minerals that includes two or more minerals in which the cations in secondary structural position are similar in chemical properties and can be present in variable but frequently limited ratios. 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 (e.g., tremolite for tremolite-actinolite-ferroactinolite).

Mineral series such as cummingtonite-grunerite and tremolite-ferroactinolite are created when one cation is replaced by another in a crystal structure without significantly altering the structure. There may be a gradation in the structure in some series, and minor changes in physical characteristics may occur with elemental substitution. Usually a series has two named end members with any intermediate minerals sometimes being separately named or otherwise assigned no discreet name but merely referred to as members of the series. Members of the tremolite-ferroactinolite series are hydroxylated calcium-magnesium, magnesium-iron, and iron silicates, with an intermediate member of this series being named actinolite.

<u>Nonasbestiform:</u> The massive non-fibrous forms of the asbestos minerals have the same chemical formula as the asbestiform variety, but 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.

<u>Other Minerals:</u> Minerals not covered by the NIOSH definition of asbestos.

<u>Platy:</u> Occurring in flaky layers.

<u>Refractory ceramic fiber (RCF):</u> An amorphous, synthetic fiber (Chemical Abstracts Services No.142844-00-6) produced by melting and blowing or spinning calcined kaolin clay or a combination of alumina (Al_2O_3) and silicon dioxide (SiO_2). Oxides (such as zirconia, ferric oxide, titanium oxide, magnesium oxide, and calcium oxide) and alkalies may be added. The percentage (by weight) of components of RCF is: alumina, 20% to 80%; silicon dioxide, 20% to 80%; and other oxides in smaller amounts.

<u>Synthetic vitreous fiber (SVF):</u> Any of a number of manufactured fibers produced by the melting and subsequent fiberization of kaolin clay, sand, rock, slag, etc. Fibrous glass, mineral wool, ceramic fibers, and alkaline earth silicate wools are the major types of SVF, also called man-made mineral fiber (MMMF) or man-made vitreous fiber (MMVF).

<u>Thoracic fiber</u>: A particle meeting the definition of a fiber that is deposited anywhere in the lung airways and the gas exchange region of the lung.

Tremolite*:* An amphibole mineral in the mineral series tremolite-ferroactinolite. Tremolite can occur in both the asbestiform and nonasbestiform mineral habits. The asbestiform variety is often referred to as tremolite asbestos.