CURRENT INTELLIGENCE BULLETIN 62

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

Revised Edition

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Centers for Disease Control and Prevention
National Institute for Occupational Safety and Health

Cover Photograph: Transitional particle from upstate New York identified by the United States Geological Survey (USGS) as anthophyllite asbestos altering to talc. Photograph courtesy of USGS.

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Foreword

Asbestos has been a highly visible issue in public health for over three decades. During the mid- to late-20th century, many advances were made in the scientific understanding of worker health effects from exposure to asbestos fibers and other elongate mineral particles (EMPs). It is now well documented that asbestos fibers, when inhaled, can cause serious diseases in exposed workers. However, many questions and areas of confusion and scientific uncertainty remain.

The National Institute for Occupational Safety and Health (NIOSH) has determined that exposure to asbestos fibers causes cancer and asbestosis in humans on the basis of evidence of respiratory disease observed in workers exposed to asbestos, and recommends that exposures be reduced to the lowest feasible concentration. As the federal agency responsible for conducting research and making recommendations for the prevention of worker injury and illness, NIOSH has undertaken a reappraisal of how to ensure optimal protection of workers from exposure to asbestos fibers and other EMPs. As a first step in this effort, NIOSH convened an internal work group to develop a framework for future scientific research and policy development. The NIOSH Mineral Fibers Work Group prepared a first draft of this *State of the Science and Roadmap for Scientific Research (*herein referred to as the *Roadmap),* summarizing NIOSH's understanding of occupational exposure and toxicity issues concerning asbestos fibers and other EMPs.

NIOSH invited comments on the occupational health issues identified and the framework for research suggested in the first draft *Roadmap*. NIOSH sought other views about additional key issues that should be identified, additional research that should be conducted, and methods for conducting the research. In particular, NIOSH sought input from stakeholders concerning study designs, techniques for generating size-selected fibers, analytic approaches, sources of particular types of EMPs suitable for experimental studies, and worker populations suitable for epidemiological study. On the basis of comments received during the public and expert peer review process, NIOSH revised the *Roadmap* and invited public review of the revised version by stakeholders. After further revision and public comment, a revised draft *Roadmap* was submitted for review by the National Academies of Science in early 2009. Based on the National Academies assessment of the draft *Roadmap*, revisions were made, and NIOSH disseminated a fourth draft version of the document for final public comment in early 2010. After considering these comments, NIOSH has developed this final revision of the *Roadmap*.

The purpose of this *Roadmap* is to outline a research agenda that will guide the development of specific research programs and projects that will lead to a broader and

clearer understanding of the important determinants of toxicity for asbestos fibers and other EMPs. NIOSH recognizes that results from such research may impact environmental as well as occupational health policies and practices. Many of the issues that are important in the workplace are also important to communities and to the general population. Therefore, NIOSH envisions that the planning and conduct of the research will be a collaborative effort involving active participation of multiple federal agencies, including the Agency for Toxic Substances and Disease Registry (ATSDR), the Consumer Product Safety Commission (CPSC), the Environmental Protection Agency (EPA), the Mine Safety and Health Administration (MSHA), the National Institute of Environmental Health Sciences (NIEHS), the National Institute of Standards and Technology (NIST), the National Toxicology Program (NTP), the Occupational Safety and Health Administration (OSHA), and the United States Geological Survey (USGS), as well as labor, industry, academia, health and safety practitioners, and other interested parties, including international groups. This collaboration will help to focus the scope of the research, to fund and conduct the research, and to develop and disseminate informational materials describing research results and their implications for establishing new occupational and public health policies.

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

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Executive Summary

In the 1970s, NIOSH determined that exposure to asbestos fibers causes cancer and asbestosis in humans on the basis of evidence of respiratory disease observed in workers exposed to asbestos. Consequently, it made recommendations to the federal enforcement agencies on how to reduce workplace exposures. The enforcement agencies developed occupational regulatory definitions and standards for exposure to airborne asbestos fibers based on these recommendations. Since the promulgation of these standards, which apply to occupational exposures to the six commercially used asbestos minerals—the serpentine mineral chrysotile, and the amphibole minerals cummingtonite-grunerite asbestos (amosite), riebeckite asbestos (crocidolite), actinolite asbestos, anthophyllite asbestos, and tremolite asbestos—the use of asbestos in the United States has declined substantially and mining of asbestos in the United States ceased in 2002. Nevertheless, many asbestos products remain in use and new asbestos-containing products continue to be manufactured in or imported into the United States.

As more information became available on the relationship between the dimensions of asbestos fibers and their ability to cause nonmalignant respiratory disease and cancer, interest increased in exposure to other "mineral fibers." The term "mineral fiber" has been frequently used by nonmineralogists to encompass thoracic-size elongate mineral particles (EMPs) occurring either in an asbestiform habit (e.g., asbestos fibers) or in a nonasbestiform habit (e.g., as needle-like [acicular] or prismatic crystals), as well as EMPs that result from the crushing or fracturing of nonfibrous minerals (e.g., cleavage fragments). Asbestos fibers are clearly of substantial health concern. Further research is needed to better understand health risks associated with exposure to other thoracic-size EMPs, including those with mineralogical compositions identical or similar to the asbestos minerals and those that have already been documented to cause asbestos-like disease, as well as the physicochemical characteristics that determine their toxicity.

Imprecise terminology and mineralogical complexity have affected progress in research. "Asbestos" and "asbestiform" are two commonly used terms that lack mineralogical precision. "Asbestos" is a term used for certain minerals that have crystallized in a particular macroscopic habit with certain commercially useful properties. These properties are less obvious on microscopic scales, and so a different definition of asbestos may be necessary at the scale of the light microscope or electron microscope, involving characteristics such as chemical composition and crystallography. "Asbestiform" is a term applied to minerals with a macroscopic habit similar to that of asbestos. The lack of precision in these terms and the difficulty in translating macroscopic

properties to microscopically identifiable characteristics contribute to miscommunication and uncertainty in identifying toxicity associated with various forms of minerals. Deposits may have more than one mineral habit and transitional minerals may be present, which make it difficult to clearly and simply describe the mineralogy.

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

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

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

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

PCM, the primary method specified by NIOSH, OSHA, and MSHA for analysis of air samples for asbestos fibers, has several limitations, including limited ability to resolve very thin fibers and to differentiate various types of EMPs. Occupational exposure limits for asbestos derive from lung cancer risk estimates from exposure of workers to airborne asbestos fibers in commercial processes. These risk assessments are based on fiber concentrations determined from a combination of PCM-based fiber counts on membrane filter samples and fiber counts estimated from impinger samples. The standard PCM method counts only fibers longer than 5 μm. Moreover, some fibers longer than 5 μm may be too thin to be detected by PCM. Thus, an undetermined number of fibers collected on each sample remain uncounted by PCM. More sensitive analytical methods are currently available, but standardization and validation of these methods will be required before they can be recommended for routine analysis. However, unlike PCM, these methods are substantially more expensive, and field instruments are not available. In addition, any substantive change in analytical techniques used to evaluate exposures to asbestos and/or the criteria for determining exposure concentrations will necessitate a reassessment of current risk estimates, which are based on PCM-derived fiber concentrations.

Epidemiological evidence clearly indicates a causal relationship between exposure to fibers from the asbestos minerals and various adverse health outcomes, including asbestosis, lung cancer, and mesothelioma. However, NIOSH has viewed as inconclusive the results from epidemiological studies of workers exposed to EMPs from the nonasbestiform analogs of the asbestos minerals. Populations of interest for possible epidemiological studies include workers at talc mines in upstate New York and workers at taconite mines in northeastern Minnesota. Others include populations exposed to other EMPs, such as winchite and richterite fibers (asbestiform EMPs identified in vermiculite from a former mine near Libby, Montana), zeolites (such as asbestiform erionite), and other minerals (such as fluoro-edenite). Future studies should include detailed characterizations of the particles to which workers are or have been exposed.

There is considerable potential for experimental animal and *in vitro* studies to address specific scientific questions relating to the toxicity of EMPs. Short-term *in vivo* animal studies and *in vitro* studies have been conducted to examine cellular and tissue responses to EMPs, identify pathogenic mechanisms involved in those

responses, and understand morphological and/or physicochemical EMP properties controlling those mechanisms. Long-term studies of animals exposed to EMPs have been conducted to assess the risk for adverse health outcomes (primarily lung cancer, mesothelioma, and lung fibrosis) associated with various types and dimensions of EMPs. Such studies have produced evidence demonstrating the importance of dimensional characteristics of mineral particles for determining carcinogenic potential of durable EMPs. Although *in vitro* studies and animal studies are subject to uncertainties with respect to how their findings apply to humans, such studies are warranted to systematically assess and better understand the impacts of dimension, morphology, chemistry, and biopersistence of EMPs on malignant and nonmalignant respiratory disease outcomes.

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

Developing a broader and clearer understanding of the important determinants of toxicity for EMPs will involve building on what is known by systematically conducting *in vitro* studies and *in vivo* animal studies to ascertain which physical and chemical properties of EMPs influence their toxicity and their underlying mechanisms of action in causing disease. The *in vitro* studies could provide information on membranolytic, cytotoxic, and genotoxic activities as well as signaling mechanisms. The *in vivo* animal studies should involve a multispecies testing approach for short-term assays to develop information for designing chronic inhalation studies and to develop information on biomarkers and mechanisms of disease. Chronic animal inhalation studies are required to address the impacts of dimension, morphology, chemistry, and biopersistence on critical disease endpoints, including cancer and nonmalignant respiratory disease. Chronic inhalation studies should be designed to provide solid scientific evidence on which to base human risk assessments for a variety of EMPs. The results of toxicity studies should be assessed in the context of results of epidemiologic studies to provide a basis for understanding the human health effects of exposure to EMPs for which epidemiologic studies are not available.

Developing information and knowledge on occupational exposures to various EMPs and potential health outcomes will involve (1) collecting and analyzing available occupational exposure information to ascertain the characteristics and extent

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

Developing improved sampling and analytical methods for EMPs will involve (1) reducing interoperator and interlaboratory variability of currently used analytical methods; (2) developing a practical analytical method that will permit the counting, sizing, and identification of EMPs; (3) developing a practical analytical method that can assess the potential durability of EMPs as one determinant of biopersistence in the lung; and (4) developing and validating size-selective sampling methods for collecting and quantifying airborne thoracic-size asbestos fibers and other EMPs.

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

Another outcome of the research that is broadly outlined in this *Roadmap* might be the development of criteria that could be used to predict, on the basis of results of *in vitro* testing and/or short-term *in vivo* testing, the potential risk associated with exposure to any particular type of EMP. This could reduce the need for comprehensive toxicity testing with long-term *in vivo* animal studies and/or epidemiological evaluation of each type of EMP. Ultimately, the results from such studies could be used to fill in knowledge gaps beyond EMPs to encompass predictions of relative toxicities and adverse health outcomes associated with exposure to other elongate particles (EPs), including inorganic and organic manufactured particles. A coherent risk management approach that fully incorporates an understanding of the toxicity of particles could then be developed to minimize the potential for disease in exposed individuals and populations.

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

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Abbreviations

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