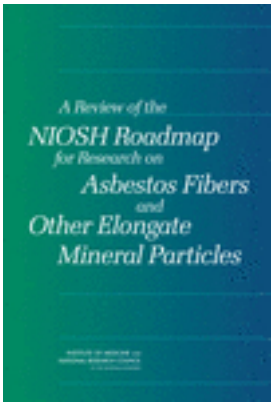

A Review of the NIOSH Roadmap for Research on Asbestos Fibers and Other Elongate Mineral Particles

Alan R. Nelson, Catharyn T. Liverman, Elizabeth A. Eide, and Eileen Abt, Editors; Committee for the Review of the NIOSH Research Roadmap on Asbestos Fibers and Other Elongate Mineral Particles; Institute of Medicine and National Research Council

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This report has been reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise, in accordance with procedures approved by the National Research Council's Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible and to ensure that the report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process. We wish to thank the following individuals for their review of this report:

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Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations, nor did they see the final draft of the report before its release. The review of this report was overseen by **Lonnie Bristow,** Consultant, Walnut Creek, California, and **John C. Bailar III,** The University of Chicago, (emeritus). Appointed by the National Research Council and Institute of Medicine, they were responsible for making certain that an independent examination of this report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the authoring committee and the institution.

Preface

The statement of task assigned to the committee for the study *Review of the NIOSH Research Roadmap on Asbestos Fibers and Other Elongate Mineral Particles*[1] asked five questions. In this report, the committee answers each question with a qualified "yes" and submits a series of recommendations that are intended to help the users of the Roadmap successfully reach their destination and address the scientific challenges and ambiguities that have beset this area of research in the past. The committee recognizes fully the technical complexity of the Roadmap and acknowledges the hard work of the staff of the National Institute for Occupational Safety and Health (NIOSH) in its development. The committee's report particularly notes and commends the extensive background research that went into the section of the Roadmap entitled "Review of Current Issues."

The committee was tasked specifically with assessing the January 2009 Roadmap document, which describes research to examine the physical and chemical characteristics of elongate mineral particles that may potentially impact human health. While recognizing the strengths of the Roadmap, the committee also identified a number of areas for improvement that are described in this report. Much discussion focused on the mineralogical terminology, nomenclature, and glossary advanced in the Roadmap. In particular, the committee carefully considered the use of the new term *elongated mineral particles* and concludes

[1]The Roadmap was drafted in 2007 and entitled *NIOSH Roadmap on Asbestos and Other Mineral Fibers*; it was extensively revised in 2008 and early 2009 with the new title *Asbestos Fibers and Other Elongated Mineral Particles: State of the Science and Roadmap for Research.* It was this latter document (hereafter called the Roadmap) that the committee was tasked to review.

that this is a nontechnical term that should be used only to describe a broad group of respirable mineral particles of certain aspect ratios. Additionally, the committee urges use of the adjective *elongate* rather than *elongated* in the purely descriptive use of this term. One of the recommendations asks NIOSH to ensure that mineralogical terminology and nomenclature in both the text and the glossary are supported by acknowledged mineralogical terminology sources. The committee makes a number of additional recommendations including a need for increased emphasis on relevant epidemiological research opportunities internationally and in the United States.

The committee, in its discussions, repeatedly referenced the need for the Roadmap to be one portion of a broader strategic plan for NIOSH, other organizations, and federal agencies—a plan that might include a statement of purpose, consideration of available resources, interdisciplinary and interagency collaboration, prioritization, time lines, and accountability. This observation is offered with the understanding that broader strategic planning may already be an ongoing activity within NIOSH and the other relevant agencies.

Finally, the committee acknowledges with gratitude the assistance of the National Academies staff in the preparation of this report, including the study director, Cathy Liverman; senior program officers, Eileen Abt and Elizabeth Eide; research associate, Franklin Branch; and program associate, Judy Estep.

Alan R. Nelson, *Chair*
Committee for the Review of the NIOSH
Research Roadmap on Asbestos Fibers
and Other Elongate Mineral Particles

Contents

APPENDIXES

Acronyms

AFM	atomic force microscopy
AGI	American Geological Institute
ATF	activating transcription factor
ATSDR	Agency for Toxic Substances and Disease Registry
CAS	Chemical Abstracts Service
CNMNC	Commission on New Minerals, Nomenclature, and Classification (IMA)
COPD	chronic obstructive pulmonary disease
CT	computed tomography
EBSD	electron backscattered diffraction
EPA	U.S. Environmental Protection Agency
EPMA	electron probe microanalysis
EXAFS	extended X-ray absorption fine structure
ICD	International Classification of Diseases
ILO	International Labour Organization
ILSI	International Life Sciences Institute
IMA	International Mineralogical Association
IOM	Institute of Medicine
MSHA	Mine Safety and Health Administration
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NRC	National Research Council

OSHA	Occupational Safety and Health Administration
PCM	phase contrast microscopy
PEL	permissible exposure limit
PET	positron emission tomography
PLM	polarized light microscopy
REL	recommended exposure limit
SEM	scanning electron microscopy
TEM	transmission electron microscopy
USBM	U.S. Bureau of Mines
XRD	X-ray diffraction
XRF	X-ray fluorescence

Summary

Although asbestos is no longer mined in the United States, prior and ongoing exposures to asbestos continue to contribute to respiratory diseases, including mesothelioma, lung cancer, and asbestosis. Asbestos exposures are estimated to have contributed to 18,068 deaths from mesothelioma in the United States from 1999–2005; asbestos-related diseases continue to be diagnosed due to the long latency period for their manifestation. U.S. workers and residents, for example, may continue to undergo hazardous exposures due to unremediated asbestos-containing materials, imported asbestos-containing products, and natural environmental occurrences of asbestos. Internationally, asbestos continues to be mined and used in manufacturing in a number of countries because of its desirable commercial properties such as strength and heat resistance. Ongoing issues include potential health effects in workplaces and in situ environmental settings as well as exposures to mineralogical mixtures that may contain asbestos and exposures to nonasbestiform elongate mineral particles of similar size and shape to asbestos particles.

To examine ongoing issues and concerns in this field, the National Institute for Occupational Safety and Health (NIOSH) drafted a research roadmap, *Asbestos Fibers and Other Elongated Mineral Particles: State of the Science and Roadmap for Research* (hereafter called the Roadmap), that provides an overview of the state of the science and a plan for future research in areas including toxicology, mineralogy, epidemiology, and exposure assessment. The focus of the proposed research is on clarifying the relationship between human health effects and the physical and chemical characteristics (e.g., mineralogy, morphology, dimension, surface properties) of a wide range of elongate mineral particles (see definition of *elongate mineral particles* below). In 2008, NIOSH asked the

Institute of Medicine (IOM) and the National Research Council (NRC) to form a committee to provide a review of the scientific and technical quality of the January 2009 draft NIOSH Roadmap document. This report provides the committee's assessment of the Roadmap and recommendations for strengthening its utility for NIOSH, other federal agencies, the private sector, and other stakeholders.

TERMINOLOGY: ASBESTOS AND OTHER ELONGATE MINERAL PARTICLES

One of the major challenges faced in conducting research in this field is the terminology. Because the term *asbestos* does not denote a single mineral but rather is used to encompass a set of minerals with specific industrial characteristics and commercial value, there have been challenges and controversies in determining both what specific set of minerals and what set of characteristics should be included in a definition of asbestos. The current regulatory definitions used by the Occupational Safety and Health Administration (OSHA) and the Mine Safety and Health Administration (MSHA) define six recognized minerals[1] as varieties of asbestos.

NIOSH recognized the need for a term to encompass a broad class of mineral particles of specific size and dimension that are the primary focus of the proposed research in the Roadmap and introduced the term *elongated mineral particles*[2] to attempt to capture this broad range of mineral particles. The committee considers the dimensions described in the NIOSH Roadmap definition ("longer than 5 μm with a minimum aspect ratio of 3:1") as a good starting point for research. The term *elongate mineral particles* is a convenient, neutral, and unified means of describing various minerals across different professional disciplines but

[1]The six mineral varieties of asbestos are (1) chrysotile (a member of the serpentine group) and five fibrous forms of the amphibole group, (2) riebeckite asbestos (also termed crocidolite), (3) cummingtonite-grunerite asbestos (also commercially termed amosite), (4) anthophyllite asbestos, (5) tremolite asbestos, and (6) actinolite asbestos.

[2]The committee urges use of the adjective *elongate* rather than *elongated*, so as to describe the physical appearance of the particles as opposed to implying that they have been actively lengthened by some means.

is not a rigorous mineralogical classification or one to which regulatory significance is assigned.

The committee makes suggestions regarding improving the scientific rigor of the glossary definitions and use of terminology and nomenclature and believes that this increased specificity will aid in clarifying the central focus of the Roadmap, which is to determine which elongate mineral particles (specific types of minerals or specific physical or chemical characteristics) have potential negative impacts on human health.

FINDINGS

Throughout this report, the committee notes the value of the Roadmap document in bringing together a substantial body of research across several varying disciplines. The committee was charged with providing a review of the Roadmap document and answering five specific questions detailed below.

Statement of Task Question 1: Is the document consistent with the state of scientific understanding of the toxicity, occupational exposures, epidemiology, and sampling or analytical methods? Should any of the content of this section be modified, based on the state of scientific understanding of these issues? Are there any significant studies that have been overlooked?

Finding 1: The NIOSH Roadmap is generally consistent with the state of scientific understanding of the toxicity, occupational exposures, epidemiology, and sampling or analytical methods. The committee identified several areas that could be strengthened and references those areas in the narrative and in the committee recommendations. The Roadmap would be made more coherent and useful if it included or refined four key components: vision or purpose, rationale, goals, and framework (systematic plan for conducting the research).

Statement of Task Question 2: Does the document clearly and adequately explain the scientific rationale for research on the mineralogy, morphology, dimensions, and surface characteristics of elon-

gate mineral particles, and is its treatment of this issue consistent with the state of scientific understanding of the toxicity, occupational exposures, and epidemiology of elongate mineral particles?

Finding 2: The Roadmap explains the scientific rationale for research on the mineralogy, morphology, dimensions, and surface characteristics of elongate mineral particles. This is presented primarily through discussions of toxicological studies of asbestos and of synthetic fibers that provide the background on why research is needed to examine mineral particle characteristics and their impact on toxicity. However, the mineralogical discussions were found lacking in many areas. Adding more information on the occupational and environmental health rationale for research in this area would be helpful, including available data on the types of occupations and environmental situations likely to result in exposure to more specific types of elongate mineral particles. As noted in its recommendations the committee urges that the Roadmap include a clear statement of the overarching vision for the research. The committee also believes that since the term *elongate mineral particle* covers a broad range of mineral particles of interest in this research, its use should be limited to research efforts and emphasizes that this term is not a rigorous mineralogical term.

Statement of Task Question 3: Does the document discuss the most significant issues regarding mineralogy, morphology, dimensions, and surface characteristics of elongate mineral particles? Should any of the discussed issues be omitted or revised, based on the state of scientific understanding of these issues? Are there any significant issues that should be added?

Finding 3: The NIOSH Roadmap provides a reasonable discussion of some of the significant issues regarding mineralogy, morphology, dimensions, and surface characteristics of elongate mineral particles as related to their potential to cause disease, but

as noted in response to Question 4 below, the committee urges a greater emphasis on the relevant mineralogical research, in particular on mineralogical characterization. The committee notes significant inconsistencies and deficiencies in mineralogical terminology and nomenclature and provides a series of recommendations to clarify and make more rigorous, consistent, and complete the terminology used in the text and the glossary in the Roadmap.

Statement of Task Question 4: Is the research proposed likely to effectively address the most significant issues regarding mineralogy, morphology, dimensions, and surface characteristics of elongate mineral particles? Should any of the discussed research be omitted or revised, based on the state of scientific understanding of these issues? Is there any significant research that should be added?

Finding 4: The research effort proposed is likely to address some of the most significant issues regarding mineralogy, morphology, dimensions, and surface characteristics of elongate mineral particles. However, as noted throughout this report and in its recommendations, the committee calls for more details to be included on mineralogical research, with an emphasis on a systematic approach to characterization of the minerals that is integrated in a meaningful way into toxicological and other studies to better understand the relative disease-causing potential of a range of elongate mineral particles relevant to human exposures. This effort is part of a consistent strategy for characterizing and testing the relative toxicities of elongate mineral particles and mixtures. Exploration of additional opportunities for epidemiological research is needed as well as careful examination of the exposure assessment methodologies. The effort is likely to be more successful if it involves interdisciplinary collaboration and integration.

Statement of Task Question 5: Was the process that was used to develop and revise the document and that is described in the Foreword,

including the mechanisms for input from the scientific and stakeholder communities, appropriate from a scientific perspective?

Finding 5: The process used by NIOSH to develop and revise the document that is described in the Foreword was, in the opinion of the committee, generally appropriate in being open and transparent with multiple opportunities for input into the Roadmap document. The process would have benefited from greater involvement of the mineralogical community throughout its formulation. An interdisciplinary approach may have been better applied in the development process.

RECOMMENDATIONS

Clarify Roadmap Structure and Vision

Because the NIOSH Roadmap brings together a great deal of information and a wealth of ideas on future directions for research, it is necessary for the document to have a clearly stated vision and rationale. The details of the Roadmap can all too easily overtake the view of the larger objective, and therefore the committee urges that the vision and rationale be clearly laid out in the early part of the Roadmap. Further, it is the committee's hope that a more systematic and tiered approach to the research agenda will allow research to be conducted in a manner that will answer the questions regarding which physical and chemical characteristics of elongate mineral particles are primary determinants of toxicity to humans, thus allowing unambiguous identification of specific types of mineral particles that would be of concern to human health.

Recommendation 1 Clarify the Vision and Rationale
NIOSH should revise the Roadmap to clearly state the overarching vision and rationale for the research program.

- **The overarching vision should point toward research that will differentiate effects from exposure to a range of elongate mineral particles and help determine the influence of size, shape, and other physical and chemical characteristics of these particles on human health. This**

research would identify which elongate mineral particles, or what characteristics of those particles, should be included in recommendations to protect the public and workers from hazardous occupational and environmental exposures.

- **The rationale for the Roadmap should clearly articulate the influence that ongoing and future research can have on improving public and occupational health.**
- **A clearer vision and purpose would help strengthen the goals that the research is intended to support. The research should be prioritized as to the hazard and exposure.**

Recommendation 2 Include Key Components
NIOSH should ensure that four key components are included or refined in the Roadmap: (1) vision, (2) rationale, (3) goals, and (4) framework.

Improve Terminology

Terminology and nomenclature have been an ongoing challenge for this area of research. Because of the ambiguous and confusing terms for asbestos and other mineral particles used in the past, it is important for the Roadmap to place strong emphasis on specificity in its use of terminology and nomenclature and on providing references to definitions from standard reference texts in each field. The Roadmap needs definitions for all technical terms, given the interdisciplinary nature of the research. The umbrella term *elongate mineral particles* provides an important starting point for discussions on the broad range of mineral particles under investigation. However, because considerable uncertainty remains regarding the range of potential toxicities within the spectrum of elongate mineral particles, it is the committee's view that at this time the term *elongate mineral particles* should not be used for regulatory purposes.

Recommendation 3 Improve Terminology
NIOSH should revise its Roadmap with careful attention to consistency in the use of nomenclature and terminology. The goal is

that authoritative terminology should permeate research and regulatory efforts, specifically:

- **For research purposes, the term *elongate mineral particles* is useful for encompassing a broad category of mineral particles of a certain dimension and aspect ratio; more specific mineralogical terminology would be needed for regulatory purposes;**
- **Revisions should be made to the Roadmap glossary using accepted mineralogical terminology or nomenclature from the current American Geological Institute's *Glossary of Geology* or other standard texts; citations should be provided for each definition; nonstandard terms should be removed from the glossary and the main text; and**
- **Terminology used in sections referring to epidemiology and toxicology should also use definitions from current standard texts and be included in the glossary with citations.**

Strengthen the Emphasis on Mineralogy

The Roadmap outlines a set of studies to improve knowledge on the potential health effects of elongate mineral particles and the ways in which human exposures could best be studied. A key piece of this research plan is the development of well-characterized reference mineral samples that could then be incorporated in toxicological studies to assess the variability in the toxicity of different types of elongate mineral particles. The identification, classification, and characterization of unknown mineral particles from workplace or environmental exposures require knowledge of and comparison to similar, well-characterized mineral particles and associated geological locales. Similarly, toxicological experiments require well-characterized reference mineral samples to allow systematic intra- and interlaboratory comparisons of results. While the Roadmap notes the need for standardized reference minerals, the committee believes that there is a need for a more detailed approach for developing a central repository of these samples. Priorities for the repository should focus on those minerals with the greatest potential for human exposures. Although the epidemiological and toxicological dis-

cussions in the Roadmap were generally thorough, greater depth and rigor is needed in the mineralogical discussions.

Recommendation 4 Strengthen the Emphasis on Mineralogical Research
NIOSH should revise the Roadmap to give greater attention to the mineralogical foundations of the proposed research. Discussions of mineralogy in the Roadmap should be strengthened by incorporating current understanding in this field using accepted terminology and by proposing research on the fundamental mineralogical properties relevant to toxicology, epidemiology, and exposure assessment. Specifically, mineralogical research is needed on physical and chemical properties, biopersistence, and mineral source characterization, including the development of standard sets of tests and methodologies.

Recommendation 5 Develop a Reference Mineral Repository
NIOSH should work with other federal agencies and organizations to develop a repository of well-characterized and standardized reference minerals for use in research.

Focus the Research Efforts

NIOSH has put together a comprehensive and broad-based research Roadmap that could be improved through further emphasis on implementing a systematic and interdisciplinary approach to the outlined research. Improved efforts on characterizing the elongate mineral particles used in toxicological research could go a long way toward ensuring that study results can be compared. Additionally, using a tiered systematic process to study the toxicity of various types of particles would assist in bringing clarity to the range of toxicities and help to identify any specific mineralogical properties of concern to human health. Because asbestosis, lung cancer, and mesothelioma likely have different mechanisms of pathogenesis, attention must be given to selecting an array of in vitro assays capable of detecting cellular events thought to be involved in pathways leading to each outcome of concern.

A wider focus in epidemiological studies and new approaches to exposure assessment will also be of great benefit in addressing these issues.

Recommendation 6 Emphasize Interdisciplinary Efforts
NIOSH should revise the Roadmap to emphasize the need for collaboration and integration of research among the mineralogical, toxicological, epidemiological, and exposure assessment disciplines.

Recommendation 7 Develop a Systematic Strategy for the Toxicological Assessment of Elongate Mineral Particles
NIOSH should revise the Roadmap to describe a systematic tiered strategy for characterizing and testing the relative toxicities of elongate mineral particles and/or their mixtures. The strategy should include the following:

- **Characterizing the chemical and physical properties of the elongate mineral particles beginning with petrographic analysis and proceeding through X-ray diffraction, transmission and scanning electron microscopy, and other techniques; and**
- **Using tiered panels of in vitro and in vivo assays of increasing complexity to identify and characterize biological responses and categorize the potential hazards.**

Recommendation 8 Emphasize Additional Research Areas
NIOSH should revise the Roadmap to include an emphasis on the following:

- **Incorporating petrographic analysis and developing new exposure assessment tools using electron microscopy methods that are mineralogically and toxicologically relevant and that minimize reliance on phase contrast microscopy methods;**
- **Toxicological mechanisms of action of a range of well-characterized elongate mineral particles with attention to early biomarkers of human health effects;**
- **Additional opportunities for epidemiological research including studies of Libby, Montana, worker and resident populations, as well as cohorts exposed to elongate mineral particles in other countries; and**
- **Statistical methods for addressing analytic variability and determining the relationships between mineralogical and exposure variables and health outcomes.**

STEPS TOWARD A RESEARCH STRATEGY

A research roadmap is one component of a larger research strategy. The final section of the NIOSH Roadmap notes that the research agenda "will require a substantial investment of time, scientific talent, and resources by NIOSH and its partners to formulate research programs and prioritize research projects to achieve the proposed goals." The committee urges NIOSH to continue its work with other federal agencies (e.g., the U.S. Environmental Protection Agency, the National Institute of Environmental Health Sciences, the U.S. Geological Survey, the Occupational Safety and Health Administration, the Mine Safety and Health Administration, and the Agency for Toxic Substances and Disease Registry) and private-sector and nonprofit organizations with a focus on developing a research strategy that details the resources, priorities, responsibilities, and commitments needed to accomplish and evaluate this research effort. Many of the issues that require additional research to better understand the relative disease-causing potential of various types of elongate mineral particles are common both to the fields of occupational health, as pertaining to work-related exposures, and environmental health, as related to exposure of the general public. Too often research programs present broad goals for important research but do not back them up with a concrete and realistic plan for accomplishing the goals.

Such a strategy might contain, in addition to the research framework and goals elaborated in the NIOSH Roadmap, the following elements:

- An interdisciplinary system for prioritizing research activities to ensure maximum efficiency in an environment in which not everything possible can reasonably be undertaken at once and multiple disciplines need to work together to determine the priorities;
- An approximation of the resources needed to carry out high- and middle-priority efforts; and
- A plan for review, evaluation, and accountability for those receiving support for research contained in the Roadmap.

As NIOSH and other partners move forward in implementing the Roadmap, discussions are needed on successful models of establishing effective partnerships and management of research efforts to ensure a coordinated approach to address specific information gaps.

1

Introduction

Although asbestos is no longer mined in the United States, prior and ongoing exposures to asbestos continue to contribute to respiratory diseases, including mesothelioma, lung cancer, and asbestosis. Asbestos exposures are estimated to have contributed to 18,068 deaths from mesothelioma in the United States from 1999–2005; asbestos-related diseases continue to be diagnosed due to the long latency period for their manifestation (MMWR, 2009). U.S. workers and residents, for example, may continue to undergo hazardous exposures due to unremediated asbestos-containing materials, imported asbestos-containing products, and natural environmental occurrences. Internationally, asbestos continues to be mined and used in manufacturing in a number of countries because of its desirable commercial properties such as strength and heat resistance. Ongoing issues include potential health effects in workplaces and in situ environmental settings as well as exposures to mineralogical mixtures that may contain asbestos and exposures to nonasbestiform elongate mineral particles of similar size and shape to asbestos particles.

To examine ongoing issues and concerns in this field, the National Institute for Occupational Safety and Health (NIOSH) drafted a research roadmap that provides an overview of the state of the science and a plan for future research in areas including toxicology, mineralogy, epidemiology, and exposure assessment.

In 2008, NIOSH asked the Institute of Medicine (IOM) and the National Research Council (NRC) to form a committee to review the Roadmap and provide recommendations on necessary changes to the document to improve its clarity, comprehensiveness, and accuracy. This report is the result of an 11-month study conducted by an ad hoc IOM-NRC committee composed of experts in the fields of toxicology, miner-

alogy, exposure assessment, public health, occupational safety and health, clinical medicine, industrial hygiene, biostatistics, and pulmonary medicine. The committee's task was to provide a review of the scientific and technical quality of the January 2009 NIOSH revised draft document *Asbestos Fibers and Other Elongated Mineral Particles: State of the Science and Roadmap for Research*, with a focus on proposed research intended to clarify the relationship between health effects and the physical and chemical characteristics (e.g., mineralogy, morphology, dimensions, surface properties) of a wide range of elongate mineral particles.[1] In particular, the committee was asked to address the following questions:

- Is the document consistent with the state of scientific understanding of the toxicity, occupational exposures, epidemiology, and sampling or analytical methods? Should any of the content of this section be modified, based on the state of scientific understanding of these issues? Are there any significant studies that have been overlooked?
- Does the document clearly and adequately explain the scientific rationale for research on the mineralogy, morphology, dimensions, and surface characteristics of elongate mineral particles, and is its treatment of this issue consistent with the state of scientific understanding of the toxicity, occupational exposures, and epidemiology of elongate mineral particles?
- Does the document discuss the most significant issues regarding mineralogy, morphology, dimensions, and surface characteristics of elongate mineral particles? Should any of the discussed issues be omitted or revised, based on the state of scientific understanding of these issues? Are there any significant issues that should be added?
- Is the research proposed likely to effectively address the most significant issues regarding mineralogy, morphology, dimensions, and surface characteristics of elongate mineral particles? Should any of the discussed research be omitted or revised, based on the state of scientific understanding of these issues? Is there any significant research that should be added?

[1]The committee urges the use of the adjective *elongate* rather than *elongated*, so as to describe the physical appearance of the particles as opposed to implying that they have been actively lengthened by some means. The committee uses the term *elongate* hereafter in this report.

- Was the process that was used to develop and revise the document and that is described in the Foreword, including the mechanisms for input from the scientific and stakeholder communities, appropriate from a scientific perspective?

The task stipulated that, in addressing these questions, the committee was not to undertake its own assessment of the potential occupational health risks from exposure to asbestos and other elongate mineral particles or to conduct a formal literature review on these topics.

To accomplish its charge, the committee held three meetings and gathered information through a scientific workshop that included a public comment session (Appendix A) and through discussions with individuals in relevant fields.

The committee provides its assessment of the January 2009 draft NIOSH Roadmap document in this report. The remainder of this chapter introduces some of the complexities involved in discussions about research in this field. Chapter 2 sets the context for this Roadmap within efforts to develop and assess roadmaps for other areas of research. In Chapter 3, the committee reviews the major scientific issues and research directions that shape the Roadmap. The report concludes with Chapter 4, which provides the committee's recommendations for strengthening the Roadmap and increasing its utility for work by NIOSH, other federal agencies, the private sector, and other stakeholders.

COMPLEXITIES OF THE ISSUES

The following brief overview identifies several issues that highlight the challenges faced in conducting research in this field and provides some introductory material for readers unfamiliar with these topics. The committee provides comments on the scope of the Roadmap and the terminology in Chapter 3.

Background to the Use of Terminology in the Roadmap

Because the term *asbestos* does not denote a single mineral but rather is used to encompass a set of minerals with specific industrial characteristics and commercial value, there have been challenges and controversies in determining both what specific set of minerals and what set of

characteristics should be included in a definition of asbestos. The current regulatory definitions used by the Occupational Safety and Health Administration (OSHA) and the Mine Safety and Health Administration (MSHA) define six recognized minerals as varieties of asbestos:[2] chrysotile (a member of the serpentine group of sheet silicates) and five fibrous forms of the amphibole group of double-chain silicates: riebeckite asbestos (also termed crocidolite), cummingtonite-grunerite asbestos (also commercially termed amosite), anthophyllite asbestos, tremolite asbestos, and actinolite asbestos (29 CFR 1910.1001(b); 29 CFR 1926.1101(b); 30 CFR 56.5001(b)(1); 30 CFR 57.5001(b)(1); 30 CFR 71.702(a)).

The 1990 NIOSH Recommended Exposure Limit (REL) outlines limits for *airborne asbestos fibers,* a term that encompasses the six minerals defined as asbestos by OSHA and MSHA and particles greater than 5 μm in length and having (1) an aspect ratio of 3:1 or greater and (2) the mineralogical characteristics (i.e., crystal structure, elemental composition) of their nonasbestiform analogs (NIOSH, 1990a,b). Table 1-1 replicates and compares the terminology used by the regulatory agencies, OSHA and MSHA, for asbestos and that suggested by NIOSH in its 1990 recommended exposure limit for airborne asbestos fibers.

The central focus of the Roadmap is on establishing research to assess the potential for asbestos, asbestos analogs, or other mineral particles with specific physical or chemical characteristics to impact human health. The generic term *elongated mineral particles* is used by NIOSH in the Roadmap to encompass a broad spectrum of mineral particles of a specific size and aspect ratio but the term has no current regulatory or mineralogical connotation. As noted above, the committee prefers the term *elongate mineral particles* (see Chapter 3 for discussion). Increasing the specificity of the terminology to the extent possible will aid in clarifying the central message of the Roadmap. Within the range of vari-

[2]29 CFR 1910.1001(b) for General Industry: "Asbestos includes chrysotile, amosite, crocidolite, tremolite asbestos, anthophyllite asbestos, actinolite asbestos, and any of these minerals that have been chemically treated and/or altered." 29 CFR 1926.1101(b) for Construction Industry: "Asbestos includes chrysotile, amosite, crocidolite, tremolite asbestos, anthophyllite asbestos, actinolite asbestos, and any of these minerals that has been chemically treated and/or altered. For purposes of this standard, 'asbestos' includes PACM, as defined below." Presumed Asbestos Containing Material (PACM) is defined as "thermal system insulation and surfacing material found in buildings constructed no later than 1980." 30 CFR 56.5001(b)(1); 30 CFR 57.5001(b)(1); 30 CFR 71.702(a): "*Asbestos* means chrysotile, cummingtonite-grunerite asbestos (amosite), crocidolite, anthophylite asbestos, tremolite asbestos, and actinolite asbestos."

ous types of elongate mineral particles, the potential health impact of exposures may vary widely, although this is yet to be fully explored.

TABLE 1-1 Minerals Addressed by OSHA and MSHA Regulations and the NIOSH Recommended Exposure Limit

OSHA and MSHA Permissible Exposure Limit for Asbestos	NIOSH 1990 Recommended Exposure Limit for Airborne Asbestos Fibers[a]
Serpentine Minerals • Chrysotile	Serpentine Minerals • Chrysotile
Amphibole minerals • Crocidolite • Amosite[b] • Anthophyllite asbestos • Tremolite asbestos • Actinolite asbestos	Amphibole minerals • Crocidolite • Amosite (cummingtonite-grunerite) • Anthophyllite • Tremolite • Actinolite
And any of these minerals that have been chemically treated and/or altered.[c]	In addition, airborne cleavage fragments from the nonasbestiform habits of the serpentine minerals antigorite and lizardite, and the amphibole minerals contained in the series cummingtonite-grunerite, tremolite-ferroactinolite, and glaucophane-riebeckite are counted as fibers provided they meet the criteria for a fiber when viewed microscopically (NIOSH, 1990b).

[a]NIOSH defines airborne asbestos fibers as those particles greater than 5 μm in length and having an aspect ratio of 3:1 or greater and the mineralogical characteristics (i.e., crystal structure, elemental composition) of the asbestos minerals and their nonasbestiform analogs.

[b]MSHA regulations state "cummingtonite-grunerite asbestos (amosite)."

[c]Specific to the OSHA regulations (29 CFR 1910.1001(b); 29 CFR 1926.1101(b)).

SOURCE: 29 CFR 1910.1001(b); 29 CFR 1926.1101(b); 30 CFR 56.5001(b)(1); 30 CFR 57.5001(b)(1); 30 CFR 71.702(a); NIOSH, 1990a,b.

Mineral Variability

Approximately 3,000 minerals exist in nature. Mineral identification is based on mineral crystal structure and crystal chemistry. Mineral crystal growth habits[3] and the chemical substitutions in the crystal structure, influenced by the variable conditions of growth of a mineral, are additional characteristics that can be used to describe a mineral and distinguish it from another. The mineral growth environment and chemical substitutions have the potential to cause variations in a mineral's optical properties, surface chemistry, and crystal structure, as well its tendency to break down or decompose. Within a particular mineral deposit or rock, the constituent minerals can be heterogeneous, even at the micrometer scale, varying in composition, crystal structure, and/or habit, for example. The potential diversity of minerals occurring in mineral deposits and rocks creates challenges when identifying those minerals associated with health impacts and when characterizing human exposures, whether at the mine site or during or following processing into manufactured products.

Nature of the Exposures

The nature and extent of human exposures to asbestos in the United States have changed over the past 50 years. In the 1970s, most asbestos mining ceased in the United States, with the final mine closing in 2002 (NTP, 2005; Virta, 2006). This ended more than a hundred years of production (1890 to 2003) of an estimated 3.29 million metric tons of asbestos. Additionally during that time, 29.6 million metric tons of asbestos were imported into the United States for industrial uses, including roofing materials, flooring, friction materials in brakes and clutches, and asbestos-cement pipes (Virta, 2006). Health consequences of exposure to asbestos, particularly its association with the development of asbestosis, lung cancer, and mesothelioma after a long latency period, became known in the 1950s and 1960s and led to regulations in the United States in 1971. Use of asbestos in the United States peaked in 1973 at 803,000 metric tons per year, and by 2003, U.S. consumption was at 4,650 metric tons (Virta, 2006). The European Union banned new uses of asbestos in 2005, and asbestos is fully or partially banned in many other countries.

[3]The habit is the general shape of the crystals, e.g., acicular, prismatic, fibrous. For a given type of crystal, the habit may vary from locality to locality depending on the environment of growth (Neuendorf et al., 2005).

Changes in occupational exposures have generally followed the trajectory of the use and regulation of asbestos. Mining, milling, and manufacturing exposures in the United States have declined, leading to reductions in long-term occupational exposures, although some exposures continue with imported asbestos-containing products. Limited information is available on the number of workers still exposed to asbestos. OSHA (2008) estimates that 1.3 million U.S. workers in construction and general industry face asbestos exposure on the job. However, exposures generally occur during remediation and abatement efforts, through demolition of buildings with asbestos-containing materials, and during excavation in areas where asbestos occurs naturally; thus, exposures tend to be shorter term and more intermittent. The Roadmap acknowledges the limitations in current understanding of exposures and recommends research on the nature and levels of occupational exposures to asbestos and other elongate mineral particles and on the number of workers exposed. Further, in the United States, although generally below the levels of occupational exposures in mines, nonoccupational exposures can occur in homes, schools, public buildings, and other locations with unabated asbestos insulation or from other exposures. Environmental exposures are possible for residents or workers near asbestos-containing waste sites and active or inactive mines; the most recent well known issues occurred in Libby, Montana, where mined vermiculite was contaminated with asbestos. Internationally, asbestos-containing products (particularly asbestos-cement products) continue to be produced and used in some countries; in 2003, the leading consumers of asbestos were Brazil, China, India, Iran, Kazakhstan, Russia, Thailand, and Ukraine (Virta, 2006).

Because the latency period between asbestos exposure and onset of disease may be several decades, the public health impact of the disease lags behind exposure reductions. For example, the number of asbestosis deaths in the United States reached a plateau in the late 1990s, in part because of the long latency period and the fact that individuals survive many years after disease onset (Moolgavkar et al., 2009). The annual number of asbestosis deaths is anticipated to decrease substantially due to exposure reductions (NIOSH, 2009).

Exposure Assessment

Further complicating the issues regarding asbestos are the challenges in exposure assessment that make it difficult to quantify current exposures and to understand how the levels of exposure were determined in prior studies. Some worker populations that have been studied in epidemiological investigations may have been exposed to complex mixtures of mineral particles, where the level of exposure may be difficult to ascertain in retrospective studies, data on cigarette smoking may not be available, and exposure assessments may have not used direct measurements of exposure but rather surrogates such as job description.

Measures of the extent to which workers or residents are exposed to hazardous airborne particles are conducted primarily by collecting air samples and then counting those that occur as single crystals or in bundles in a representative section of the air sample filter. Cleavage fragments, when identifiable, may or may not be counted depending on the analytic methodology. Detailed methodologies for identifying and counting asbestos fibers have been developed by NIOSH, ASTM International, the International Organization for Standardization, and other organizations using phase contrast microscopy, polarized light microscopy, scanning electron microscopy, or transmission electron microscopy. Electron microscopy methods allow higher spatial resolution and can provide further definition to the nature of the crystalline habit, previously characterized through polarized light microscopy and/or the mineral's chemical composition. Challenges in assessing exposure include variations in the particle distribution on sample filters, ensuring consistency in inter- and intralaboratory counting techniques, varying methods for preparation of samples, the assumption that small samples represent actual exposures, and subjectivity in assessing what particles are countable in a given analytical method (see Chapter 3).

Broader Context of Research on Exposure to Airborne Particulates

In addition to the research addressed in the NIOSH Roadmap, it is important to recognize the wide breadth of ongoing research on exposures to and health effects from airborne particulates. For example, occupational inhalation exposures to crystalline silica dust are well documented to contribute to silicosis, and coal dust exposure of miners is

closely associated with pneumoconiosis. Research on synthetic vitreous fibers is also relevant. Because of the relevance of related research on airborne particulates, it is important for the Roadmap to draw from these other experiences and to coordinate research using an interdisciplinary approach.

Chapter 2 examines recent efforts to develop research roadmaps and discusses the key elements and larger context for framing a broader research strategy.

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2

Key Components of the Roadmap

NIOSH states, "The purpose of the *Roadmap* is to outline a research agenda that will guide the development of specific research programs to be conducted by NIOSH and others, both within and across disciplines, to provide answers to current scientific questions, reduce scientific uncertainties, and provide a sound scientific foundation for future policy development" (NIOSH, 2009a, p. i). The NIOSH Roadmap is divided into three major sections: "Review of Current Issues," "Framework for Research," and "The Path Forward." The review of current issues (62 pages) describes in detail the state of the science, including terminology issues; trends in usage, exposures, and asbestos-related disease; sampling and analytical issues; and physical and chemical properties related to toxicity. The framework for research (24 pages) presents the research goals and objectives and acknowledges that the framework is not all encompassing. The Roadmap states, "Within each of the goals and objectives laid out in this framework, a more detailed research program will have to be developed. . . . Any research project that is undertaken should ensure that the results can be interpreted and applied within the context of other studies in the overall program and lead to outcomes useful for decision-making and policy-setting" (NIOSH, 2009a, p. 65). The path forward (2 pages) describes the next steps in implementing the Roadmap including identifying specific research to be conducted, prioritizing research to achieve the proposed goals, and building partnerships to see the research to fruition.

The remainder of this chapter considers the process used to develop the Roadmap, considers how the Roadmap fits into a broader research strategy intended to implement the research, and examines and discusses the organization and key components of the Roadmap. Chapter 3 ad-

dresses the major scientific issues of the draft Roadmap including an evaluation of the state of the science, the rationale for proposed research, and research needs.

PROCESS OF DEVELOPING THE ROADMAP

NIOSH released its draft Roadmap document *Asbestos and Other Mineral Fibers: A Roadmap for Scientific Research* in February 2007 and posted it on the public docket. In May 2007, NIOSH held a public meeting on the Roadmap at which a number of presentations were made on proposed changes to the document (NIOSH, 2009b). The Roadmap was also submitted to a panel of expert reviewers. The draft document was revised in response to reviewer comments and was released in June 2008 (NIOSH, 2009c). The June version was further revised in response to public review. Table 2-1 summarizes this timeline. The January 2009 version entitled *Revised Draft NIOSH Current Intelligence Bulletin. Asbestos Fibers and Other Elongated Mineral Particles: State of the Science and Roadmap for Research* (NIOSH, 2009a) is the version that was reviewed by this committee and is referred to throughout this report as "the Roadmap."

The committee recognizes the considerable effort and expertise that went into developing the Roadmap. Further, NIOSH has sought input from a number of stakeholders and expert peer reviewers. The process has been open and iterative and has provided several opportunities for comments by interested parties.

The challenge in developing and implementing the research program outlined in the Roadmap lies in the interagency and interdisciplinary nature of the research questions. Because NIOSH is not the only federal agency involved in efforts on asbestos and numerous stakeholders are interested in these issues, implementation of the Roadmap will involve many other entities. Having wider authorship of the Roadmap beyond NIOSH would have been challenging. Another possibility might have been to have had an external independent organization develop the Roadmap as was done for the Environmental Protection Agency's (EPA's) research strategy on airborne particulate matter, a congressionally mandated effort that is discussed below (NRC, 1998). Having said this, the committee believes that the multiple opportunities to comment on the Roadmap have engaged a wide range of stakeholders and the

TABLE 2-1 NIOSH Roadmap Timeline

February 2007	First draft released for public comment and review, *Asbestos and Other Mineral Fibers: A Roadmap for Scientific Research*
February–May 2007	Public docket of the first draft
May 4, 2007	Public meeting on the Roadmap
June–September 2007	Peer review of the Roadmap and compilation of reviewers' comments
June 2008	Revised draft released for public comment, *Asbestos Fibers and Other Elongated Mineral Particles: State of the Science and Roadmap for Research*
June–September 2008	Public docket for the revised draft
September–December 2008	Revision of revised draft
January 2009	Public docket for the January 2009 draft, *Revised Draft NIOSH Current Intelligence Bulletin. Asbestos Fibers and Other Elongated Mineral Particles: State of the Science and Roadmap for Research*
January 2009	First meeting of the National Academies' Committee for the Review of the NIOSH Research Roadmap on Asbestos Fibers and Other Elongate Mineral Particles

important work ahead to implement the Roadmap will have to involve the relevant federal agencies, organizations, associations, and interested parties.

A BROADER RESEARCH STRATEGY

A roadmap is defined as "a detailed plan to guide progress toward a goal" (Merriam-Webster, 2009). The NIOSH Roadmap comports with this definition and takes an important step toward articulating a research

agenda for examining the potential toxicities of all elongate mineral particles. In thinking about the key components of a roadmap, the committee first considered the broader picture of how a research agenda is implemented and then examined other examples of research strategies and the ways in which these strategies incorporate a research roadmap (NRC, 1998, 2007, 2009).

In 1998 the National Research Council produced *Research Priorities for Airborne Particulate Matter* (NRC, 1998). This report (along with three subsequent companion reports) presented a policy-relevant research strategy for addressing uncertainties surrounding the setting of the national ambient air quality standards for particulate matter. The report presented a conceptual framework for an integrated national program of particulate matter research, identified the most important research priorities, and described the recommended short-term and long-term timing and estimated costs of such research in an integrated strategy (NRC, 1998). This series of reports had substantial positive impact on EPA's long-term research planning, the coordinated implementation of intramural and extramural research efforts to address knowledge gaps, and congressional funding for the particulate matter research program.

In 2007 the NRC report *A Review of the Ocean Research Priorities Plan and Implementation Strategy* reviewed a plan that established the first coordinated national interagency research planning effort to support ocean science. The NRC report was supportive of the research plan but found that it lacked some important elements including a vision for ocean research in the next decade, a ranking of either long-term or near-term priorities, a discussion of the level of needed funding, an implementation strategy, and metrics by which the plan would be evaluated.

The NRC conducted a review of the federal strategy for environmental, health, and safety research on nanotechnology and outlined the following important elements of a research strategy in its report, *Review of the Federal Strategy for Nanotechnology-Related Environmental, Health, and Safety Research* (NRC, 2009):

- ***Vision, or statement of purpose.*** What is the ultimate purpose of conducting the research?
- ***Goals.*** What specific research goals should be achieved?
- ***Evaluation of the state of science.***
- ***Roadmap.*** What is the plan of action to achieve the stated goals? What are the specific objectives, and when do they need to be achieved? How will other efforts and initiatives be leveraged, in-

cluding industry and international initiatives? How will the roadmap be adjusted in light of new knowledge? What is the time required for the plan to become effective?

- ***Evaluation.*** How will progress be measured, and who will be responsible for measuring it? Are there measurable milestones that can be evaluated against a clear timeline?
- ***Review.*** How will the strategy be revised in light of new findings, to ensure that it remains responsive to the overarching vision and goals?
- ***Resources.*** Are there sufficient resources to achieve the stated goals? If not, what are the plans to obtain new resources or to leverage other initiatives to achieve the goals?
- ***Mechanisms.*** What are the most effective approaches to achieving the stated goals? How will exploratory and targeted research be used? What will the balance be between principal investigator-driven and goal-driven research and between intramural and extramural research programs? How will research efforts be coordinated to ensure a coherent approach to achieving the stated goals? What provisions are there for enabling interdisciplinary research that crosses established funding and agency boundaries?
- ***Accountability.*** How will stakeholders participate in the process of developing and evaluating a research strategy? Who will be accountable for progress toward stated goals? Who will be responsible for disseminating information generated within the research strategy and ensuring its use in raising awareness and making decisions?

As outlined above, the NIOSH Roadmap is one part of a larger research strategy. The committee urges NIOSH to consider working with other agencies and organizations to develop a strategy to ensure that the Roadmap will move forward with adequate funding and accountability.

The current Roadmap suggests that the next steps will involve parsing out the activities to five independent study groups. Although this is a common approach, the committee believes that the nature of the issues requires combined attention from all disciplines. Sampling and characterization issues should be the concern of toxicologists and epidemiologists as well as mineralogists. Toxicology, epidemiology, and risk assessment overlap in interests and goals. Moving away from discipline-specific review groups would go a long way toward achieving the integrated understanding that is necessary. The committee urges considera-

tion of an interdisciplinary and comprehensive research strategy to ensure the implementation of this research (Chapter 4).

KEY COMPONENTS OF THE NIOSH ROADMAP

The focus of this report is on one part of the research strategy—the research roadmap. In drawing from the examples above and the committee's expertise with similar documents, the committee has concluded that the NIOSH Roadmap needs to be strengthened to clearly address the following key components:

- Overarching vision
- Rationale for the endeavor—in this case, the public and occupational health rationale
- Research goals
- Research framework—the systematic plan for conducting the research

Each of these components is discussed below in terms of how it is currently presented and how it could be improved in the Roadmap.

Overarching Vision

The fundamental research questions discussed in the Roadmap revolve around how to assess the relative health hazards of exposures to the full spectrum of elongate mineral particles. The Roadmap needs a clearly stated vision that points toward research that will rank or define the range of potential health hazards of exposures to a spectrum of elongate mineral particles and help determine the influence of size, shape, and other physical and chemical characteristics of elongate mineral particles on human health. This research would identify which elongate mineral particles, or what characteristics of those particles, should be included in recommendations to protect workers and others from hazardous occupational and environmental exposures. For example, what research should be conducted if confronted with exposures to previously untested mineral particles at a mine site or in a construction workplace? What procedures should be undertaken to define the inherent toxicity of the elongate mineral particles, to rank their toxicity against those of par-

ticles having known potential for causing harm, and to define the exposure levels of concern?

Rationale

A roadmap for developing an extensive body of scientific work provides the rationale for the research in order to help justify the needed resource investments. The committee strongly supports NIOSH in its development of the Roadmap but considers that the Roadmap, in addition to providing the scientific rationale, should clearly articulate the influence that ongoing and future research can have on improving public and occupational health. For example, although the Roadmap provides data on the health effects of asbestos exposure and their related latency, it would be helpful if it also included a discussion of exposures to other elongate mineral particles, the numbers of workers potentially affected, and the extent of environmental exposures that might impact public health. This information would help clarify and solidify the purpose of the Roadmap and provide a justification for funding and interagency collaboration.

Goals

The NIOSH Roadmap clearly describes the research program's goals (Box 2-1). However, the goals are presented as independent "silos" of effort to address toxicology, mineralogy, epidemiology, and analytical methods separately, rather than emphasizing the interdependent, interdisciplinary nature of this research. Greater integration of the goals across disciplines is necessary to ensure that the research results can be drawn together and to foster the needed collaboration among scientists and across agencies. Further, the goals have to be structured so as to drive the research program. The current goals are written broadly. An effort is needed to make the goals more focused and explicit so that they inform the systematic exploration of the potential toxicity of various types of elongate mineral particles related to specific physical, chemical, and surface properties and other factors that might affect human health.

BOX 2-1
NIOSH Roadmap's Strategic Research Goals and Objectives

NIOSH Current Intelligence Bulletin.
Asbestos Fibers and Other Elongated Mineral Particles:
State of the Science and Roadmap for Research (NIOSH, 2009a)

I. Develop a broader understanding of the important determinants of toxicity for asbestos fibers and other elongated mineral particles.[a]

- Conduct *in vitro* studies to ascertain what physical, chemical, and surface properties influence the toxicity of asbestos fibers and other elongated mineral particles; and
- Conduct animal studies to ascertain what physical and chemical properties influence the toxicity of asbestos fibers and other elongated mineral particles.

II. Develop information and knowledge on occupational exposures to asbestos fibers and other elongated mineral particles and related health outcomes.

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

III. Develop improved sampling and analytical methods for asbestos fibers and other elongated mineral particles.

- Reduce inter-operator and inter-laboratory variability of the current analytical methods used for asbestos fibers;
- Develop analytical methods with improved sensitivity to visualize thinner elongated mineral particles to ensure a more complete evaluation of airborne exposures;
- Develop a practical analytical method for air samples to differentiate between exposures to asbestiform fibers from asbestos minerals and exposures to elongated mineral particles from their nonasbestiform analogs;
- Develop analytical methods to assess durability of elongated mineral particles; and

- Develop and validate size-selective sampling methods for elongated mineral particles.

[a]As discussed in Chapter 3, the committee prefers the term *elongate mineral particles* and does not believe that the acronym should be used.
SOURCE: NIOSH, 2009a, pp. 64-65.

Research Framework

As discussed in detail in Chapters 3 and 4, NIOSH has done a commendable job of describing the current state of knowledge. However, the Roadmap lacks a vision of how to use the science in a prospective way to assess potential hazards or a plan for developing the ability to do so. A standardized stepwise process for assessing the nature and extent of potential health hazards of inhaled elongate mineral particles is needed to address concerns that arise when a previously unstudied exposure situation (e.g., as occurred at Libby, Montana) is encountered. The same systematic approach would be useful for characterizing and ranking hazards from materials encountered in currently known exposure situations.

A generalized systematic framework for characterizing exposure and hazards from inhaled materials is readily conceived, and such stepwise testing frameworks have been developed for other materials (e.g., ILSI Risk Science Institute Working Group, 2005). A step-by-step approach would allow evaluation of the toxicities of elongate mineral particles across the spectrum of potential human exposures to identify which fraction of the spectrum is most problematic for human health. Although selection of the specific procedures and tests to be used remains, at least in part, a knowledge gap to be addressed by research, the Roadmap should explicitly point to the need for developing such a generalized framework. The framework should be presented to fit into the broader scope of research on airborne particulates.

The framework of tiered testing would begin with the identification and physical and chemical characterization and identification of the mineral(s) involved in the exposure and proceed through increasingly complex biological screening steps until the biological hazard was judged to be adequately classified.

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3

Major Scientific Issues: State of the Science and Future Research Directions

The NIOSH Roadmap (NIOSH, 2009) proposes a set of studies to improve knowledge on the potential health effects of elongate mineral particles and the ways in which human exposures can best be studied. The proposed studies are founded upon a broad span of scientific literature on these topics that has been well summarized in the draft Roadmap. This chapter provides the committee's review of the major scientific issues discussed in the Roadmap.

TERMINOLOGY AND NOMENCLATURE

The NIOSH Roadmap devotes considerable attention to mineralogical terminology and nomenclature. In the last several years it has become increasingly clear that the terminology historically used to describe asbestos in workplace or environmental exposures is inadequate and is often applied incorrectly or inconsistently. Examples include minerals not currently listed in regulatory language, such as winchite and richterite asbestos. This is not to say that the proper mineralogical terminology does not exist. Rather, the terminology used by mineralogists is very specific and covers the full range of minerals and properties that are identified for study in the NIOSH Roadmap, but this terminology is not consistently applied in the Roadmap document. One problem is that mineralogical terminology has frequently been misinterpreted in the scientific literature, commercial publications, and regulatory language, resulting in confusion regarding the exact meaning of mineralogical terms, including those used in describing the physical characteristics of minerals.

The Roadmap includes a glossary to attempt to clarify for the reader the ambiguities in meanings and concepts. However, the glossary presently contains many words that are not scientifically or technically valid, as well as definitions of scientific terms that are incorrect or need greater detail.[1] The committee emphasizes the need to establish and maintain scientific rigor in the glossary definitions and use of terminology in the Roadmap. The committee strongly endorses the use of correct mineralogical terminology and believes that using accepted and scientifically rigorous terminology and nomenclature throughout the Roadmap, including the Roadmap glossary and in subsequent research activities, is the best means to ensure an accurate understanding of proposed research directions and, ultimately, research outcomes. A complementary goal is that this rigor in terminology may eventually be applied consistently in the regulatory setting. In creating a new acceptable paradigm for risk assessment in this area, the Roadmap should not continue the historical use of ambiguous terminology occasionally found in some existing standards and guidelines. To ensure proper scientific terms, a modern technical glossary or other standard reference text, appropriate for the field of study, should be used and cited. For example, the American Geological Institute *Glossary of Geology* may be appropriate for many of the mineralogical or geological terms (Neuendorf et al., 2005). Other reference texts should be consulted for words not found in the AGI glossary or for toxicological or epidemiological terms. Words or terms that are not scientifically or technically valid should be removed from the glossary and the text.

NIOSH has also recognized a problem with or deficiency in existing terminology that has caused confusion and concern for researchers, policy makers, and others involved in these issues. NIOSH has introduced the term *elongated mineral particle* to encompass the broad range of mineral particles that are the primary focus of the proposed research. The committee urges the use of the descriptive term *elongate,* rather than *elongated* so as to describe the physical appearance of the particles as opposed to implying that they have been actively lengthened (see also

[1]Suggestions for terms that need well-referenced definitions include *acicular, actinolite, amphibole, anthophyllite, asbestiform, asbestos, chrysotile, cleavage fragment, crocidolite, fiber, fibril, fibrous, solid solution series,* and *tremolite*. Note that the terms *asbestiform* and *asbestos* are not equivalent to *fibrous* or *fiber*; nonasbestiform minerals and synthetic materials can also be fibrous. Suggestions for terms to consider removing from the glossary include *countable particle, covered mineral,* and *fragility*. Terms to consider adding to the glossary include *crystal* and *petrographic thin section*.

Chapter 1). The committee does not believe that the acronym EMP should be used. Use of the acronym could impart more rigor and homogeneity to a term that actually describes a diverse group of mineral particles of a certain length and aspect ratio.

An elongate mineral particle is defined as "any fiber or fragment of a mineral longer than 5 μm with a minimum aspect ratio of 3:1 when viewed microscopically using NIOSH Analytical Method #7400 ('A' rules) or its equivalent" (NIOSH, 2009, p. 61). This term as introduced in the Roadmap is all-encompassing and includes not only asbestos and nonasbestiform mineral particles but also those minerals or particles that are defined, for example, as acicular or prismatic or as cleavage fragments. Nonetheless, the committee considers the dimensions described in the definition ("longer than 5 μm with a minimum aspect ratio of 3:1") as a good starting point for research since this encompasses the respirable size range. The committee believes that as knowledge of these mineral particles and their potential for health effects accumulates, the definition of these dimensions should be periodically revisited and refined with the goal of providing a more evidence-based justification. However, this definition used by NIOSH also applies to non-respirable mineral particles as it does not place an upper bound on diameter. For example, a fiber with a diameter of 6 μm and an aspect ratio of 3:1 would likely not be respirable but would be counted under the 7400A rules. While this may not be a problem with most traditional asbestos samples, as more elongate particles are evaluated, this lack of differentiation may prove problematic. Additionally, while this definition has been adopted by NIOSH in rulemaking, it is not consistent with other recognized fiber counting schemes such as the World Health Organization method which does place an upper bound on fiber diameter as do the NIOSH 7400B counting rules. It is also important for the Roadmap to acknowledge that the term *elongate mineral particle* is not a rigorous mineralogical classification or one to which regulatory significance is assigned, but rather serves a useful purpose in encompassing the full continuum of minerals from asbestiform through nonasbestiform, within specified dimensions. As such, the term *elongate mineral particle* is a convenient, neutral, and uniform means for the disciplines of mineralogy, toxicology, and epidemiology to discuss broad categories of mineral particles with potentially widely varying potency for causing cancer and other health effects. In the NIOSH Roadmap and in this report, the focus is on minerals, which are naturally occurring substances; discussions of research on synthetic materials are included to provide examples of potential research direc-

tions or to provide information within the broader context of airborne particulates.

Regarding other terminology issues, the committee highlights a few terms in this chapter that require attention. The term *asbestos* is a commercial term generally referring to the Occupational Safety and Health Administration (OSHA) and Mine Safety and Health Administration (MSHA) regulatory definitions that specify six minerals: chrysotile, cummingtonite-grunerite asbestos (commercially termed amosite), anthophyllite asbestos, riebeckite asbestos (crocidolite), tremolite asbestos, and actinolite asbestos (29 CFR 1910.1001(b); 29 CFR 1926.1101(b); 30 CFR 56.5001(b)(1); 30 CFR 57.5001(b)(1); 30 CFR 71.702(a); Ampian, 1976). Other authors have used the term more broadly to include minerals that occur in the asbestiform habit, but usage is usually restricted to minerals of the amphibole group and the mineral chrysotile (Lowers and Meeker, 2002). Importantly, nonasbestiform analogs of these six minerals also exist and often occur in similar sizes and shapes as specified in the various regulations and definitions.

The term *cleavage fragment*, a fragment of a crystal that is bounded by cleavage faces (Neuendorf et al., 2005), has often been used incorrectly in describing both asbestos and nonasbestiform analogs. This is significant because several toxicity studies appear to suggest that cleavage fragments, which are not regulated currently by OSHA or MSHA, are less toxic than asbestiform particles of the same mineral (Addison and McConnell, 2008). While more research is needed to address this issue, the existing research does not support extending these findings beyond cleavage fragments to the broader class of prismatic to fibrous particles. Conversely, the term *asbestos* has often been used inappropriately to describe any particle that meets the counting criteria of a particular analytical method (e.g., 3:1 aspect ratio and greater than 5 μm length). The potential health effects of some nonasbestiform mineral particles have not been studied, and the potency of respirable prismatic, acicular, and fibrous particles that do not meet the definitions of commercial asbestos is not known. NIOSH has identified in the Roadmap some research that may help to clarify these issues and to resolve questions now being debated.

Another consideration with regard to terminology is the naming or identification of specific minerals. Mineral names in the geological community are endorsed by the International Mineralogical Association (IMA) Commission on New Minerals, Nomenclature, and Classification (CNMNC), which is charged with approving, defining, and occasionally

redefining or reassigning mineral names (IMA, 2009). The CNMNC recognizes that its nomenclature serves only as a recommendation to the mineralogical community (Nickel and Grice, 1998). Although the IMA nomenclature is accepted by the primary mineralogical research journals, and therefore its use is generally required for publication in those journals, the IMA nomenclature carries no actual statutory authority in the United States.

An issue encountered in the application of IMA terminology to asbestos outside the mineralogical community is that the IMA CNMNC continues to refine and redefine mineral names for mineralogical research purposes based on new data and understanding of minerals. An example is the redefinition of amphibole names by the IMA Committee on Amphibole Nomenclature, which has revised the amphibole nomenclature three times since 1978. An additional proposal for another major reorganization of amphibole nomenclature has recently been proposed to the mineralogical community (Hawthorne and Oberti, 2007). These changes in mineral names far outpace the ability of the rulemaking and legislative processes in the United States and have caused considerable confusion and misunderstanding, as is evident in recent legal actions relating to asbestos contamination in Libby, Montana. Finally, the correct application of IMA amphibole nomenclature (Leake et al., 1997, 2004) requires analytical precision and accuracy that is generally beyond the capability of the standard asbestos analysis methods used for exposure assessment purposes. This presents difficulties for the comparison of analytical results between, and even within, laboratories.

Within the chemical community, the Chemical Abstracts Service (CAS) Registry provides definitions of chemical substances including asbestos. Unlike the IMA, the CAS Registry does carry some statutory authority. However, CAS Registry definitions can often be vague. An example is the general definition of asbestos (CAS 1332-21-4) from the online Chemical Abstracts Registry database as *"*a grayish, noncombustible fibrous material" consisting "primarily of impure magnesium silicate minerals"—a definition that could apply to several hundred silicate minerals. The CAS definition for asbestos was ruled applicable by the U.S. Ninth Circuit Court of Appeals for the Clean Air Act (U.S. Court of Appeals, 2007). This dichotomy between the generally precise IMA definitions and the less detailed and less precise CAS definitions presents significant difficulties for those involved in work on asbestos and other elongate minerals.

The committee believes that the rigor of established mineralogical terminology is critical to the research process and the ultimate understanding of the mechanisms of toxicity. Therefore, the committee suggests that the Roadmap remain consistent in its use of referenced mineralogical nomenclature rather than commercial names (e.g., amosite). It must also be recognized that mineralogical definitions and nomenclature have changed and may change in the future. It is therefore important that the specific mineral nomenclature scheme used in any publications, such as the Leake et al. (1997, 2004) nomenclature for amphiboles, always be referenced so as to make clear the specific definitions being applied.

Issues of terminology also arise in other relevant research disciplines. The problem of the incorrect use and corruption of terminology extends beyond the question of misunderstanding and unintentional misuse in that it provides an opportunity for exploitation of the terminology to achieve an expedient outcome. It is therefore extremely important that researchers, policy makers, regulatory staff, and others working on these issues take great care in using terminology that is precise and fully developed so that the intent is totally clear. Clear and consistent use of conventional terminology in the Roadmap is thus essential.

With the terminology considerations suggested above, this chapter subsequently highlights a mineral characterization scheme for establishing and using mineral standards that have been well-characterized physically and chemically for use in toxicological research.

MINERAL CHARACTERIZATION AND STANDARDIZED REFERENCE MINERALS

Mineralogy is a fundamental science relating an enormous number of naturally occurring solid materials. A robust, systematic classification scheme for minerals exists based on rigid compositional and structural (crystallographic) criteria. These criteria are well defined and can be quantified. The Roadmap would benefit from further emphasis on the mineralogical research needed and from discussion of the development of standardized reference mineral samples that could be used in toxicological studies to assess the variability in the toxicity of different types of elongate mineral particles. Major issues faced in research in this area include (1) that the bulk rock or ore may contain a complex suite of minerals and that this complexity, although relevant to the toxicological

properties of the dust, may not be detectable in the respirable dust derived from the bulk because of analytical limitations, (2) the relative percentage of different minerals present, and (3) the physical characteristics, which may vary with the size fraction after attrition. For these reasons, characterizing the fundamental properties of elongate mineral particles is essential.

Mineral Characterization

Minerals have fundamental properties that can be defined in terms of physical (e.g., growth habit, hardness, cleavage), chemical (e.g., chemical composition, surface reactivity, solubility), optical (e.g., translucence, refractive indices), and electrical (e.g., conductivity, resistivity) characteristics, among others. A degree of variability in the compositional and structural makeup of specific minerals in nature also exists, reflecting differences in petrogenesis and mineral source (natural conditions of formation). Therefore, minerals exhibit a range of physical and chemical properties that result in varied responses to conditions imposed during extraction, processing, and experimentation. Research on the degree of variability between mineral species and within mineral groups, due to their natural conditions of formation, and the extent to which these varying characteristics influence toxicity is largely absent from the Roadmap and more detail is needed.

Key variables of relevance in studying minerals include surface crystal structure and chemistry, size and shape characteristics, and mineral habit—all of which will vary depending on the composition, environment of growth, and response to physical and chemical processing of mineral samples. Essential to the consistent rigorous characterization of minerals is the consideration of mineralogical properties in a similar way throughout the mineral "life cycle"—from extraction or liberation at the source to processing for use in manufactured products or as research materials. Modern methods of mineral characterization can also provide a statistical representation of the range of minerals and their physical characteristics. This form of minerals characterization is used routinely by the mineral industry to identify and quantify mineral samples in terms of their variability in composition, size, and shape.

Whether establishing a new reference mineral sample for eventual use in health-related research or characterizing an unknown suite of elongate mineral particles from an air sample filter, a basic set of mineral

characterization techniques can be employed in a tiered fashion. Additional characterization techniques can then be employed if required. The level of analytical detail will depend upon the goal of the research. Table 3-1 outlines a basic characterization sequence and suggests potential outcomes of the research that can be used to plan further research in a systematic way. Such an approach to mineral characterization is currently absent from the Roadmap.

The committee believes that a fundamental problem with the proposed research in the Roadmap is the reliance on limited and outdated analytical methods such as phase contrast microscopy (PCM). Other methods such as transmission electron microscopy (TEM) or scanning electron microscopy (SEM) are not recommended for use exclusively or as "stand-alone" analytical methods. Rather, TEM or SEM can be used most effectively in conjunction, if possible, with the petrographic techniques listed in Table 3-1. The need to develop new methods based on electron microbeam analysis techniques is critical and should not be limited by existing regulatory constraints or existing policy. The committee strongly believes that the science should drive the policy and regulation, not the reverse.

Prediction and prevention are linked to having well-characterized sample sets for experimental work and analysis. The Roadmap recognizes that workers may be exposed to any number of crushed and ground and/or contaminant particles introduced during mining, milling, manufacturing, and demolition of the materials. In these cases, the size and shape criteria used to describe elongate mineral particles encompass many mineral groups in addition to asbestos and analogous minerals. Mineral source and petrogenetic studies can be used to help characterize mineralogical materials in terms of source (original geological source for the mineral and formation conditions). By using statistically reasonable sample populations from diverse natural sources and rock localities (e.g., mines), including historical data sets, minerals from an air sample filter may be classified not only by mineral composition, optical properties, size, and shape, but also by petrogenetic history. This type of approach also has the potential to aid in the design of tailored toxicological studies linked specifically to a particular mineral source and could provide predictive assessment for materials derived from similar geological settings.

TABLE 3-1 Tiered Approach to Mineral Characterization

Characterization Step	Purpose	Further Application
1. Examine original rock from source and determine mineral content, mineral habits, textures, and chemistry in situ (petrographic analysis of thin sections and hand specimen analysis [polarized light microscopy, PLM]; electron probe microanalysis [EPMA]).	Establishes mineral characteristics, mineral chemical variations, basic growth habit of single crystals and aggregates of minerals (e.g., equant, granular, acicular, radiated growth habits). Yields a quantitative appreciation of the distribution of minerals in situ and their growth relationships. Note that cleavage fragments are fragments of single crystals and are not regulated by MSHA and OSHA.	This step creates the initial data set of relevant mineralogy and mineralogical associations that will be further developed through subsequent stages.
2. Comminute the sample to different, relevant size fractions and characterize the minerals optically in terms of shape, habit, texture, size, and chemistry using optical mineralogy and/or electron beam techniques. These characteristics may also be applied to an unknown mineral set from an air sample filter.	Establishes the range of habits—from fibrous to acicular to prismatic, etc.—that may be present in a mixed mineral sample that has undergone various degrees of processing and the degree to which specific minerals may persist through greater levels of processing.	This step identifies and refines the list of relevant criteria related to potential health impacts.

Continued

TABLE 3-1 Continued

Characterization Step	Purpose	Further Application
3. Analyze the thin sections, or crushed samples, in controlled size fractions by EPMA, XRD, XRF, PLM, SEM, and TEM.	In combination with PLM, SEM provides an option for larger data sets that are more representative of the sample population. TEM measurements can provide diffraction information to help distinguish the crystallographic differences among various asbestos minerals. New technologies in quantitative mineralogy and image analysis aid with size distribution and counting statistics.	Mineralogically characterized samples can be used further in controlled toxicological research.
4. Detailed analysis of individual grains, such as that offered by surface analysis provides information on oxidation-reduction state, electrostatic behavior, and other potentially relevant properties.	Methods include EXAFS, Auger, AFM, Mössbauer spectroscopy, EBSD, synchrotron, and three-dimensional analysis combined with knowledge of biodurability and length of residency of particles with specific characteristics.	Further understanding of the surface characteristics of specific grain populations can be useful for toxicological studies of human tissue and fluids.

NOTES: AFM = atomic force microscopy; EBSD = electron backscattered diffraction; EPMA = electron probe microanalysis; EXAFS = extended X-ray absorption fine structure; PLM = polarized light microscopy; SEM = scanning electron microscopy; TEM = transmission electron microscopy; XRD = X-ray diffraction; XRF = X-ray fluorescence. When analyzing natural materials for basic mineralogical research and characterization, data from steps 1 and 2 are required, whether from historical sources or newly collected by the analyst. Steps 3 and 4 involve progressively more sophisticated types of analysis for mineralogical and, eventually, toxicological research purposes. For rapid identification and characterization of unknown samples from worker air sample filters for regulatory purposes, steps 2 and 3 are the relevant actions to employ.

Research is also needed into the potentially toxicological responses of exposure to mixtures of elongate mineral particles. The complexities of this research underscore the need to have well-characterized mineral samples in the context of their natural sources and petrogenesis in order to understand the controlling variables in the toxicological experiments.

Standardized Reference Minerals

Well-characterized reference mineral samples are important for research on the potential health effects of elongate mineral particles, and the need for a well-managed repository should be emphasized. The identification, classification, and characterization of unknown mineral particles from workplace or environmental exposures require comparison to rock-forming minerals that have been characterized mineralogically by conventional petrographic techniques. Similarly, designing and conducting meaningful toxicological experiments require well-characterized reference mineral samples to allow systematic intra- and interlaboratory comparisons of results. The Roadmap notes the need for standardized reference mineral samples but should include more details on an approach to developing a central repository for systematically characterizing and standardizing the samples. This type of repository provides better precursor material for research of the sort proposed in the Roadmap.

Ideally, all minerals studied by laboratory inhalation exposures should either be obtained from the repository or be matched with smaller samples that are well characterized and included in the repository. It should be noted that substantial quantities of minerals would be necessary if the repository intends to support long-term whole-body inhalation studies. (Smaller quantities are needed for nose-only inhalation studies.) For example, tens of kilograms of respirable minerals would be required to conduct a multi-dose inhalation study of sufficient magnitude to test carcinogenic potential. This does not obviate the need for a repository of smaller samples of standardized minerals. A few grams could support comparative in vitro tests that would help place the effects of inhaled minerals into context, even if the study sample did not come from the repository.

Several sets of standardized reference minerals have been developed in laboratories of the National Institute of Environmental Health Sciences (NIEHS) and the former U.S. Bureau of Mines (USBM), as well as other groups, and could be included in a central repository.

During the mid-1970s, approximately 500 pounds of respirable crocidolite (from South Africa), chrysotile (from Canada and California), grunerite (from South Africa), and tremolite (from a New York State tremolitic talc deposit) were prepared and mineralogically characterized in conjunction with asbestos-related research conducted by the USBM (Campbell et al., 1980). The existing mineral samples vary in the extent to which they have been characterized, and all existing samples and new mineral samples would eventually have to be examined and represented by the same types of basic analytical data, generated using viable modern techniques (see Table 3-1). Most respirable particle size ranges can be classified or developed from these types of standard minerals. Modest initial studies could, for example, be undertaken using the USBM's well-characterized asbestos and tremolitic talc samples, as available. The samples originally characterized by the USBM could serve as precursor material. These studies could include petrographic thin sections made from drill cores and/or initial primary crushing samples from the mine, mine run, or crushing runs. Petrographic analysis of thin sections and particle analysis of crushed materials could be augmented by X-ray diffraction, TEM, and SEM. These petrographic analyses could make use of the <2 μm limit of the optics of the petrographic microscope. This type of work could also characterize the minerals needed for future research, including biological testing. Concurrent studies for discriminating asbestos from cleavage fragments and other particle types using samples from personal monitors worn in mines could also be conducted. Once samples are well characterized by these initial studies, the results could be applied to non-mine-related OSHA and Environmental Protection Agency (EPA) monitor samples. This is an example of a tiered approach to the NIOSH research plan (Table 3-1).

Important descriptive and quantitative parameters needed in a unified characterization of standards include the following:

- Mineralogy of all phases of the sample including quantification of all accessory minerals
- Chemical compositional variability of the mineral of interest
- Size, shape, and degree of mineral fabric and texture, including the habit and single-crystal development
- Source (including, if available, the geological and petrogenetic history of the deposit from which the samples are derived and the mineralogy of the source material)
- Industrial or manufacturing history

- Characterization of the aerodynamic properties of the minerals, and the composition of the other materials for toxicological studies
- Surface chemistry, surface structure, and charge

One of the fundamental parameters for reference and testing materials is particle dimension. However, the Roadmap does not deal with the issue of particle dimension, except obliquely as may be inherent to the different source materials. The importance of particle dimension to health cannot be conclusively determined on the basis of comparing results of studies that contrast two different mineral assemblages, each of which varies in particle size and surface area. A few studies have investigated the degree to which particle dimension in samples of the same mineral is a determinant of toxicity (Davis et al., 1991; Berman et al., 1995; Bernstein and Hoskins, 2006; Bernstein et al., 2006). To expand on these studies, researchers will need samples of the same mineral type (whether from the same source or from well-characterized standards) differentiated by size, shape, dimension, and growth habit. A national mineral repository could meet this need. While not trivial to establish, particularly with the need for processing, characterization, storage, and curatorial facilities, such a repository could include suites of minerals with varying size fractions and growth habits as well as suites of minerals with varying chemistry for use as benchmark samples. Without such a repository, much of the proposed Roadmap research will have diminished value. Given likely developments in instrumentation and classification, the standards should be assessed to allow for future enhancements in the data set.

TOXICITY SCREENING AND TESTING

State of Science and Future Directions

As discussed in Chapter 2, the Roadmap needs to explicitly outline a standardized approach to screening for the potential hazards of elongate mineral particles whose biological effects have not yet been characterized. A systematic, tiered structure of increasingly complex in vitro and in vivo assays would be useful not only for screening for toxicity, but also for placing the nature and extent of the hazard of the new material in the context of what is known about the hazards of previously tested mineral particles. The screening process would begin with the assessment of the physical and chemical nature of the mineral particles that would pro-

vide information to begin to assess where the different types of elongate mineral particles fall along the spectrum of materials for which some information on biological hazard exists. In this and subsequent steps, it is important to ensure that the mineral particles being evaluated represent the physical and chemical characteristics of the respirable material to which humans are, or may be, exposed. If exposures involve mixtures of minerals, the tested samples should represent those mixtures. Separation of mixed exposures into different types would only be appropriate at later stages to assess the components that may impact toxicity.

Careful consideration should be given to selecting the screening tests. The assumption must be that the tests reflect types of responses and perturbations of biological response pathways that are most likely to be caused by elongate mineral particles. It is possible that important responses may not be probed by the selected tests. As knowledge of response mechanisms and critical pathways improves, the selection of tests may evolve (NRC, 2007).

After a series of intermediate steps, the screening may, in certain cases, have to be carried through to long-term inhalation studies of animals. However, an underlying goal would be to establish a screening process and knowledge base where extension to chronic animal studies would rarely be needed to assess the extent to which human exposures should be limited (that is, to establish a regulatory categorization). The following steps (tiers) comprise the proposed framework. This framework is similar to the tiered testing system for natural and synthetic fibers proposed by the International Life Sciences Institute (ILSI, 2005). The intent of the committee's framework is for research needs to flow from present limitations in addressing each of the steps (Figure 3-1).

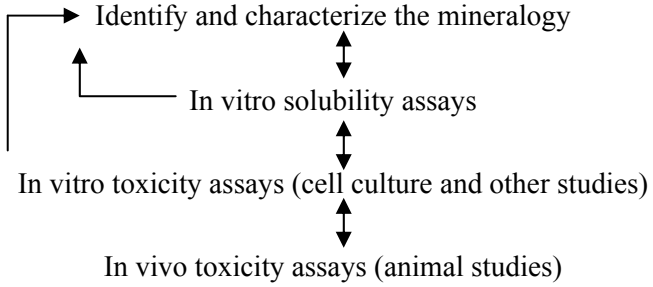

FIGURE 3-1 Overview of a possible testing strategy for elongate mineral particles.
NOTE: If at any point, human data are available, those data should have priority in assessing toxicity and the potential for health impacts.

Physical and Chemical Characteristics

First the Roadmap should identify the types of studies needed to better understand the biologically relevant physical and chemical characteristics of elongate mineral particles. As noted above, a thorough mineralogical characterization of the mineral particles, particularly their chemical structure, physical dimensions, and biopersistence, is needed for meaningful comparisons of toxicological responses. Regard must be given to the several technical issues related to sampling and characterization, noted in subsequent sections, to ensure that the mineral samples studied accurately reflect the minerals to which humans are exposed. By relating biological responses to standardized mineralogical nomenclature, a knowledge base can be developed that progressively reduces the range of mineralogical particle types that need to be tested de novo in order to classify their hazard potential. The following stepwise approach could be undertaken to examine and categorize the mineral particles. It is possible that having addressed these steps, further investigation of some mineral particles may not be needed.

1. What are the physical dimensions of the mineral particles to which people are exposed? What is the aerodynamic size distribution of the airborne mineral particles? What is the distribution of the dimensions of the bulk particles?

   If the particle is respirable or of a thoracic size fraction, it should be considered potentially hazardous and warrants further evaluation. Concern is heightened if the inhaled particles include dimensions that are consistent with other known harmful elongate mineral particles.

2. What are the mineralogical characteristics of the respirable and thoracic size fractions of particles to which people are exposed? Is this homogeneous or a mixture of particles? Is the particle similar to those for which health hazards are already known?

   If the particle is analogous to previously studied particles, its toxicity should be considered comparable until proven otherwise. The confidence in the assessment should be proportional to the degree of similarity between the particles.

3. What are the potential exposure concentrations? Specifically, what are the exposure concentrations of the thoracic fraction of the particles? What is the duration of the exposure?

   If exposures to the particles meet or exceed accepted exposure limits for the general class of particle, the exposure scenario should be considered problematic. If the exposure is below accepted limits for a new elongate mineral particle, some preliminary toxicity testing may still be needed to evaluate the need for a more extensive effort if the particle has characteristics that suggest the potential for toxicity. The magnitude of exposure must be considered in making this decision.

In Vitro Solubility

Elongate mineral particles must reside in the lung for extended times to produce disease beyond the transient inflammation that might be associated with the deposition of any poorly soluble material. Because in vivo solubility is one of the characteristics that determine the persistence of elongate mineral particles, the next step is to assess the solubility of the particle in biological media using state-of-the-art methodologies. A current approach for assessing in vitro solubility uses a lung fluid stimulant, such as Gamble's solution (de Meringo et al., 1994; Zoitos et al., 1997), to provide a rapid and inexpensive approximation of likely in vivo solubility. Existing data on the relative solubility of several types of elongate mineral particles in this assay (Hesterberg and Hart, 2001; Hesterberg et al., 2002) helps place the results in context; this is particularly valuable when toxicity data may also be available for these other elongate mineral particles. Although solubility assays are reproducible using the same type of elongate mineral particles, the assay should include concurrent control particles with known solubility. Extreme acid, base, or enzymatic solutions should be avoided at this step; solubility in an already-accepted lung fluid stimulant has proven to adequately mirror in vivo biopersistence. It is recommended that solubility studies be conducted at two pHs—one slightly acidic, reflecting the pH inside macrophage phagolysosomes, and the other neutral, reflecting the pH on the surface of the alveoli (Christensen et al., 1994; Sebastian et al., 2002; Maxim et al., 2006).

Elongate mineral particles have a range of solubility and biopersistence, and there is not a well-established cut-off point below which a mineral particle would not be of concern. Developing a quantitative database of how well-characterized minerals respond to dissolution experiments in human and animal tissues and fluids will provide valuable information in deciding what mineral particles should undergo further toxicological testing. Mineral surface structure, chemistry, and electrostatic charge behavior are additional important parameters and require accurate characterization of the test particles used. At present such a description of this type of research is missing from the Roadmap.

> *Decision point: If the solubility of the elongate mineral particle falls within the range of similar particles known to be biopersistent and to cause disease, it should be considered potentially pathogenic.*

In Vitro Toxicity Assays

As noted in the Roadmap, numerous in vitro methods have been developed for exploring the mechanisms of toxicity produced by elongate mineral particles. The appeal of these cellular and tissue assays is that they are more rapid and less costly than in vivo assays, and apart from primary embryo fibroblasts, most do not require live animals. The in vitro studies provide useful information on dose-response toxicity of the mineral particles. The studies also can be used to assess the effects of dimension, chemical composition, and interaction of particles with other environmental toxicants such as chemical carcinogens, viruses, or radiation (radon) in modulating the biological behaviors of the elongate mineral particles. Taking advantage of advances in toxicogenomics, bioinformatics, and computational toxicology as applicable, the goal should be improvement in the utility of in vitro assays for classifying the potential hazard of newly encountered particles and ultimately predicting in vivo health outcomes of exposure without the need for in vivo studies. However, considerable advancement will be necessary before in vivo studies can be discarded; thus, the primary purpose of in vitro tests in the near term will be to screen materials for further investigation. In vitro toxicity studies using single cell types do not reflect complex interactions among tissues and organs, do not include the modifying effects of deposition patterns and clearance by mucociliary actions and macrophages, and cannot be used to ascertain the contribution from biopersistence. In

vitro assays have the potential for indicating false positives for causing disease, particularly at the very high concentrations used in some of these studies. For example, vitreous fibers and wools, although positive in many short-term toxicity assays, including cell killing, apoptosis, and generation of reactive radical species (for example, reactive oxygen and reactive nitrogen species), have low potential for causing disease in vivo. At this time, none of the in vitro assays have been validated as predictors of disease in animals or humans to provide the confidence for their use as the sole determinant to predict health hazards of new elongate mineral particles.

In vitro assays have provided rankings of the relative inflammatory and carcinogenic potential of varieties of asbestos having known in vitro toxicity and have also provided insights into the cellular mechanisms of response. Further research and validation may enable in vitro assays to fill a similar role for certain classes of elongate mineral particles. A clearly positive response in vitro would signal the need for further testing and might suggest the longer-term health outcomes to be investigated. A very low or negative response on multiple in vitro assays might be useful for assigning the particle to a low-risk category. Because asbestosis, lung cancer, and mesothelioma likely have different mechanisms of pathogenesis, attention must be given to selecting an array of in vitro assays capable of detecting cellular events thought to be involved in pathways leading to each outcome of concern.

The goal would be to establish an efficient testing approach that uses a small number of assays to estimate in vivo toxicity based on in vitro responses. More than one type of assay would be necessary to explore the range of potential toxicity responses (e.g., genotoxicity, inflammogenicity). The thoracic or respirable fraction of the elongate mineral particles would be tested using a range of doses reflecting those that may occur during human exposure, depending on the choice of the in vitro target cell, in parallel with control particles having extremes of responses in each assay.

> *Decision points: A tentative assignment of hazard level would result from ranking in vitro toxicity relative to those of elongate mineral particles having known in vivo toxicity. A benign ranking in combination with evidence from existing tiers of low potential toxicity might result in no further testing. Otherwise, the nature of in vitro toxicity would help focus subsequent in vivo assessment on the most likely health outcomes.*

In terms of the state of scientific understanding of the toxicity of elongate mineral particles, several opportunities exist to improve the Roadmap. Most carcinogenic asbestos and glass fibers can morphologically transform rodent fibroblast cell lines (Hesterberg and Barrett, 1984; Mikalsen et al., 1988) but not primary human epithelial cells (see Hei et al., 2000, for review). This has been attributed to the extremely low transformation frequency observed in primary cells. As a result, virally immortalized human epithelial cells have been used successfully in morphologic transformation studies with certain types of asbestos (Hei et al., 1997; Wang et al., 2004; Bertino et al., 2007). The results are consistent with the observation that SV40 may act as a co-carcinogen with asbestos in the pathogenesis of mesothelioma (Bocchetta et al., 2000). However, because of the cost and long lag time required for the transformation of human epithelial cells in culture, no dose-response data are available and most of the studies lack adequate asbestos controls. Nevertheless, these studies provide a platform for mechanistic analyses of the neoplastic transforming process (Zhao et al., 2000; Piao et al., 2001; Cacciotti et al., 2005). In the future, a focus on the molecular mechanisms of compensatory cell proliferation and transformation to malignancy will prove to be useful in understanding the disease process.

The description of genetic toxicology studies in the Roadmap needs to be improved. Although various types of asbestos have been shown to induce chromosomal aberrations and sister chromatid exchanges in human mesotheliomas and lung cancers and in cultured human and mammalian cells, mutagenic studies at most mammalian genetic loci have largely been negative (Jaurand, 1996; Hei et al., 2000; Schins and Hei, 2006, for review). This has been attributed to the findings that asbestos induces, either directly or indirectly[2] through the production of reactive radical species, multilocus deletions that are not easily recoverable at the *hprt* and *oua* loci.[3] The observation is consistent with data obtained using other mutagenic assays that are proficient in detecting either large deletions, homologous recombinations, or score mutants located on a nonessential gene (Both et al., 1994; Park and Aust, 1998). These findings provide a direct link between chromosomal abnormalities that have frequently been demonstrated in human and rodent cell lines exposed to

[2]Directly through either surface chemistry or phagocytosis or indirectly through secondary lipid peroxication, NADPH oxidase, or mitochondrial membrane damage.

[3]The *hprt* loci encodes enzyme hypoxanthine phosphoribosyltransferase, while the *oua* loci encodes the enzyme that is the receptor for ouabain, a cardiac glycoside, which is a potent inhibitor of the sodium pump.

asbestos and carcinogenicity in vivo. If an elongated mineral particle type is found to be mutagenic in any in vitro genotoxic endpoint, it needs to be further evaluated.

The Roadmap describes in detail the cell-signaling pathways including nuclear factor kappa B, mitogen-activated protein kinase, and c-Jun-N-terminal kinase, that are activated in murine mesothelial cells and immortalized human bronchial epithelial cells treated with either asbestos or nonasbestiform analogs. However, what is missing is a statement on the specificity of these signaling end points for asbestos toxicology. The observation that antioxidants such as vitamin E and catalase can ameliorate the response indicate that this is a general response to oxidative damage. As such, glass fibers, for example, of similar aspect ratio as asbestos that are noncarcinogenic in vivo are likely to be positive in the activation of these signaling end points.

Recent studies on gene expression profile in human mesothelial cells treated with asbestos suggest that the activating transcription factor-3 (ATF3), which modulates the production of inflammatory cytokines (Shukla et al., 2009), is an important marker in asbestos-treated cultures. In addition, there is evidence that extranuclear targets, including mitochondria, are relevant to asbestos toxicology (Xu et al., 2007). These recent findings provide a conceptual link from frustrated phagocytosis of asbestos to reactive radical species, to cytokine production, to tissue inflammation, and ultimately to fibrosis or carcinogenesis.

In Vivo Toxicity Assays

Elongate mineral particles ranked as likely hazardous based on their mineralogical characteristics or having characteristics that prevent close correspondence to particles of known toxicity would be tested in vivo. It should be acknowledged that the three general types of responses of greatest concern, based on experience with asbestos, are fibrosis, mesothelioma, and lung cancer. Moreover, the most important physical and chemical characteristics probably differ among the three outcomes (Lippmann, 1988). The highest standard for in vivo assessment would be repeated inhalation exposures of animals, by which these outcomes could be revealed. Other routes of administration (e.g., intrapleural, intraperitoneal injection) might be useful for certain types of mechanistic studies, but their relevance to human exposure conditions is considerably less certain. Intracavitary injection is not an acceptable substitute for deposi-

tion via the respiratory tract. Although results of animal studies can rarely be extrapolated to estimates of human risks with absolute confidence (a point that the Roadmap should make more clearly), reliance on animal inhalation studies as a basis for regulatory classification is a well-established practice.

The Roadmap reviews the testing of elongate mineral particles in animals, but does not indicate which animal models have been validated. Although the Roadmap states that "it remains uncertain which species of animal(s) best predict(s) …" (NIOSH, 2009, p. 74), there are publications addressing this issue. For example, the European Union has adopted the in vivo biopersistence protocol ECB/TM/27 rev.7 which is a well-validated 90-day intratracheal test for respirable fibers and particles (European Commission Joint Research Centre, 1999). The Roadmap would benefit from including summary tables, such as those presented by Hesterberg (2009), showing the correlation between disease in animals and humans with various elongate mineral particles known to be nonhazardous. Indeed, the data presented in the Roadmap appear adequate to provide such a correlation. If the correlations were adequately reviewed, it might become clear which types of animal studies would or would not be useful to predict the relative toxicity of an unknown elongate mineral particle with a reasonable degree of certainty. The committee considers that existing data may be sufficient to provide guidance on the design of animal studies. In that context, the following points are presented.

- The particles to be used in toxicological studies need to be well characterized and to the extent possible, the exposure should be designed to achieve target-tissue dosing that simulates dosing in human exposures. A positive control may be warranted if comparative toxicity is an important issue. A negative control may not be necessary if the model has been adequately validated.
- Inhalation appears to be the most relevant route of exposure as proposed by the International Life Sciences Institute (ILSI, 2005) for the study of manufactured vitreous fibers. Other routes can be considered depending on the characteristics of the unknown mineral.
- The rat appears to be the most appropriate rodent species, based on past experience (Mauderly, 1997). Syrian hamsters are known to be less useful in chronic studies because of their susceptibility to infection, and studies of mice may not add significantly to the findings in rats.

- Both genders of rats may not be required because very few studies of asbestos have shown a gender difference (Wagner et al., 1973, 1974, 1982). However, females have demonstrated greater responses than males to some nonelongate particles (Nikula et al., 1995). The potential for gender-based differences in response to elongate mineral particles is unknown.
- Animals should be exposed to multiple concentrations. Exposure levels should be selected based on several considerations, such as maximum tolerated dose, number of thoracic elongate mineral particles in the aerosol having the length range of concern (e.g., >20 μm long), and levels relevant to human exposure. The spacing of dose levels should be chosen to provide the best data for risk assessment. Caution should be exercised to avoid exposures that deposit unrealistically large doses of mineral particles, in order to avoid nonspecific fibrotic and proliferative responses to overloading, such as have occurred with some non-fibrous particles (Oberdörster, 1995).
- Differences in the aerodynamic sizes of particles that are respirable by humans and rats (thoracic size fraction) should be considered. Aerodynamically larger particles can be inhaled and deposited in the thorax of humans in comparison to rats. Accordingly, only a portion of a highly polydisperse population of elongate mineral particles may actually deposit in the lungs of rats. Characterization of the aerodynamic particle size range of the aerosol is necessary to determine whether or not the full range of human exposure is being tested. Dogs and nonhuman primates more accurately model the initial deposition of highly polydisperse elongate particles in humans and could be used for acute studies of initial deposition.
- Subchronic (90-day) exposures may be adequate. ILSI (2005) suggests that a 90-day exposure followed by a 90-day recovery period should be adequate to determine the relative toxicity of elongate mineral particles if subchronic data are available for other materials for comparison. In some cases, lifetime exposures may be warranted. As part of this study, it would be valuable to conduct lung burden evaluations to determine biopersistence, changes in elongate mineral particle morphology, (e.g., splitting and breaking), and changes in the distribution of the elongate mineral particles in the respiratory tract over time.

- Pulmonary fibrosis is a useful predictive end point. ILSI (2005) concluded that pulmonary fibrosis was a useful screening end point for subsequent outcomes such as interstitial fibrosis, COPD (chronic obstructive pulmonary disease), lung cancer, and mesothelioma. In the rat, pulmonary fibrosis has consistently preceded the development of lung cancer and mesothelioma from inhaled elongate mineral particles. However, pulmonary fibrosis is not always followed by the other diseases. In this sense, pulmonary fibrosis in the rat represents a conservative end point for estimating longer-term hazards. In some cases, the longer-term outcomes may have to be explored by lifetime inhalation studies.

  Decision point: If pulmonary fibrosis is observed, the material in question should be considered likely to be hazardous. Because not all fibrosis leads to cancer, the development of fibrosis does not confirm a carcinogenic hazard.

It must be stressed that adequate human data should always take priority over animal data in characterizing the risk from elongate mineral particles. Robust positive data from humans are sufficient for regulatory action. However, negative data from humans may not be adequate to discount long-term risks from exposures to elongate mineral particles because of the relatively long latency period in humans for some diseases. Toxicological testing, both in vitro and in vivo, is appropriate in the absence of data, or the absence of robust data, from humans.

EXPERIMENTAL DESIGN ISSUES

For toxicological experiments involving multiple characteristics of the mineral particles of interest (e.g., length-to-width ratio, biopersistence) it is often not possible to study all combinations of all characteristics as would be done in a full factorial design. In many cases, however, this may not be necessary because the focus is less on estimating and testing high-order interactions and more on screening the many potentially important characteristics to determine which do and which do not impact a toxicological outcome of interest. In this case, a fractional factorial design should be considered because it will greatly reduce the number of required experimental conditions and provide the ability to

screen large numbers of potentially important risk variables and estimate their direct (main) effects and in some cases even obtain unconfounded tests of their two-way interactions.

When the factors or characteristics of interest are continuous variables and cannot be readily dichotomized to fit within the context of a 2^k design, a reasonable alternative strategy is response-surface methodology. The basic idea is to look at a more limited number of combinations of a variety of factors and to identify areas in the high-dimensional response surface that are associated with maximal biological activity. Related methods for further exploration of the response surface (e.g., steepest ascent methods) can then be used to more carefully explore the areas of higher biological activity. Appendix C provides a more detailed overview of these potentially useful experimental design tools.

EPIDEMIOLOGY

Assessment of the State of the Science

The Roadmap discusses epidemiological studies of workers with mining and/or milling exposures to mineral particles that have been reported to be nonasbestiform from three different regions: the talc mining region of upstate New York, the Homestake gold mine in South Dakota, and the taconite iron ore mines in northeastern Minnesota. The Roadmap section reviews in sufficient detail the published reports of the epidemiological studies of these occupational cohorts through 2007.

The subsection on studies of the New York talc miners and millers concludes with a summary indicating that an excess of pneumoconiosis and pleural plaques is "well recognized to have occurred among workers exposed to talc" (NIOSH, 2009, p. 22). The dust from these talc mines has been reported to contain nonasbestiform tremolite, asbestos anthophyllite altering to talc at the nanometer scale (considered as unregulated by OSHA), and antigorite-lizardite particles (NIOSH, 1980; Kelse, 2005). However, the NIOSH study and others document the presence of asbestos. Mesothelioma rates have been reported to have been elevated in Jefferson County, the site of much of the talc industry in New York (Vianna et al., 1981; Enterline and Henderson, 1987; Hull et al., 2002), but these studies used a nonspecific International Classification of Diseases (ICD) code for malignant neoplasms of the pleura that may have included cancers metastatic to the pleura. Data from 1999 to 2004

using a specific ICD-10 code for malignant mesothelioma show no excess of mesothelioma in Jefferson and St. Lawrence counties (NIOSH, 2009). The most controversial aspect of the published epidemiological studies from the New York talc industry is excess lung cancer mortality. While this finding has been consistently reported, so has the lack of an exposure-response relationship.

The subsection on studies of Homestake gold miners notes that three different groups of investigators have reported on lung cancer risk among these workers (Gilliam et al., 1976; McDonald et al., 1978; Brown et al., 1986, which was updated by Steenland and Brown, 1995). The dust from this mine has been reported to contain nonasbestiform mineral particles that are mostly cummingtonite-grunerite, along with accessory tremolite-actinolite and other amphibole varieties. No excess of mesothelioma has been documented among these gold miners. Although small excesses of lung cancer deaths were found in the most recent study (Steenland and Brown, 1995), there was again a lack of a cumulative dust exposure response. However, the subsection also notes that total dust is likely a poor surrogate for exposure to nonasbestiform mineral particles, making this study largely uninformative about the risk of lung cancer associated with such exposure. This subsection concludes that the studies of the Homestake gold miners provide at best weak evidence of an excess risk of lung cancer, and there are inadequate data on worker exposures to nonasbestiform minerals.

The subsection on studies of taconite iron ore miners and millers in northeastern Minnesota indicates that recent sampling and analysis of the ores from the taconite iron ore mines reported no asbestos, but did find ferroactinolite, ferrian sepiolite, grunerite-ferroactinolite, and actinolite, some of which was fibrous. The subsection concludes with a summary noting that cohort mortality studies (Higgins et al., 1983; Cooper et al., 1988, 1992) have not provided any evidence of an increased risk of respiratory cancer or mesothelioma. In contrast, recent reports from the Minnesota Department of Health (MDH, 2007; Brunner et al., 2008) have documented an excess of mesotheliomas among males, but not females, in this region of Minnesota and many of these cases had been workers in the taconite industry. There is evidence that at least some of the cases may have had exposures to asbestos, but further research to resolve this issue is ongoing.

The summary of the section states that the results from these studies of workers reportedly exposed to nonasbestiform mineral particles "do not provide clear answers regarding the toxicity" (NIOSH, 2009, p. 26)

because of a number of limitations. First, all three populations of workers studied were exposed to complex mixtures of particles that included only a relatively small percentage of nonasbestiform mineral particles. Second, data on past exposures to those particles are inadequate, and exposure to total dust is likely a poor surrogate for such exposure. Third, the reliability of death certificate information for mesothelioma diagnosis prior to 1999 may be poor. Fourth, the lack of individual smoking data is another major limitation for interpretation of any lung cancer risk among these populations. Because of these limitations, the section concludes that "the findings from these studies should best be viewed as providing inconclusive as opposed to negative evidence regarding the health hazards associated with exposures to nonasbestiform elongated mineral particles" (NIOSH, 2009, p. 27). This conclusion is judged by the committee to be appropriate. To be useful for causal inference, epidemiological studies require sufficient data on the relevant exposures, health outcomes, and confounding factors. Unfortunately, sufficient data on exposures, outcomes, and confounders do not appear to be available for any of the three U.S. populations. Information or research needs on the potential for synergistic interactions between smoking and elongate mineral particle exposure should be detailed.

The section further concludes that additional studies of these three populations would need improved characterization of exposures to elongate mineral particles, diagnosis of mesothelioma, information on smoking, and information about exposures in other employment; additional studies should be attempted only if "these improvements are deemed feasible" (NIOSH, 2009, p. 27). The committee agrees with this conclusion. Although improved exposure assessment may be possible through reanalysis of archived samples from the three mining sources, it is unclear that improved information on smoking and other employment can be obtained for the New York talc and the Homestake mining populations. Perhaps adequate additional information on mesothelioma diagnosis, smoking, and other employment can be obtained through the ongoing study of the Minnesota taconite-exposed population.

The committee agrees with the Roadmap's assessment of the results of the epidemiological studies on elongate mineral particles as inconclusive.

Gaps in the Roadmap and Research Directions

The epidemiological studies discussed in the Roadmap reflect NIOSH's concern with the potential toxicity of elongate mineral particles, and the committee appreciates this concern. The Roadmap however, as currently titled and configured, is intended to outline a research framework for asbestos as well as other elongate mineral particles. In this light, attention to epidemiological studies of workers and nonworkers exposed to vermiculite from the mine in Libby, Montana, is important. NIOSH investigators have been involved in the study of Libby miners and millers for many years (Amandus and Wheeler, 1987; Sullivan, 2007). Because the amphiboles in the Libby ore have been recently reclassified using 1997 IMA amphibole nomenclature to be predominantly winchite and richerite rather than tremolite, it behooves the Roadmap to specify the ongoing research efforts to better understand the exposure-response relationships for various health outcomes (pleural plaques, pulmonary fibrosis, mesothelioma, lung cancer) among both workers and residents. The risk of asbestosis from exposure to elongate mineral particles in nonoccupational settings has not been studied adequately. Significant excess mortality from nonmalignant respiratory disease has been reported by NIOSH among Libby workers with relatively low cumulative lifetime exposures (i.e., at a level allowable by the current OSHA standard over a 45-year working life) (Sullivan, 2007). Such an exposure-response is striking and deserves further investigation. In addition to discussions of occupational exposures, further attention to environmental exposures is needed in keeping with the goal of setting out a research plan that could be used by multiple federal agencies and other organizations to address the range of potential exposures. In examining the impact of environmental exposures it will be important for researchers to explore the effects of childhood exposures as well as exposures in other potentially vulnerable populations.

Further, the document discusses only U.S. epidemiological studies. Multiple international studies of exposure to amphibole particles have not been included. While the committee understands that the Roadmap was not intended to be a comprehensive review of the asbestos epidemiological literature, some attention to these studies seems relevant for planning future research on the health effects of exposure to elongate mineral particles. Several studies have shown risk of pleural plaques and/or mesothelioma to be associated with exposure to amphibole particles in either soil or whitewash derived from soil in some Mediterranean countries and in New Caledonia (Sakellariou et al., 1996; Luce et al.,

2000, 2004; Senyiğit et al., 2000; Menvielle et al., 2003). It is important to determine to what extent it is possible to extrapolate from exposures and health outcomes recognized in these studies to populations with occupational exposures.

Scientific Rationale and Research Directions

As noted in discussions in Chapter 2, efforts are needed to clarify the goals of the roadmap and to lay out the research hypotheses. The Roadmap states that "research is needed to assess and quantify potential human health risks associated with occupational exposures to other mineral fibers and elongated mineral particles, as well as to better understand and quantify the epidemiology of asbestos-related diseases using more refined indices of exposure" (NIOSH, 2009, p. 76). The committee agrees with both aspects of this statement.

The Roadmap recommends that "it would be reasonable to thoroughly review, assess, and summarize the available information on asbestiform amphiboles that have not been commercially exploited as asbestos" (NIOSH, 2009, p.77). The committee agrees that such a review could be informative. The Roadmap specifically indicates that it is not meant to be a comprehensive review of the scientific literature. However, such a review (with the literature search methodology thoroughly detailed) would provide NIOSH with a foundation on which to build a focused research program by identifying specific data gaps that are relevant to worker protection as well as potential opportunities for collaboration with partners in the United States (e.g., EPA, Agency for Toxic Substances and Disease Registry [ATSDR]) regarding issues in Libby, Montana, and in other countries where populations have been exposed to amphiboles that have not been commercially exploited.

The Roadmap also notes the need to determine whether elongate amphibole particles pose a risk to human health and recommends that an expert panel be assembled to evaluate whether the existing epidemiological evidence could support development of a likely maximum risk estimate associated with exposure to these elongate mineral particles. Based on the review of the epidemiological literature contained in this document, it does not appear that the epidemiological evidence is sufficiently robust for such an endeavor.

Section 2.3.2 of the Roadmap briefly discusses the possibility of using new tools for the diagnosis of asbestos-related health effects at earlier stages of disease such as "modern medical pulmonary imaging tech-

niques" (positron emission tomography [PET] scanning is specifically mentioned) or "bioassays of circulating levels of cytokines or other biochemical factors associated with disease processes" (NIOSH, 2009, p. 78). The committee notes that although the development of sensitive bioassays for intermediate end points on the pathways from exposure to asbestos and other elongate mineral particles to pulmonary fibrosis, lung cancer, and mesothelioma is a laudable research goal, the application of such bioassays to medical surveillance of exposed workers would require a major and lengthy validation effort given the long latency of these health outcomes. Research is needed on radiographic changes induced by elongate mineral particles other than asbestos to determine if these differ from asbestos-induced changes. Because chest computed tomography (CT) scanning is a better tool than the standard chest X-ray to detect fiber-induced change, it would play a major role in such research.

Modern chest imaging techniques such as high-resolution CT or PET scanning are not likely to be useful in medical surveillance of asbestos- or other related disease in the near term due to the level of radiation exposure, lack of portable equipment, and expense. More details are needed in the Roadmap on NIOSH's effort to advance the International Labour Organization's (ILO's) pneumoconiosis radiographic classification scheme and the NIOSH B-reader certification program into the modern era of digital chest radiographic imaging. This effort is vitally important to the ability to sustain asbestos medical surveillance programs as well as conduct epidemiological research in populations exposed to asbestos or other elongate mineral particles. The committee encourages NIOSH to continue to support its program to develop digital images of the ILO standard films and software to project these images correctly.

The Roadmap discusses the possibility of conducting new studies of (1) worker populations exposed to amphibole cleavage fragments such as the New York talc and Minnesota taconite miners and millers; (2) populations such as Libby workers and residents incidentally exposed to a range of mineral particles from mines; (3) populations exposed to less well-studied elongate mineral particles such as wollastonite and attapulgite; and (4) meta-analyses of data from previous studies of populations exposed to mineral particles with various attributes (NIOSH, 2009). The section specifically lists criteria for selecting and prioritizing such studies, including adequacy of exposure information and work histories, sufficiency of latency and sample size, and availability of data on potential confounding factors such as cigarette smoking. The committee agrees that these criteria should be considered before any new epidemiological

study of an exposed population is begun. It is recommended that priority be given to epidemiological studies that will contribute to better understanding of elongate mineral particle characteristics that determine toxicity and to ensuring that rigorous mineralogical characteristics are established. Research should include identifying biomarkers of toxicity that can be studied in human populations as has been discussed at a recent expert panel meeting held by ATSDR (ATSDR, 2008).

Further, the Roadmap states that opportunities for epidemiological studies of workers exposed to asbestos and the other elongate mineral particles are present in other countries. As noted above, the committee urges more discussion of these opportunities in the Roadmap.

EXPOSURE ASSESSMENT

Exposure assessment issues are cross-cutting and are centrally related to all components of the Roadmap. Exposure assessment encompasses issues associated with sampling strategy, exposure characterization, and air sampling and analysis. Issues associated with sampling and analysis are described in the background and the third strategic goal of the Roadmap, while exposure characterization is mentioned only superficially under objective one of the second research goal (see Box 2-1).

Exposure Characterization

The Roadmap contains a thorough discussion of issues associated with sample analytical techniques. There is also recognition of the importance of developing and employing comprehensive sampling strategies to characterize exposures that comprise more than one type of mineral particle (mixed exposures). There is tremendous value in performing comprehensive exposure characterizations in workplaces with mixed exposures regardless of the suitability of these workplaces for health effect studies. Detailed exposure characterizations should be multidimensional and focus on spatial and temporal variability in elongate mineral particle number, size distribution, and other physical and chemical characteristics. The exposure characterization should go beyond analyzing or reanalyzing previously collected samples. Sampling should be task- or activity-based with sufficient power to provide statistically valid estimates of exposure, a detailed description of important physical and

chemical properties, and key exposure determinants. In the review section of the Roadmap the need for such an assessment is recognized: "these initial efforts should be supplemented with efforts to systematically identify, sample, and characterize elongated mineral particle exposures throughout U.S. industry" (NIOSH, 2009, p. 76). Roadmap section 2.3.1 recognizes the need to conduct such an assessment. These data will be important for designing, conducting, and interpreting epidemiological and toxicological studies.

Bulk samples of airborne material from selected well-characterized workplaces can be collected as reference samples to be included in the national repository of asbestos and related minerals only after rigorous mineralogical characterization. Attention should be paid to conducting source characterization studies in order to link sources of elongate mineral particles associated with ambient and/or nonoccupational exposure. Similar tools used for bulk-sample characterization in the workplace can also be applied to identifying sources associated with environmental exposures.

Sampling and Analysis

The review of current issues in the Roadmap covers the methods of sampling and analysis for standardized industrial hygiene surveys (e.g., PCM), analytical methods for research, and a short section on differential counting and other proposed methods. One of the strategic goals of the Roadmap is to "develop improved sampling and analytical methods for asbestos fibers and other elongated mineral particles" (NIOSH, 2009, p. 65). Five specific areas of research are listed:

1. Reduce the inter-operator and inter-laboratory variability of the current analytical methods used for asbestos.
2. Develop analytical methods with improved sensitivity to visualize thinner elongate mineral particles to ensure a more complete evaluation of airborne exposures.
3. Develop a practical analytical method for air samples to differentiate between asbestos exposures and exposures to nonasbestiform elongate mineral analogs.
4. Develop analytical methods to assess the durability of elongate mineral particles.

5. Develop and validate size-selective sampling methods for elongate mineral particles (NIOSH, 2009, p. 65).

A more comprehensive review of all microscopy methods, including SEM, for counting should be presented in the Roadmap's review of current issues. Modern SEM holds promise as an analytical tool and, as a result, the discussion of SEM capabilities should be expanded. There is little discussion of the variability associated with asbestos counting in the section of the Roadmap that reviews current issues; yet this topic is one of the priority research areas. Additional discussion of this issue will help to justify its importance as a research priority.

Section 1.7 of the Roadmap discusses the use of analytical methods for industrial hygiene surveys as separate from analytical methods for research. The discussion focuses on integrating the use of optical microscopy methods for surveys and electron microscopy for research. The value of maintaining this distinction needs to be reconsidered. The use of drastically different exposure assessment tools for these two cases will magnify uncertainty about exposure and risk. Phase contrast microscopy methods have been used for more than 40 years. Many of the research gaps identified in the Roadmap and in this report are the result of inherent weaknesses of PCM. Advancement of our understanding of the risk associated with elongate mineral particles will not be achieved until we move aggressively to develop new techniques and employ suitable methods (e.g., PLM) already available. The Roadmap and its proposed research provide an important opportunity to make this case. The limitations of electron microscopy mentioned in the Roadmap (Section 2.4) should not be used as an excuse to maintain the status quo. Electron microscopy methods are used routinely for environmental analysis. In addition, occupational hygienists routinely collect samples that require sophisticated analyses that take days to weeks to turnaround. These limitations seem like a reasonable trade-off. Another way to look at the difference between a routine assessment tool and a research tool is that a routine assessment is less comprehensive, not an inferior method.

The document presents a good case for why PCM is an inadequate tool for elongate mineral particle exposure assessment yet falls short of recommending that it be replaced with PLM and electron microscopy techniques. PCM does not provide the detailed exposure characterization needed to conduct the complex risk assessments described in the Roadmap. Research by its nature drives the development of new technology. The Roadmap focuses to too great an extent on current costs and time

delays associated with electron microscopy methods. As noted on page 82, "in some workplace situations, such as in construction, increases in the time needed to analyze samples and identify elongated mineral particles could potentially delay the implementation of appropriate control measures to reduce exposures." The discussion should rather be focused on research to develop new tools.

The committee believes that the Roadmap should place a high priority on developing new electron microscopy-based methods and a lower priority on improving PCM. The Roadmap should also include a recommendation that research be conducted to relate old methods to new methods to maintain a direct link to information determined using PCM.

The Roadmap also needs to emphasize the importance of integrating the development of new and/or improved sampling and analytical methods in parallel with toxicological and epidemiological research. Since sampling and analytical methods are designed for risk assessment purposes, their development should be driven by hazard assessment information produced in these studies. For example, it does not make sense to develop solubility-based methods until toxicology studies better assess the boundaries of dissolution that are risk-based.

The Roadmap emphasizes the need to characterize thoracic elongate mineral particle deposition. The rationale for this choice must be presented. It is not clear that a thoracic-based metric is appropriate for all disease outcomes. Is a respirable elongate mineral particle metric more appropriate for mesothelioma risk? It is conceivable that different size-based exposure metrics may be appropriate for different health outcomes.

Regardless of method used, more discussion of the statistics of elongate mineral particle counting and counting quality control is needed. The advancement of science with respect to elongate mineral particle exposure assessment requires nationally recognized quality control programs. Expectations should be changed so that each count is presented as an estimate with a range of expected variability (see below).

The Roadmap should include a specific recommendation that automated counting methods be explored and compared to human counting with respect to precision and accuracy.

Counting Strategies

In reviewing the literature on asbestos counting, there appears to be considerable variability in counts from analyst to analyst within a given laboratory as well as between laboratories. As a consequence, a new observed count from a particular analyst from a particular laboratory may deviate considerably from the true value. In an effort to provide a connection between observed and true counts and characterize the uncertainty in the true count, Dulal Bhaumik and colleagues have extended the ideas of Gibbons and Bhaumik (2001) and Bhaumik and Gibbons (2005) to the case of a Poisson random variable, which is the appropriate distribution for rare-event count data. Appendix B provides a brief sketch of one potential methodology for addressing the variability as well as an illustration of the application of this methodology. Statisticians who are also familiar with exposure data analysis should be actively involved in addressing some of the challenging data analysis issues in this area of research.

Additional Statistical Issues

There is considerable discussion in the NIOSH Roadmap on the effect of fiber counts and fiber dimensions on exposure risk. Thus the distribution of these quantities is of obvious interest. For exposure assessment, it is important to characterize the joint distribution of fiber length and width for a given material. Several researchers (see Cheng, 1986; Baron, 2001; Cheng et al., 2006) have investigated this problem and noticed that fiber length and width typically have a bivariate lognormal distribution. Data analysis based on the bivariate lognormal distribution can be complicated, depending on the parameter or parameters for which inference is desired. Likelihood based results for testing or constructing confidence intervals for one or more parameters of the distribution often produce undesirable results (e.g., inflated type 1 error rates or low coverage probability) when sample sizes are small. In order to overcome this problem one can explore procedures based on the novel concepts of generalized p-values (for hypothesis testing) and generalized confidence intervals (for computing confidence intervals) for univariate and bivariate lognormal distributions (see Krishnamoorthy and Mathew, 2003; Krishnamoorthy et al., 2006; Bebu and Mathew, 2008). Major advantages of such procedures are that they are accurate and are applicable

to small samples. The concepts of generalized p-values and generalized confidence intervals also provide accurate methodology for comparing two lognormal distributions (for example, to compare the arithmetic means of fiber lengths obtained from two different sites or materials).

The NIOSH Roadmap also addresses the issue of comparing thoracic samplers. To compare thoracic samplers, the OSHA criterion for establishing the equivalence of a sampling device to a reference device requires that "90 percent of the readings of the sampling device should be within plus or minus 25 percent of the readings obtained by the reference device, or within plus or minus 25 percent of the actual airborne chemical concentration." In this context one can use rigorous statistical tests developed by Krishnamoorthy and Mathew (2002) for comparing two samplers, and Krishnamoorthy et al. (2009) for comparing several samplers. The OSHA criterion, or a suitable version of it, appears to be the right criterion to compare thoracic samplers. Traditional approaches for comparison of samplers based on geometric means using t-tests are generally inadequate.

SPECIFIC COMMENTS

In addition to the major issues discussed throughout this chapter, the following paragraphs highlight a few specific suggestions for consideration to improve the Roadmap.

Some minor changes to the front matter might help readers understand the full context of the report and the iterations it has gone through. This could include detailing the specific drafts and dates of the drafts and pointing out that the peer reviewers listed on page xii reviewed the February 2007 draft. A timeline (see Table 2-1 of this report) may be helpful since the Roadmap has undergone several iterations. The committee also believes that the goal of the document should be reflected in the title and the cover. If the research is intended to address all elongate mineral particles, not just asbestos or its analogs, a different title might be appropriate. If the Roadmap is expanded at some point to include a larger range of elongate particles, more generally (whether minerals, man-made materials [e.g., ceramics], organic materials [e.g., wool and cotton], or others), the title should reflect that intent. Given the broad spectrum of elongate mineral particles addressed in the Roadmap, the cover photographs and design should also reflect this wide range of particles with

captions that are informative regarding the scale bars, labels, and other information.

Care should be taken to ensure that descriptions of studies written prior to the release of the Roadmap use the same terminology used in the original article. If necessary, a note could be added to clarify or update the terminology. Because *elongate mineral particle* is a broad descriptive term and not a rigorous mineralogical term, the preference when feasible is for providing the correct mineral names.

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4

Recommendations and Next Steps

Throughout this report, the committee notes the value of the NIOSH Roadmap in bringing together a substantial body of research across several varying disciplines. In assessing the draft Roadmap and making suggestions for improvement, the committee provides the following findings and recommendations toward ensuring that research is focused on addressing the potential for health concerns of workers and communities exposed to asbestos and the other elongate mineral particles. The report concludes with the committee's thoughts on next steps for facilitating a sustained effort to implement and disseminate the findings of the research.

FINDINGS

In its statement of task the committee was charged with providing a review of the Roadmap document and answering five specific questions detailed below. The text of the previous three chapters discusses the issues presented in the task and provides the specific details that form the basis for the findings, each of which answers one of the task questions.

Statement of Task Question 1: Is the document consistent with the state of scientific understanding of the toxicity, occupational exposures, epidemiology, and sampling or analytical methods? Should any of the content of this section be modified, based on the state of scientific understanding of these issues? Are there any significant studies that have been overlooked?

Finding 1: The NIOSH Roadmap is generally consistent with the state of scientific understanding of the toxicity, occupational exposures, epidemiology, and sampling or analytical methods. The committee identified several areas that could be strengthened and references those areas in the narrative and in the committee recommendations. The Roadmap would be made more coherent and useful if it included or refined four key components: vision or purpose, rationale, goals, and framework (systematic plan for conducting the research).

Statement of Task Question 2: Does the document clearly and adequately explain the scientific rationale for research on the mineralogy, morphology, dimensions, and surface characteristics of elongate mineral particles, and is its treatment of this issue consistent with the state of scientific understanding of the toxicity, occupational exposures, and epidemiology of elongate mineral particles?

Finding 2: The Roadmap explains the scientific rationale for research on the mineralogy, morphology, dimensions, and surface characteristics of elongate mineral particles. This is presented primarily through discussions of toxicological studies of asbestos and of synthetic fibers that provide the background on why research is needed to examine mineral particle characteristics and their impact on toxicity. However, the mineralogical discussions were found lacking in many areas. Adding more information on the occupational and environmental health rationale for research in this area would be helpful, including available data on the types of occupations and environmental situations likely to result in exposure to more specific types of elongate mineral particles. As noted in its recommendations, the committee urges that the Roadmap include a clear statement of the overarching vision for the research. The committee also believes that since the term *elongate mineral particle* covers a broad range of mineral particles of interest in this research, its use should be limited to

research efforts and emphasizes that this term is not a rigorous mineralogical term.

Statement of Task Question 3: Does the document discuss the most significant issues regarding mineralogy, morphology, dimensions, and surface characteristics of elongate mineral particles? Should any of the discussed issues be omitted or revised, based on the state of scientific understanding of these issues? Are there any significant issues that should be added?

Finding 3: The NIOSH Roadmap provides a reasonable discussion of some of the significant issues regarding mineralogy, morphology, dimensions, and surface characteristics of elongate mineral particles as related to their potential to cause disease, but as noted in response to Question 4 below, the committee urges a greater emphasis on the relevant mineralogical research, in particular on mineralogical characterization. The committee notes significant inconsistencies and deficiencies in mineralogical terminology and nomenclature and provides a series of recommendations to clarify and make more rigorous, consistent, and complete the terminology used in the text and the glossary in the Roadmap.

Statement of Task Question 4: Is the research proposed likely to effectively address the most significant issues regarding mineralogy, morphology, dimensions, and surface characteristics of elongate mineral particles? Should any of the discussed research be omitted or revised, based on the state of scientific understanding of these issues? Is there any significant research that should be added?

Finding 4: The research effort proposed is likely to address some of the most significant issues regarding mineralogy, morphology, dimensions, and surface characteristics of elongate mineral particles. However, as noted throughout this report and in its recommendations, the committee calls for more details to be included on mineralogical research, with an emphasis on a systematic approach to characteriza-

tion of the minerals that is integrated in a meaningful way into toxicological and other studies to better understand the relative disease-causing potential of a range of elongate mineral particles relevant to human exposures. This effort is part of a consistent strategy for characterizing and testing the relative toxicities of elongate mineral particles and mixtures. Exploration of additional opportunities for epidemiological research is needed as well as careful examination of the exposure assessment methodologies. The effort is likely to be more successful if it involves interdisciplinary collaboration and integration.

Statement of Task Question 5: Was the process that was used to develop and revise the document and that is described in the Foreword, including the mechanisms for input from the scientific and stakeholder communities, appropriate from a scientific perspective?

Finding 5: The process used by NIOSH to develop and revise the document that is described in the Foreword was, in the opinion of the committee, generally appropriate in being open and transparent with multiple opportunities for input into the Roadmap document. The process would have benefited from greater involvement of the mineralogical community throughout its formulation. An interdisciplinary approach may have been better applied in the development process.

RECOMMENDATIONS

Clarify Roadmap Structure and Vision

Because the NIOSH Roadmap brings together a great deal of information and a wealth of ideas on future directions for research, it is necessary for the document to have a clearly stated vision and rationale. The details of the Roadmap can all too easily overtake the view of the larger objective, and therefore the committee urges that the vision and rationale be clearly laid out in the early part of the Roadmap. Further, it is the

committee's hope that a more systematic and tiered approach to the research agenda will allow research to be conducted in a manner that will answer the questions regarding which physical and chemical characteristics of elongate mineral particles are primary determinants of toxicity to humans, thus allowing unambiguous identification of specific types of mineral particles that would be of concern to human health.

Recommendation 1 Clarify the Vision and Rationale
NIOSH should revise the Roadmap to clearly state the overarching vision and rationale for the research program.

- **The overarching vision should point toward research that will differentiate effects from exposure to a range of elongate mineral particles and help determine the influence of size, shape, and other physical and chemical characteristics of these particles on human health. This research would identify which elongate mineral particles, or what characteristics of those particles, should be included in recommendations to protect the public and workers from hazardous occupational and environmental exposures.**
- **The rationale for the Roadmap should clearly articulate the influence that ongoing and future research can have on improving public and occupational health.**
- **A clearer vision and purpose would help strengthen the goals that the research is intended to support. The research should be prioritized as to the hazard and exposure.**

Recommendation 2 Include Key Components
NIOSH should ensure that four key components are included or refined in the Roadmap: (1) vision, (2) rationale, (3) goals, and (4) framework.

Improve Terminology

As discussed in Chapter 3, terminology and nomenclature have been an ongoing challenge for this area of research. Because of the ambiguous and confusing terms for asbestos and the other mineral particles used in the past, it is important for the Roadmap to place strong emphasis on

specificity in its use of terminology and nomenclature and on providing references to definitions from standard reference texts in each field. The Roadmap needs definitions for all technical terms, given the interdisciplinary nature of the research and the need to maintain consistency across disciplines.

The umbrella term *elongate mineral particles* provides an important starting point for discussions on the broad range of mineral particles under investigation. However, because considerable uncertainty remains regarding the range of potential toxicities within the spectrum of elongate mineral particles, it is the committee's view that at this time the term *elongate mineral particles* should not be used for regulatory purposes.

Recommendation 3 Improve Terminology

NIOSH should revise its Roadmap with careful attention to consistency in the use of nomenclature and terminology. The goal is that authoritative terminology should permeate research and regulatory efforts, specifically:

- **For research purposes, the term *elongate mineral particles* is useful for encompassing a broad category of mineral particles of a certain dimension and aspect ratio; more specific mineralogical terminology would be needed for regulatory purposes;**
- **Revisions should be made to the Roadmap glossary using accepted mineralogical terminology or nomenclature from the current American Geological Institute's *Glossary of Geology* or other standard texts; citations should be provided for each definition; nonstandard terms should be removed from the glossary and the main text; and**
- **Terminology used in sections referring to epidemiology and toxicology should also use definitions from current standard texts and be included in the glossary with citations.**

Strengthen the Emphasis on Mineralogy

The Roadmap outlines a set of studies to improve knowledge on the potential health effects of elongate mineral particles and the ways in which human exposures could best be studied. A key piece of this research plan is the development of well-characterized reference mineral samples that could then be incorporated in toxicological studies to assess the variability in the toxicity of different types of elongate mineral particles. The identification, classification, and characterization of unknown mineral particles from workplace or environmental exposures require knowledge of and comparison to similar, well-characterized mineral particles and associated geological locales. Similarly, toxicological experiments require well-characterized reference mineral samples to allow systematic intra- and interlaboratory comparisons of results. While the Roadmap notes the need for standardized reference minerals, the committee believes that there is a need for a more detailed approach for developing a central repository of these samples. Priorities for the repository should focus on those minerals with the greatest potential for human exposures. Although the epidemiological and toxicological discussions in the Roadmap were generally thorough, greater depth and rigor is needed in the mineralogical discussions.

Recommendation 4 Strengthen the Emphasis on Mineralogical Research
NIOSH should revise the Roadmap to give greater attention to the mineralogical foundations of the proposed research. Discussions of mineralogy in the Roadmap should be strengthened by incorporating current understanding in this field using accepted terminology and by proposing research on the fundamental mineralogical properties relevant to toxicology, epidemiology, and exposure assessment. Specifically, mineralogical research is needed on physical and chemical properties, biopersistence, and mineral source characterization, including the development of standard sets of tests and methodologies.

Recommendation 5 Develop a Reference Mineral Repository
NIOSH should work with other federal agencies and organizations to develop a repository of well-characterized and standardized reference minerals for use in research.

Focus the Research Efforts

NIOSH has put together a comprehensive and broad-based research Roadmap that could be improved through further emphasis on implementing a systematic and interdisciplinary approach to the outlined research. Improved efforts on characterizing the elongate mineral particles used in toxicological research could go a long way toward ensuring that study results can be compared. Additionally, using a tiered systematic process to study the toxicity of various types of mineral particles, as outlined in Chapter 3, would assist in bringing clarity to the range of toxicities and help to identify any specific mineralogical properties of concern to human health. A wider focus in epidemiological studies and new approaches to exposure assessment will also be of great benefit in addressing these issues.

Recommendation 6 Emphasize Interdisciplinary Efforts
NIOSH should revise the Roadmap to emphasize the need for collaboration and integration of research among the mineralogical, toxicological, epidemiological, and exposure assessment disciplines.

Recommendation 7 Develop a Systematic Strategy for the Toxicological Assessment of Elongate Mineral Particles
NIOSH should revise the Roadmap to describe a systematic tiered strategy for characterizing and testing the relative toxicities of elongate mineral particles and/or their mixtures. The strategy should include the following:

- **Characterizing the chemical and physical properties of the elongate mineral particles beginning with petrographic analysis and proceeding through X-ray diffraction, transmission and scanning electron microscopy, and other techniques; and**
- **Using tiered panels of in vitro and in vivo assays of increasing complexity to identify and characterize biological responses and categorize the potential hazards.**

Recommendation 8 Emphasize Additional Research Areas
NIOSH should revise the Roadmap to include an emphasis on the following:

- **Incorporating petrographic analysis and developing new exposure assessment tools using electron microscopy methods that are mineralogically and toxicologically relevant and that minimize reliance on phase contrast microscopy methods;**
- **Toxicological mechanisms of action of a range of well-characterized elongate mineral particles with attention to early biomarkers of human health effects;**
- **Additional opportunities for epidemiological research including studies of Libby, Montana, worker and resident populations, as well as cohorts exposed to elongate mineral particles in other countries; and**
- **Statistical methods for addressing analytical variability and determining the relationships between mineralogical and exposure variables and health outcomes.**

STEPS TOWARD A RESEARCH STRATEGY

As discussed in Chapter 2, a research roadmap is one component of a larger research strategy. The final section of the NIOSH Roadmap notes that the research agenda "will require a substantial investment of time, scientific talent, and resources by NIOSH and its partners to formulate research programs and prioritize research projects to achieve the proposed goals" (NIOSH, 2009, p. 92). The committee urges NIOSH to continue its work with other federal agencies (e.g., the U.S. Environmental Protection Agency, the National Institute of Environmental Health Sciences, the U.S. Geological Survey, the Occupational Safety and Health Administration, the Mine Safety and Health Administration, and the Agency for Toxic Substances and Disease Registry) and private sector and nonprofit organizations with a focus on developing a research strategy that details the resources, priorities, responsibilities, and commitments needed to accomplish and evaluate this research effort. Many of the issues that require additional research to better understand the relative disease-causing potential of various types of elongate mineral particles are common both to the fields of occupational health, as pertaining

to work-related exposures, and environmental health, as related to exposure of the general public. Too often research programs present broad goals for important research but do not back them up with a concrete and realistic plan for accomplishing the goals.

Such a strategy might contain, in addition to the research framework and goals elaborated in the Roadmap, the following elements:

- An interdisciplinary system for prioritizing research activities to ensure maximum efficiency in an environment in which not everything possible can reasonably be undertaken at once and multiple disciplines need to work together to determine the priorities;
- An approximation of the resources needed to carry out high- and middle-priority efforts; and
- A plan for review, evaluation, and accountability for those receiving support for research contained in the Roadmap.

As NIOSH and other partners move forward in implementing the Roadmap, discussions are needed on successful models of establishing effective partnerships and management of research efforts to ensure a coordinated approach to address specific information gaps.

REFERENCE

NIOSH (National Institute for Occupational Safety and Health). 2009. *Revised draft. NIOSH current intelligence bulletin. Asbestos fibers and other elongated mineral particles: State of the science and roadmap for research*. *January 2009*. Department of Health and Human Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health. http://www.cdc.gov/niosh/docket/pdfs/NIOSH-099b/099B-040109AsbestosNAReviewDoc.pdf (accessed September 18, 2009).

A

Meeting Agendas

INSTITUTE OF MEDICINE
NATIONAL RESEARCH COUNCIL

Committee for the Review of the NIOSH Research Roadmap
on Asbestos and Other Mineral Fibers
First Meeting
January 15–16, 2009
Keck Center of the National Academies
500 5th Street, N.W.
Room 105
Washington, DC

AGENDA

Goals for the First Committee Meeting:

1. **Introduce committee members to each other and to the National Academies**
2. **Conduct the bias and conflict-of-interest discussion**
3. **Hold open session with representatives of the sponsoring agency and other speakers to understand the background and context for this study**
4. **Agree on study charge and approach to the task**
5. **Plan workshop**
6. **Discuss a framework for conducting the study; develop report outline and work plan**

Thursday, January 15, 2009 — Open Session

11:00 a.m. **Welcome and Introductions**
Alan Nelson, Committee Chair

Sponsor's Charge to the Committee and Background Information
Lewis Wade, Senior Science Advisor, Office of the Director, National Institute for Occupational Safety and Health (NIOSH)
David Weissman, Director, NIOSH Division of Respiratory Disease Studies
Paul Middendorf, Senior Scientist, NIOSH Office of the Director

Discussion

12:30 p.m. **Lunch**

1:15 **Overview of the Major Issues and Context of the Study**

1:15–1:30 Mineralogy—Terminology
Greg Meeker, U.S. Geological Survey (USGS)

1:30–1:45 Mineralogy—Analytics
Ann Wylie, University of Maryland

1:45–2:15 Discussion

2:15–2:30 Toxicology
Morton Lippmann, New York University

2:30–2:45 Epidemiology
Jonathan Samet, University of Southern California (via phone)

2:45–3:30 Discussion

3:30 **Adjourn Open Session**

INSTITUTE OF MEDICINE
NATIONAL RESEARCH COUNCIL

Workshop on the NIOSH Research Roadmap on Asbestos Fibers and Other Elongated Mineral Particles

Second Meeting

Monday, March 30, 2009
Lecture Room
National Academy of Sciences
2100 C Street, N.W.
Washington, DC

AGENDA

Questions for Discussion:

- Is the NIOSH Research Roadmap document consistent with the state of scientific understanding of the relevant toxicity, occupational exposures, epidemiology, and sampling or analytical methods?
- What are the future research directions needed to clarify the relationship between health effects and the physiochemical characteristics (e.g., mineralogy, morphology, dimensions, surface properties) of elongated mineral particles? What changes are needed in the Roadmap document to address these research directions?

8:00 a.m. **Welcome**
Alan Nelson, Committee Chair

8:15 **Panel 1: Toxicology**
Moderator, Thomas Hei
8:15–8:45 Panel Presentations
Thomas Hesterberg, Navistar
Brooke Mossman, University of Vermont
Ron Dodson, Dodson Environmental Consulting, Inc.

8:45–9:30 Discussion

9:30 a.m. **Panel 2: Mineralogy**
Moderator, Karin Hoal
9:30–10:00 Panel Presentations
James Webber, Wadsworth Center, New York State Department of Health
Geoffrey Plumlee, U.S. Geological Survey
Mickey Gunter, University of Idaho

10:00–10:45 Discussion

10:45 **Break**

11:00 **Panel 3: Epidemiology and Exposure Assessment**
Moderator, Patrick Breysse
11:00–11:30 Panel Presentations
Laura Welch, Center for Construction Research and Training
John Cherrie, Institute of Occupational Medicine
James Weeks, Johns Hopkins University

11:30–12:15 Discussion

12:15 p.m. **Lunch**

1:00 **Panel 4: Perspectives from Federal Agencies**
Moderator, Robert Gibbons
1:00–1:30 Panel Presentations
Mark Wesolowski, Mine Safety and Health Administration (MSHA)
Danielle DeVoney, Environmental Protection Agency (EPA)
Dan Crane, Occupational Safety and Health Administration (OSHA)

1:30–2:15 Discussion

2:15 **Public Comment—Registered Speakers**
(3 minutes per speaker)
Moderator, Alan Nelson

Mark Ellis, Industrial Minerals Association North America
Randy Rabinowitz, American Association of Justice
William Ford, National Stone, Sand & Gravel Association
Jonathan Ruckdeschel, Ruckdeschel Law Firm
Frank Ehrenfeld, International Asbestos Testing Laboratories
Noor Jehan, University of Peshawa
Roger McClellan, Toxicology and Human Health Risk Analysis
Adel Abrams, American Society of Safety Engineers

3:30 **Adjourn Open Session**

INSTITUTE OF MEDICINE
NATIONAL RESEARCH COUNCIL

Committee for the Review of the NIOSH Research Roadmap on Asbestos and Other Elongated Mineral Particles
Third Meeting
May 28–29, 2009
The Arnold and Mabel Beckman Center
100 Academy Way
Irvine, California

AGENDA

Goals for the Third Committee Meeting:

1. **Discuss draft report text and identify areas for further revisions**
2. **Decide on the committee's conclusions and recommendations**
3. **Discuss steps to complete the report; discuss report review**

CLOSED SESSION

B

Counting Strategies[1]

In reviewing the literature on asbestos fiber counting, there appears to be considerable variability in counts from analyst to analyst within a given laboratory as well as between laboratories. As a consequence, a new observed count from a particular analyst in a particular laboratory may have considerable deviation from the true value. In an effort to provide a connection between observed and true counts and to characterize the uncertainty in the true count, Dulal Bhaumik and colleagues have extended the ideas of Gibbons and Bhaumik (2001) and Bhaumik and Gibbons (2005) to the case of a Poisson random variable, which is the appropriate distribution for rare-event count data. This appendix provides a brief sketch of a potential methodology for addressing the variability and includes an illustration of this methodology using data from the New York state inter-laboratory asbestos testing program.

POTENTIAL METHODOLOGY

Let y_{ij} be the jth observation from the ith laboratory, $j = 1, \ldots, n_i$, and $i = 1, \ldots, k$. We assume that the count variable y_{ij} follows a Poisson distribution with parameter λ_{ij}. To model the interlaboratory variability,

[1]We would like to thank Professor Dulal K. Bhaumik of the University of Illinois at Chicago and his student Yoonsang Kim for help with statistical derivations and analyses, and Dr. James Webber of the Wadsworth Center of the New York State Department of Health for providing the data and helpful comments on an earlier draft. We would also like to thank the statistical reviewer for making several helpful comments and helping us expand the scope of the statistical discussion.

we assume a mixed-effect Poisson regression model with random parameters β_0 and β_1. We further assume that the joint distribution of β_0 and β_1 is bivariate normal, with mean vector γ_0 and covariance matrix Σ. Hence, regarding the complete distributions of y_{ij}, our assumptions are as follows:

$$y_{ij} \sim P(\lambda_{ij}), \text{ and } \ln(\lambda_{ij}) = \beta_{0i} + \beta_{1i} x_{ij},$$

where β_{0i} and β_{1i} are respectively the random intercept and slope parameters for the *i*th laboratory and x_{ij} is the true count in the *j*th measurement from the *i*th laboratory. Of course, we never know the true count (i.e., x_{ij}), but a reasonable substitute is a consensus estimate based on a series of leading laboratories or analysts.

At this stage, we assume that all of the y_{ij} and the corresponding x_{ij} are known. We estimate the model parameter Σ by the method of marginal maximum likelihood (MML). The resulting estimate of Σ denoted by $\hat{\Sigma}$ is consistent and MML also provides the standard error of $\hat{\Sigma}$. Given MML estimates of the means and covariance matrix, we can obtain empirical Bayes estimates of β_{0i} and β_{1i}, denoted by $\hat{\beta}_{0i}$ and $\hat{\beta}_{1i}$.

Let y_{il} be a new observation from the *i*th laboratory. We do not know the value of the corresponding true observation x_{il}. Our goal is to estimate x_{il} and construct a confidence region for x_{il} using the previous estimates $\hat{\Sigma}$, $\hat{\beta}_{0i}$, and $\hat{\beta}_{1i}$ of Σ, β_{0i}, and β_{1i}, respectively. We follow the likelihood-based procedure to estimate x_{il} (i.e., maximize the likelihood function of y_{il} with respect to x_{il} using $\hat{\Sigma}$, $\hat{\beta}_{0i}$, and $\hat{\beta}_{1i}$). Denote this estimate of x_{il} by $\hat{x}_{il}$. The expression of $\hat{x}_{il}$ is as follows:

$$\hat{x}_{il} = \frac{\ln(y_{il}) - \hat{\beta}_{0i}}{\hat{\beta}_{1i}}. \qquad (1)$$

This estimate is valid provided $y_{il} > 0$. In the case of $y_{il} = 0$ we must set $x_{il} = 0$. Also note that the above estimate of x_{il} becomes nega-

tive if $\ln(y_{ij}) < \hat{\beta}_{i0}$. In such a scenario we also set $x_{il} = 0$. $\hat{x}_{il}$ is asymptotically unbiased for large values of $\mathbf{x}'_{il} \sum \mathbf{x}_{il}$, where $\mathbf{x}'_{il} = (1\ x_{ij})$. The standard errors of $\hat{\beta}_{0i}$ and $\hat{\beta}_{1i}$ are obtained directly via MML. The laboratory-specific estimate of the conditional variance of y_{il} is $\exp(\hat{\beta}_{0i} + \hat{\beta}_{1i} x_{ij})$. Using the Delta method, we obtain the estimate of the variance of $\ln(y_{il})$ as $\exp(-\hat{\beta}_{0i} - \hat{\beta}_{1i} x_{ij})$. Hence an approximate expression for the variance of $\hat{x}_{il}$ is $\exp(\mathbf{x}'_{ij} \sum \mathbf{x}_{ij} / 2) / (SE(\hat{\beta}_{1i}))^2$. Thus, the standard error of $\hat{x}_{il}$ is $\mathrm{SE}(\hat{x}_{il}) = \sqrt{\exp(\mathbf{x}'_{ij} \sum \mathbf{x}_{ij} / 2) / (SE(\hat{\beta}_{1i}))^2}$. Let us denote the 95 percent asymptotic confidence region of x_{il} by $\Re_1(x_{il})$, where

$$\Re_1(x_{il}) = \{x_{il} : -1.96 \le (\hat{x}_{il} - x_{il}) / SE(\hat{x}_{il}) \le 1.96\}. \quad (2)$$

The aforementioned confidence region of x_{il} is based on the assumption that we had samples from the *i*th laboratory and we estimated the laboratory-specific parameters and also estimated $\sum$ borrowing strength from all of the laboratories. However, if the new observation y_{il} comes from an arbitrary new laboratory and the estimates of its parameters are not available, then we should estimate x_{il} globally (i.e., based on the expected values of the laboratory-specific parameters).

Based on these methods, we can now obtain a point estimate of the true number of asbestos fibers in the sample (x_{il}), and a 95 percent confidence region for that true count. There are several useful things that we can do with these quantities. First, we can now always provide an uncertainty interval surrounding our best estimate of the true fiber count. Second, we can determine if the lower confidence limit is greater than zero. If it is, then we can have 95 percent confidence that the true number of asbestos fibers in the sample is greater than 0. Third, we can determine the detection limit, which is the smallest observed count for which the true count is greater than zero. To do this, we begin by setting the true count to zero (i.e., $x_{il} = 0$) and then compute the upper 95 percent prediction limit for the observed *y*. Any observed *y* greater than the prediction limit will indicate that the true count is greater than zero. The

prediction limit for y given $x = 0$ can be computed via simulation using the following expressions of the unconditional mean and variance of y:

$$E(y) = \exp(\gamma_0 + \sigma_{11}/2), \text{ and}$$
$$V(y) = \exp(\gamma_0 + \sigma_{11}/2) + \left[\exp(\gamma_0 + \sigma_{11}/2)\right]\left[\exp(\sigma_{11} - 1)\right].$$

ILLUSTRATION

To illustrate the statistical methodology for inter-laboratory calibration of counts and to obtain a better feel for the magnitude of the variability within and between laboratories, we obtained de-identified data from the New York State inter-laboratory asbestos testing program, which were graciously provided by Dr. James Webber of the Wadsworth Center of the New York State Department of Health. Results based on both transmission electron microscopy (TEM) and phase contrast microscopy (PCM) were analyzed. For TEM, there were a total of 327 samples from 43 laboratories. For PCM there were a total of 9400 airborne asbestos samples analyzed by several hundred laboratories, though participation in a single round ranged from 100 to 150 laboratories. The data were collected as a part of the New York State Environmental Laboratory Approval Program (ELAP) based on the semiannual proficiency testing of laboratories analyzing airborne asbestos, based on the Asbestos Hazard Emergency Response Act (AHERA) criteria and of laboratories analyzing airborne fibers by the NIOSH 7400 method (NIOSH, 1994b). For TEM, our analysis focuses on cummingtonite-grunerite (amosite; AM) counts from 11 rounds. Two additional rounds were not considered because they contained impractically high counts (>6,000 structures/mm^2). (All data are expressed in structures/mm^2.)

In order to apply the previously described methodology based on a mixed-effects Poisson regression model, we must obtain an estimate of true count for each sample. To this end, we used the overall mean count over all of the laboratories that analyzed each sample. In addition to fitting the Poisson regression model, we also used the alternative minimum level described by Gibbons et al. (1997), Zorn et al. (1997) and Gibbons and Coleman (2001), to obtain estimates of the critical level (L_C), detection limit (L_D) and quantification limit (L_Q) for these data (see Currie, 1968, for an excellent review). The L_C is a threshold used to determine whether or not detection has occurred. The L_D is the lowest

level for which there is simultaneous high confidence that: (a) detection will occur if the true value is at the detection limit; (b) there will NOT be detection if the true value is zero. The L_Q is the lowest level at which a specified (estimated) relative standard deviation is achieved, typically 10 percent, 20 percent, or 30 percent.

TEM Analyses

Figure B-1 displays the raw TEM asbestos counts on the y-axis and the mean asbestos counts on the x-axis (i.e., best available estimate of the true count).

Figure B-1 reveals that the absolute variability is proportional to the true (i.e., average) count. This is consistent with a Poisson random variable and can be modeled either via a Poisson regression model or a model that allows for non-constant variability in the calibration function as described by Gibbons and colleagues (1997, 2001). We next fit a mixed-effects Poisson regression model to the TEM AM asbestos data. The model is $\ln(\lambda) = (\gamma_0 + \gamma_1 x) + (u_0 + u_1 x)$ where u has a normal distribution with mean 0 and a variance-covariance matrix Σ. x is the true count divided by 1,000 (done to obtain parameter estimates in a metric of reasonable magnitude for the purpose of interpretation since the model is for the log count as shown above). The parameter estimates, standard errors and tests of significance are displayed in Table B-1.

The term $\Sigma(2,2)$ is the variance of the slopes of the inter-laboratory calibration curves, which reveals a standard deviation of 0.58, which is 58 percent of the mean slope (1.0128) of the calibration curve over all of the 45 laboratories. This is an enormous relative standard deviation, indicating that the laboratories exhibit considerable variability in their individual calibration curves (i.e., differential sensitivity to changing numbers of particles from lab to lab).

Figure B-2 presents empirical Bayes estimates of the individual laboratory calibration functions. Note that the y-axis is in log-scale. Figure B-2 confirms that there is considerable variability in the slopes of the estimated calibration functions.

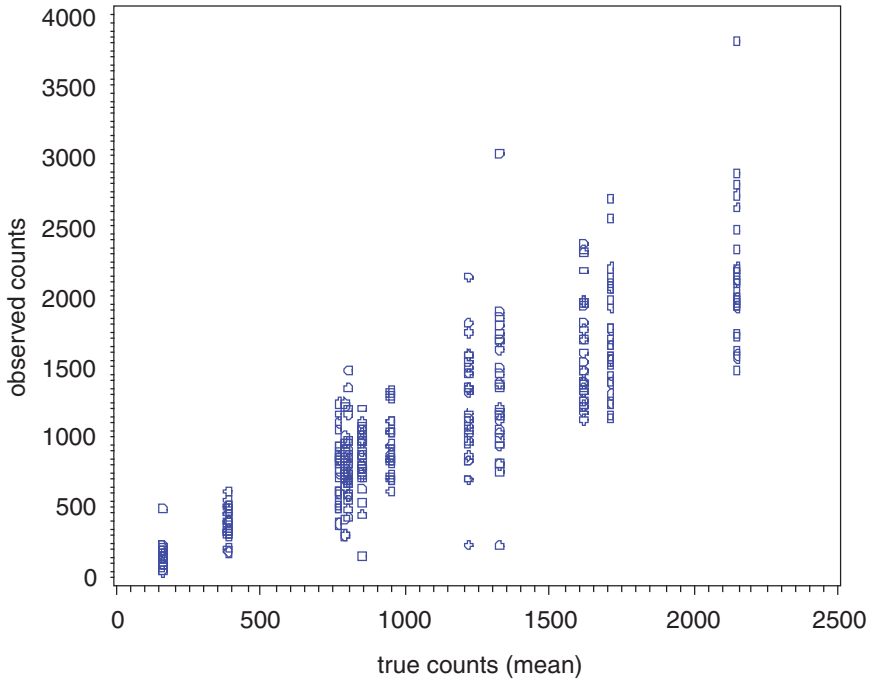

FIGURE B-1 Raw asbestos (AM) counts analyzed by TEM.

TABLE B-1 Marginal Maximum Likelihood Estimates of the Mixed-effects—Poisson Regression Model for TEM Data

Parameters	Estimates	SE	z-value	p-value
γ_0	5.8000	0.0718	80.73	< .0001
γ_1	1.0128	0.0965	10.50	< .0001
$\Sigma(1,1)$	0.1792	0.0416		
$\Sigma(1,2)$	−0.2321	0.0552		
$\Sigma(2,2)$	0.3388	0.0773		

NOTE: SE = standard error.

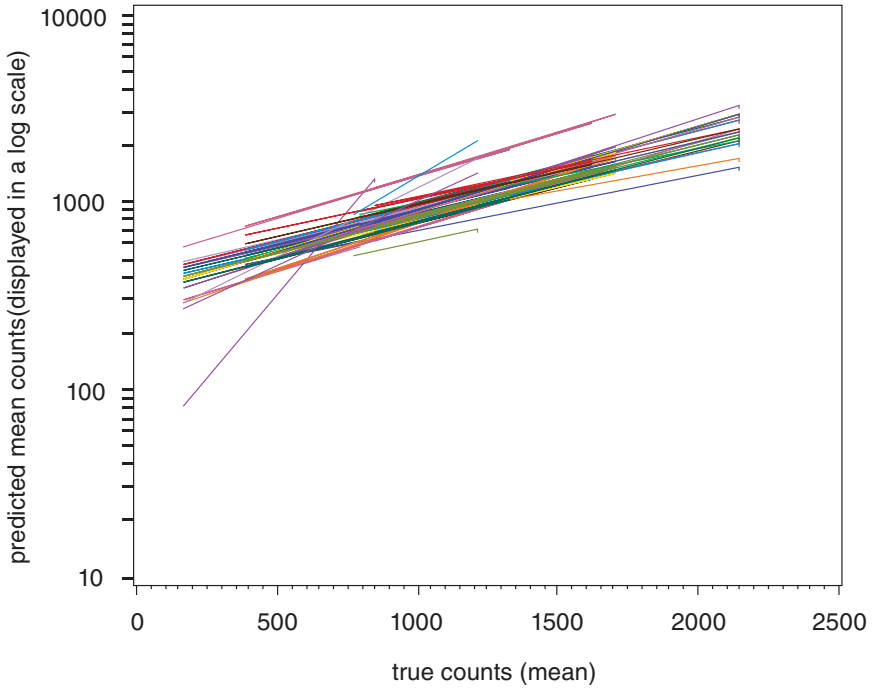

FIGURE B-2 Individual laboratory estimated calibration functions.
NOTE: The *y*-axis is in a log scale with base = 10.

Next, we estimated detection and quantification limits from these data using the AML method described by Gibbons and colleagues (1997). The results are displayed graphically in Figure B-3.

Figure B-3 reveals that the critical level (L_C) is 481 fibers, the detection limit (L_D) is 1335 fibers and the quantification limit (L_Q) is 3003 fibers. At the L_Q, the relative standard deviation is still reasonably large (i.e., 23 percent).

Figure B-4 presents the variance function, for which the best fit was based on the Rocke and Lorenzato Model (Rocke and Lorenzato, 1995) and reveals that the variability increases linearly from 100 to 2,500 fibers.

Finally, Figure B-5 displays a plot of the relationship between average counts and the relative standard deviation (RSD). This figure reveals that considerable uncertainty exists in asbestos counts throughout all of the samples investigated, regardless of the number of fibers. However, the RSD stabilizes at around 20 percent for true concentrations around 2,000.

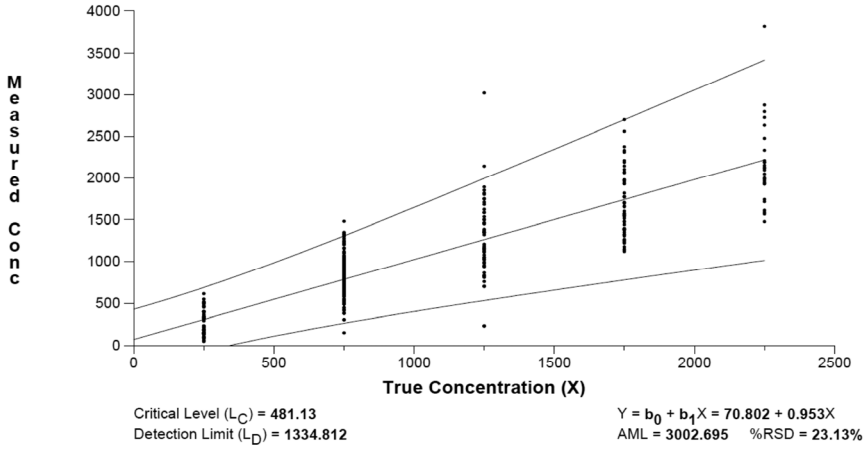

FIGURE B-3 Alternative minimum level model with 99 percent interval for asbestos TEM samples in mm^2.

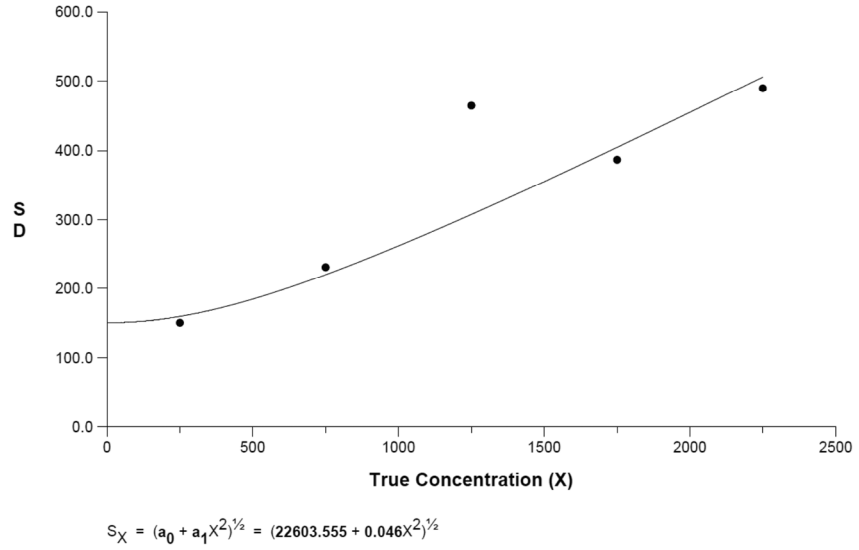

FIGURE B-4 Standard deviation vs. concentration for asbestos TEM samples in mm^2.

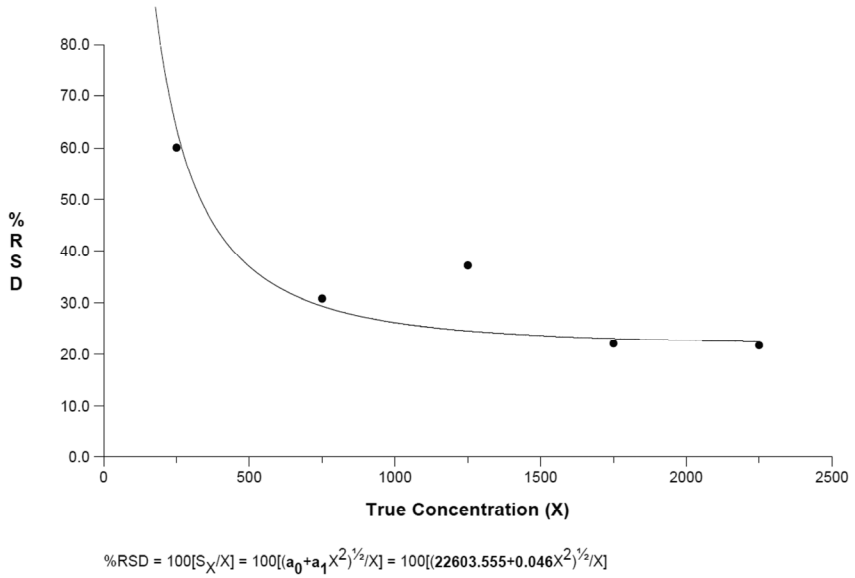

FIGURE B-5 Percent relative standard deviation vs. concentration for asbestos TEM samples in mm^2.

PCM Analyses

In contrast to TEM, there were several extreme values (in excess of counts of 5,000) associated with the PCM data, despite the fact that the highest average concentration never exceeded 800 counts (see Figure B-6).

Exclusion of the 12 extreme counts reveals a more consistent pattern in the raw data (see Figure B-7). Results of the analysis of the raw PCM data excluding outliers are presented in Table B-2. For PCM, the true counts were divided by 100 to place the estimates on a scale that is more easily interpreted.

The inter-laboratory standard deviation is 0.40, which is 67 percent of the mean slope (0.60) of the calibration curve over all of the laboratories. This is an even larger relative standard deviation than obtained for TEM, indicating also that the laboratories exhibit considerable variability in their individual calibration curves (i.e., differential sensitivity to changing numbers of particles from lab to lab) for PCM.

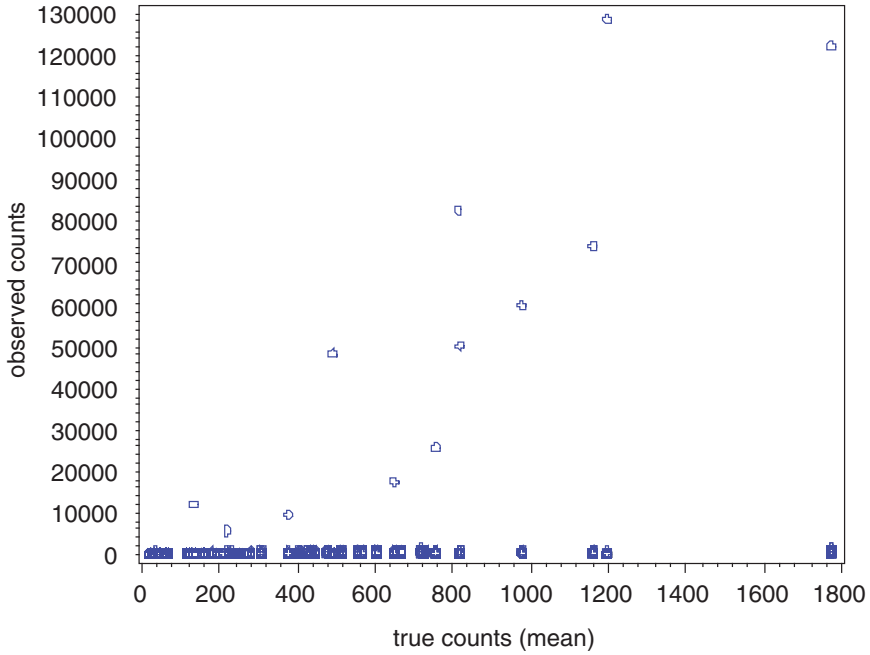

FIGURE B-6 Raw PCM data.

TABLE B-2 Marginal Maximum Likelihood Estimates of the Mixed-effects—Poisson Regression Model for PCM Data

Parameters	Estimates	SE	z-value	p-value
γ_0	3.8559	0.0864	44.63	< .0001
γ_1	0.6006	0.0498	12.07	< .0001
$\Sigma(1,1)$	0.5158	0.0526		
$\Sigma(1,2)$	-0.2128	0.0265		
$\Sigma(2,2)$	0.1593	0.0182		

Figure B-8 presents empirical Bayes estimates of the individual laboratory calibration functions. Note that the y-axis is in log-scale. This figure confirms that there is considerable variability in the slopes of the estimated calibration functions.

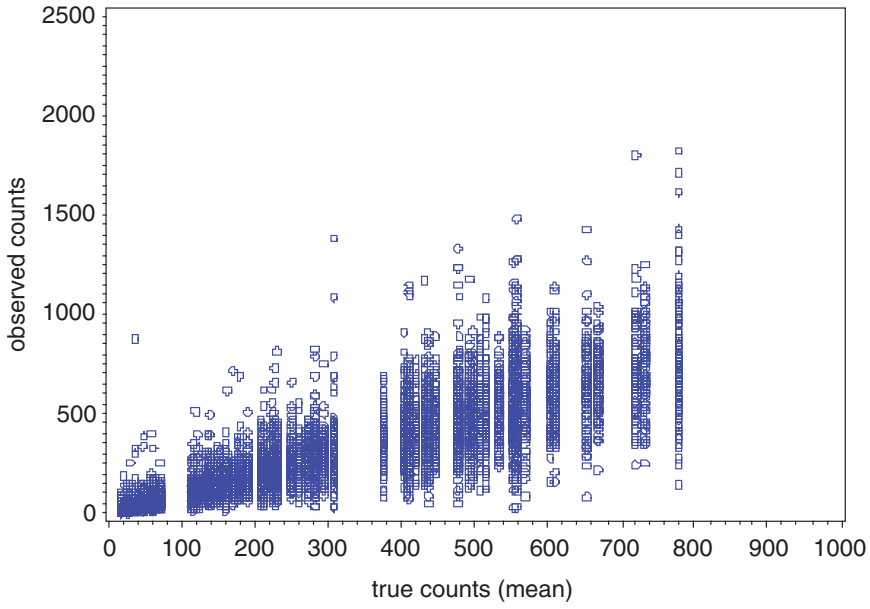

FIGURE B-7 Raw PCM data excluding outliers.

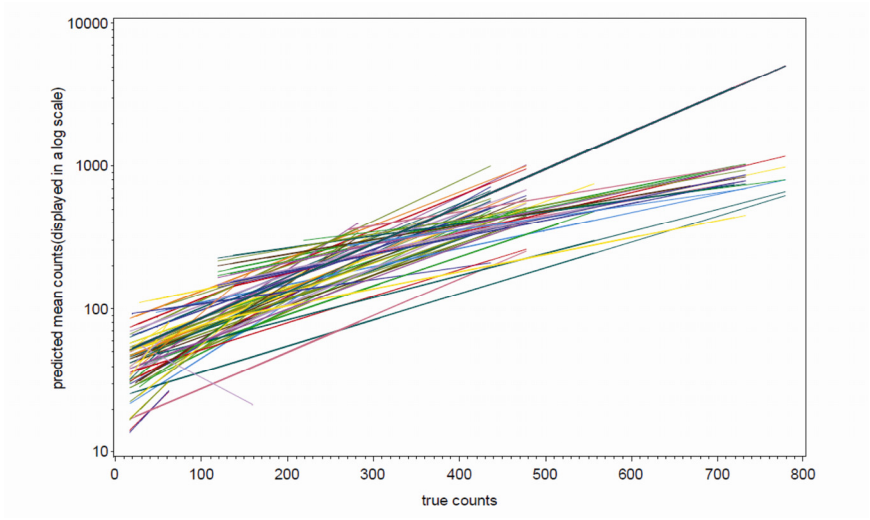

FIGURE B-8 Individual laboratory estimated calibration functions for PCM.
NOTE: The *y*-axis is in a log scale with base = 10.

Next, we estimated detection and quantification limits for the PCM data. The results are displayed graphically in Figure B-9. This figure reveals that the critical level (L_C) is 127 fibers, the detection limit (L_D) is 589 fibers and the quantification limit (L_Q) is 924 fibers. At the L_Q, the relative standard deviation is still quite large (i.e., 32 percent). Figure B-9 also reveals that outliers still remain in the data; however, the prediction intervals are conservative due to the large number of measurements.

Figure B-10 presents the variance function, for which the best fit was based on the Rocke and Lorenzato Model (Rocke and Lorenzato, 1995). The figure reveals that the variability is constant below 100 fibers and then increases linearly from 100 to 800 fibers.

Finally, Figure B-11 displays a plot of the relationship between average counts and the relative standard deviation. The figure shows that considerable uncertainty exists in PCM asbestos counts throughout all of the samples investigated, regardless of the number of fibers. However, the RSD stabilizes at around 30 percent for fiber counts around 500.

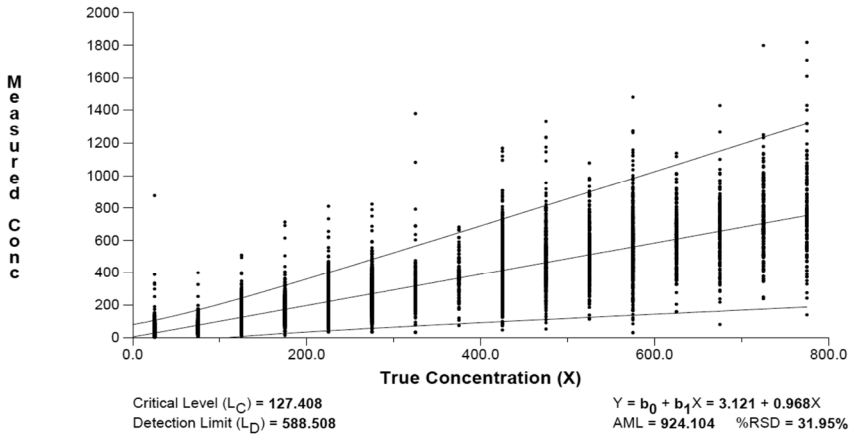

FIGURE B-9 Alternative minimum level model with 99 percent prediction interval for asbestos PCM samples in mm^2.

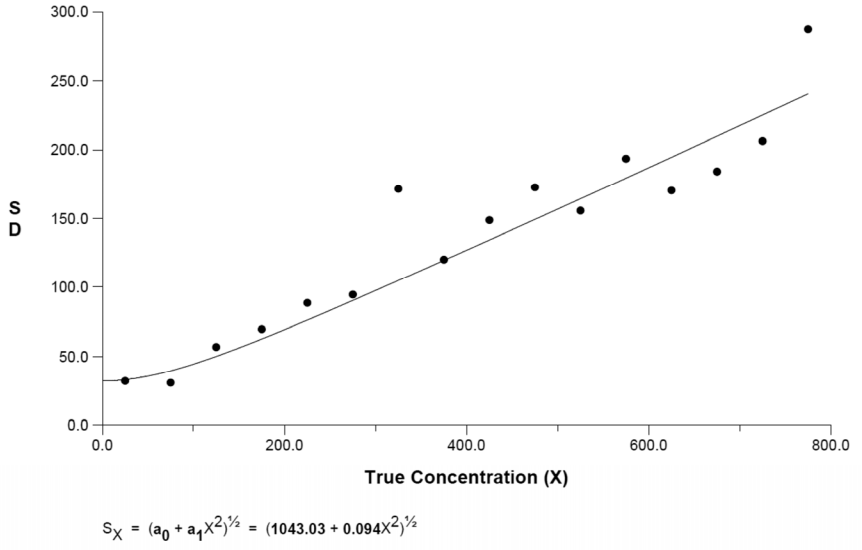

FIGURE B-10 Standard deviation vs. concentration for asbestos PCM samples in mm^2.

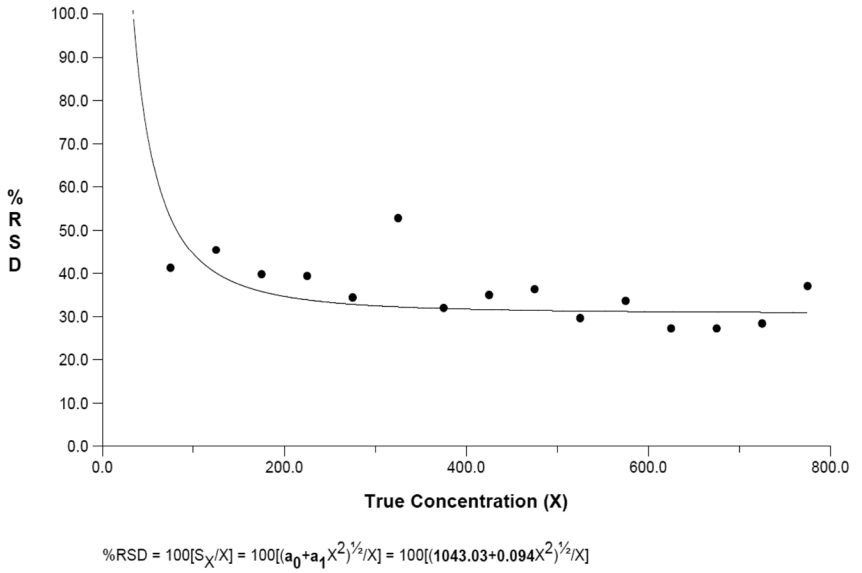

FIGURE B-11 Percent relative standard deviation vs. concentration for asbestos PCM samples in mm^2.

Discussion

Fiber-counting protocols must be considered as a contributor to variability. The AHERA method was produced in 1987 as a simplification of the EPA Level II analysis (U.S. EPA, 1987). "Clusters" of fibers are counted as one structure under the AHERA method, whereas a more detailed and prescriptive method, ASTM D6281, requires the analyst to count and measure individual fibers within clusters (ASTM, 2008). In fact, a separate inter-laboratory study, which used AM filters from one of the batches discussed here, produced a relative standard deviation of only 11 percent at a concentration of ~400 s/mm^2 when the ASTM D6281 method was used. No inter-laboratory data are available for the NIOSH 7402 TEM method, where PCM-equivalent fibers (length >5-μm, width >0.25 μm, aspect ratio >3) are counted (NIOSH, 1994a). Variability would probably be similar to the ASTM method, but NIOSH 7402 does not allow counting of fibers thinner than 0.25 μm, so this method would not monitor the very thin fibers that are considered to be the most hazardous.

Filter type and preparation techniques are other sources of variability. MCE filters sometimes have surficial defects that cause skewed deposition across the filter face, but the skewing is not obvious once the filter is collapsed. Furthermore, differences in collapsing methods and in etching rates (poorly defined and inconsistently calibrated) add to the variability (Webber et al., 2007).

Another source of variation that cannot be de-coupled is the difference in filters received by each laboratory for each PT batch. In-house validation of homogeneity of AM filters has been checked by analyzing 5 filters from each generation batch of 109 filters. Relative standard deviations for these counts, by the same analyst and same instrument, are typically 10 percent around a concentration of 1,000 s/mm^2.

In both the examples, asymptotic normality is used (see Tables B-1 and B-2) in order to arrive at the reported p-values. This is appropriate since the sample sizes are large. However, if the number of laboratories and/or the count data within each lab are sparse, asymptotic methods for hypothesis testing may yield biased results. One option is to use small sample asymptotic theory that has recently become available (see Brazzale et al., 2007 and Bellio, 2003). The relevant theory would need to be developed for the mixed effects Poisson regression model proposed here and is likely to be quite valuable in the context of the Rocke-Lorenzato model as well.

Taken as a whole, the current analysis reveals that there is considerable variability in asbestos fiber counting under both TEM and PCM methodologies. Although detection limits are smaller for PCM than for TEM, PCM cannot be considered an alternative because it cannot detect the thin fibers of most concern and it cannot even determine if a fiber is asbestos. It is critically important for the analytic community to address the issue of TEM variability so that more reliable exposure concentrations can be determined.

THE PROBLEM OF NON-DETECTS

A complication in the statistical analysis of environmental data in general and asbestos in particular is the presence of non-detects. Even if the measured concentrations have a known distribution (e.g., normal, lognormal, Poisson) the overall distribution may not because of a mass of probability associated with a count of zero, or samples in which the material has not been detected. In the case of an asbestos count, it may be the case that there are more zeros (i.e., non-detects) than are expected based on a Poisson distribution. In this case, one may consider extensions to the Poisson model, such as a zero-inflated Poisson model (Lambert, 1992). General discussions of the treatment of nondetects in environmental data analysis can be found in Helsel (2005) and Gibbons et al. (2009).

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C

Experimental Design Strategies

FRACTIONAL FACTORIAL DESIGNS

Factorial designs are used to study the joint effect of several factors on a response. In a factorial design we assume that there are a number of factors present and each factor has several levels. In a 2^k factorial design there are k factors and every factor has only two levels (e.g., high versus low or experimental versus control). Thus the total number of level combinations is 2^k. Consider an example of a 2^3 factorial design where the three factors are denoted by A, B, and C. The eight combinations of levels are denoted by 1, a, b, c, ab, bc, ca, abc. Here, a is the main effect of the factor A, ab is the interaction effect of the factors A and B. All other level combinations have similar interpretations. The main goal of a factorial design is to study the main effects of factors involved in the design. An experimenter may also be interested in studying the two factor interaction effects or even higher-order interactions. To run a complete 2^k factorial design, the experimenter needs to have 2^k experimental conditions (e.g., groups). Sometimes, to achieve better efficiency, the design is replicated several times. To estimate the average of the main effect of factor A in a 2^3 factorial design replicated n times, we use the following formula:

$$A = \frac{1}{4n}(a-1)(b+1)(c+1) = \frac{1}{4n}(abc + ab + ac - bc + a - b - c - 1),$$

where abc is the total number of observations in n replicates with all factors at the high level, and all other symbols have similar interpretations.

The interaction effect of A and B is

$$AB = \frac{1}{4n}(a-1)(b-1)(c+1) = \frac{1}{4n}(abc - ac - bc + ab + c - a - b + 1).$$

The sum of squares due to factor A, denoted by SSA, is

$$SSA = \frac{1}{8n}(abc + ab + ac - bc + a - b - c - 1)^2.$$

Similarly, the sum of squares due to the AB interaction is

$$SSAB = \frac{1}{8n}(abc - ac - bc + ab + c - a - b + 1)^2.$$

The total sum of squares SST is

$$SST = \sum_{i=1}^{2}\sum_{j=1}^{2}\sum_{k=1}^{2}\sum_{l=1}^{n}\left(y_{ijkl} - \bar{y}\right)^2.$$

To get the sum of squares due to error (i.e., SSE) we subtract the sum of all the 7 factor level combinations (except 1) from SST. The degree of freedom for any factor combination is 1 and that of SSE is $8(n - 1)$. The significance of the interaction effect AB is tested by constructing the F-statistic,

$$F = \frac{SSAB}{SSE/8(n-1)}.$$

As we see from the previous discussion, if the number of factors k in a 2^k factorial design increases, the total number of runs in a complete factorial design outgrows the resources of most experimenters. If the experimenter believes that higher-order interactions are negligible, the main effects and the lower-order interactions can be estimated by running only a fraction of the complete experiment. Let us assume that in a 2^3 factorial design the second-order interactions are not significant and the experimenter can provide only four conditions (i.e., experimental

and/or control groups) to estimate the main effects. In order to conduct this experiment in only four conditions to estimate the main effects we have to select the treatment level combinations appropriately. To choose the appropriate level of treatment combinations we first define a generator that is generally a higher-order interaction. Let our generator be *ABC*. In each of the above average factor effect expressions (i.e., *A, B*, etc.) 1 has either a + or a – sign. Choose only those factor levels effects that have –1 sign (those are *A*, *B*, *C*, and *ABC*). The average effects of these factors in this ½ fractional factorial design are determined by

$$A = \frac{1}{2}(a - b - c + abc)$$

$$B = \frac{1}{2}(-a + b - c + abc)$$

$$C = \frac{1}{2}(-a - b + c + abc),$$

and the sums of squares due to these factors are

$$SSA = \frac{1}{4}(a - b - c + abc)^2$$

$$SSB = \frac{1}{4}(-a + b - c + abc)^2$$

$$SSC = \frac{1}{4}(-a - b + c + abc).$$

No degrees of freedom are left for the error. Hence we can estimate the main effects but we cannot test their significance. Generally, this is not the case for ½ fractional factorial designs in which there are four or more factors.

In terms of confounding, 2^3 ½ fractional replicate designs can estimate main effects, but they are confounded with two-factor interactions. 2^4 ½ fractional replicate designs can estimate main effects that are unconfounded by two-factor interactions; however, the two-factor interactions may be confounded with other two-factor interactions. 2^5 ½ fractional replicate designs can estimate unconfounded main effects and two-factor interactions, but three-factor interactions may be confounded

with two-factor interactions. Finally, 2^6 ½ fractional replicate designs can estimate main effects and two-factor interactions unconfounded by three-factor or less interactions, but three-factor interactions may be confounded with other three-factor interactions.

The previous examples illustrate the *resolution* of the fractional factorial design. Resolution II designs are completely undesirable because even the main effects are confounded with each other. Resolution III designs (e.g., 2^{3-1} which represents a ½ replicate of a 2^3 design) can estimate main effects, but the main effects may be confounded with two-factor interactions. Resolution IV designs can estimate both main effects and two-factor interactions, but some of the two-factor interactions are confounded with each other. Resolution V designs can estimate main effects that are unconfounded by three-factor (or less) interactions, and two-factor interactions that are unconfounded by other two-factor interactions, but the two-factor interactions may be confounded with three-factor interactions. Finally, resolution VI designs can estimate unconfounded main effects (four-factor or less) and two-factor interactions (three-factor or less), and estimate three-factor interactions, but they may be confounded by other three-factor interactions. As such, if we are interested in preserving the integrity of both main effects and two-factor interactions in a 2^k fractional factorial design, we require a resolution V or higher design. If all that we care about are the main effects, a resolution III design will allow us to estimate them, but a resolution IV design is required if we want to both estimate and test the significance of the main effects. Resolution IV 2^k fractional factorial designs include 2^{4-1}, 2^{6-2}, 2^{7-2}, 2^{7-3}, 2^{8-3}, 2^{8-4}, 2^{9-3}, 2^{9-4} designs, where for example, a 2^{9-4} design reduces the total number of experimental conditions (i.e., factor level combinations) from $2^9 = 512$ to a far more manageable $2^5 = 32$ and still permits estimates and tests of main effects that are unconfounded by two-factor interactions. Resolution V 2^k fractional factorial designs include 2^{5-1}, 2^{8-2}.

An alternative strategy is to use a resolution III fractional factorial design to conduct a screening experiment, which would then be followed by a more complete but lower-dimensional factorial design. For example, Neter et al. (1996) describe a resolution III 2^{10-6} design, involving 16 experimental conditions out of the 1,024 conditions needed for a full factorial design, that was used to study the effects of six process variables and four ingredient variables on the extent of crystallization in ice cream. The 16 conditions included in the screening study are as follows:

X1	X2	X3	X4	X5	X6	X7	X8	X9	X10
–1	–1	–1	–1	–1	–1	–1	–1	+1	+1
+1	–1	–1	–1	+1	–1	+1	+1	–1	–1
–1	+1	–1	–1	+1	+1	–1	+1	–1	–1
+1	+1	–1	–1	–1	+1	+1	–1	+1	+1
–1	–1	+1	–1	+1	+1	+1	–1	–1	+1
+1	–1	+1	–1	–1	+1	–1	+1	+1	–1
–1	+1	+1	–1	–1	–1	+1	+1	+1	–1
+1	+1	+1	–1	+1	–1	–1	–1	–1	+1
–1	–1	–1	+1	–1	+1	+1	+1	–1	+1
+1	–1	–1	+1	+1	+1	–1	–1	+1	–1
–1	+1	–1	+1	+1	–1	+1	–1	+1	–1
+1	+1	–1	+1	–1	–1	–1	+1	–1	+1
–1	–1	+1	+1	+1	–1	–1	+1	+1	+1
+1	–1	+1	+1	–1	–1	+1	–1	–1	–1
–1	+1	+1	+1	–1	+1	–1	–1	–1	–1
+1	+1	+1	+1	+1	+1	+1	+1	+1	+1

Three factors were identified as important, and these factors were then studied in a 2^3 full factorial design.

The 2^{k-f} designs that have highest possible resolution have been identified and catalogued for choices of k and f that are of general interest by Box and colleagues (2005) and are also provided online by the National Institute of Standards and Technology at http://www.itl.nist.gov/div898/handbook/pri/section3/pri3347.htm.

Response Surface Methodology

The previous discussion of fractional factorial designs is based on discrete levels of each factor (e.g., high or low, experimental or control). In some cases, the factors of interest may be continuous variables, for which simple dichotomization is not possible. An alternative approach for exploring the effects of individual factors, low-level interactions, and nonlinear relations is based on response surface methodology (RSM). In RSM we first model the response function, which is influenced by several variables, and then we optimize this function. Suppose that we have a quantitative index of carcinogenicity Y in a test animal that depends on the length-to-width ratio (x_1) and size (x_2) of a particular mineral particle to which the animal is exposed. The scientific objective is to determine the levels of x_1 and x_2 in order to achieve a certain value of Y, say y_0. Let

us assume that the relationship between Y and (x_1, x_2) is modeled by a function f: i.e., $y = f(x_1, x_2) + \varepsilon$, where ε represent noise in response y. Let $E(Y) = \eta = f(x_1, x_2)$. The surface represented by $\eta = f(x_1, x_2)$ is called the response surface. In RSM the functional form of f is unknown. We generally try a linear function or a polynomial function to model this relation. When there is a variation of this relation from laboratory to laboratory, a mixed-effects polynomial model can be used and the method of maximum likelihood or marginal maximum likelihood can be used to estimate model parameters. Once the parameters have been estimated, we can use the estimated response surface to evaluate the values of x_1 and x_2 for a specific targeted value of y_0—for example, a carcinogenetic threshold. A contour plot may help in this regard to estimate levels of x_1 and x_2 corresponding to a particular level of carcinogenic risk. The RMS method may not provide a reasonable solution for the true functional relationship over the entire space of the independent variables x_1 and x_2. In that case a small region for the independent variables is chosen and RMS is used sequentially. The interested reader is referred for further discussion on these issues to Box and Draper (2007).

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D

Biographical Sketches

COMMITTEE

ALAN R. NELSON, M.D. (*Chair*), is an internist-endocrinologist who was in private practice in Salt Lake City, Utah, until becoming chief executive officer (CEO) of the American Society of Internal Medicine (ASIM) in 1992. Following the merger of ASIM with the American College of Physicians (ACP) in 1998, Dr. Nelson headed the Washington Office of ACP-ASIM until his semiretirement in January 2000; he currently serves as special adviser to the executive vice president and CEO of the college. A member of the Institute of Medicine (IOM) of the National Academy of Sciences, he was a member of the Roundtable on Environmental Health Sciences Research. He also was chair of the IOM Committee on Ethnic and Racial Disparities in Health Care and is a coeditor of the study report *Unequal Treatment: Confronting Racial and Ethnic Disparities in Health Care* (2003). He has served on approximately a dozen IOM committees and review panels, including the Committee on Redesigning Health Insurance Benefits, Payment, and Performance Improvement Programs from 2004 to 2006. Dr. Nelson was a member of the Medicare Payment Advisory Commission (MedPAC) from 2000 to 2006. MedPAC advises the U.S. Congress on Medicare policies concerning payment, quality, and access to care. Dr. Nelson was president of the American Medical Association in 1989–1990 after serving two years as chair of the board and was president of the World Medical Association in 1991–1992. Prior to moving to the Washington, DC, area, Dr. Nelson was clinical professor of medicine at Utah, where he received the Outstanding Clinical Faculty Award in 1989. Dr. Nelson was born in Logan, Utah, in 1933, attended Utah State University, and received his M.D. degree from Northwestern University in 1958.

SARKIS G. AMPIAN, is an industrial minerals consultant and geochemist, retired from the U.S. Bureau of Mines (USBM) after nearly 40 years of service. Mr. Ampian served in the USBM Research and Commodity Groups. His work in the Commodity Group centered on monitor-

ing all domestic and offshore clay, oil shale, zircon, barium and strontium, and drilling-mud activities. Mr. Ampian also served as a principal mineralogist in the USBM with research outreach to all federal, state, and international regulatory agencies, including publishing and lecturing on the Department of Interior's position on asbestos, crystalline silica, and clay locatable matters. Currently, he serves as a consultant on crystalline silica.

JOHN R. BALMES, M.D., is professor of medicine at the University of California, San Francisco, and chief of the Division of Occupational and Environmental Medicine at San Francisco General Hospital. He is also professor of environmental health sciences at the University of California, Berkeley, and director of the Northern California Center for Occupational and Environmental Health. His research is in the area of occupational and environmental respiratory disease. He studies the acute effects of inhalation exposures to ambient air pollutants in his human exposure laboratory at San Francisco General Hospital and the chronic effects of such exposures in epidemiological studies with collaborators at the University of California, San Francisco, and the University of California, Berkeley. He is also interested in genetic determinants of responses to air pollutants. For the past five years, Dr. Balmes has been leading research, funded by the Centers for Disease Control and Prevention (CDC), to assist in the development of a national program to link environmental hazards with health outcomes data to improve the tracking of diseases potentially related to environmental exposures. Dr. Balmes received the Environmental and Occupational Medicine Academic Award from the National Institute of Environmental Health Sciences (NIEHS), 1991–1996. He was appointed the physician member of the California Air Resources Board in December 2007. Dr. Balmes received his M.D. from Mt. Sinai School of Medicine in 1976.

PATRICK N. BREYSSE, Ph.D., is professor in the Department of Environmental Health Sciences and director of the Division of Environmental Health Engineering at the Johns Hopkins University Bloomberg School of Public Health. He is also program director of the Industrial Hygiene Training Program and director of the Center for Childhood Asthma in the Urban Environment. His main research interest is in exposure assessment, including pollutant source characterization, exposure measurement and interpretation, development and use of biomarkers of exposure-dose-effect, and evaluating relationships between sources,

exposure, doses, and disease. Dr. Breysse co-directed a medical screening program for former Department of Energy workers at the Los Alamos National Laboratory and currently serves on the laboratory's Beryllium Health and Safety Committee. He is also a former chair of the American Conference of Governmental Industrial Hygienists Worldwide. Dr. Breysse received his M.H.S. in occupational safety and health and his Ph.D. in environmental health engineering from the Johns Hopkins University.

ROBERT D. GIBBONS, Ph.D., is a professor of biostatistics and psychiatry and director of the Center for Health Statistics at the University of Illinois at Chicago. He received his doctorate in statistics and psychometrics from the University of Chicago in 1981. He received a Young Scientist Award from the Office of Naval Research (1981), a Career Scientist Award from the National Institutes of Health (NIH; 1995), and numerous other NIH grants. His research spans the areas of medical, biological, and environmental statistics, with particular emphasis on statistical problems in mental health, health services research, longitudinal data analysis, and environmental regulatory statistics. Dr. Gibbons is a fellow of the American Statistical Association and twice received the Youden Prize for statistical contributions to chemistry, and the Harvard Award for contributions to psychiatric epidemiology and biostatistics. Dr. Gibbons has served on several IOM committees including the Committee on Halcion, the Committee on Organ Procurement and Transplantation, and the Committee on the Assessment of the U.S. Drug Safety System. He has authored more than 180 peer-reviewed papers and four books. His most recent work is in the general area of drug safety with particular emphasis on understanding the relationship between central nervous system (CNS) drugs and suicide. Dr. Gibbons is a member of the Institute of Medicine.

TOM K. HEI, Ph.D., is professor of environmental health sciences and deputy director of the Center for Environmental Research at the Mailman School of Public Health and professor and vice chairman of radiation oncology, College of Physicians and Surgeons, Columbia University. Dr. Hei's research focuses on environmental carcinogenesis, specifically mechanisms of chemical and radiation carcinogenesis-mutagenesis at the cellular and molecular levels. Dr. Hei's ongoing funded research programs focus on the basic cellular and molecular mechanisms of environmental carcinogens such as tobacco smoke, radon, asbestos fibers, and

heavy metals. Immortalized human bronchial and breast epithelial cell models are used to examine the molecular mechanisms involved in the multistage nature of human cell carcinogenesis. Dr. Hei received his doctorate in experimental pathology from Case Western Reserve University.

KARIN O. HOAL, **Ph.D., P.G.,** is director of the Advanced Mineralogy Research Center and research professor in the Department of Geology and Geological Engineering at Colorado School of Mines. Her areas of expertise are in mineral characterization, automated mineralogy, petrology, diamond geology, and geometallurgy. Dr. Hoal received a Ph.D. in geology from the University of Massachusetts, Amherst; an M.Sc. from McGill University; and a B.Sc. from St. Lawrence University. She was a postdoctoral fellow at the University of Cape Town, South Africa, specializing in mantle metasomatism. She is a fellow of the Society of Economic Geologists; a member of the Society for Mining, Metallurgy, and Exploration; a member of the National Association of Women Business Owners; a certified professional geologist; and a past member of Sigma Xi. She has served on several university committees, as well as the current advisory committee for the 2009 Gemological Research Conference, Gemological Institute of America and the review committee for the 2008 International Geological Congress Travel Grant Awards. She has 31 peer-reviewed publications. Dr. Hoal has 24 years' experience in academia, industry, and government and is currently spearheading the development of integrated mineral analysis using quantitative mineralogy techniques.

JOE L. MAUDERLY, D.V.M., is vice president and a senior scientist of the Lovelace Respiratory Research Institute in Albuquerque, New Mexico; director of the National Environmental Respiratory Center; and former director of the Inhalation Toxicology Research Institute. He is a research professor in the University of New Mexico Health Sciences Center. After receiving his doctorate in veterinary medicine from Kansas State University and brief periods in clinical practice and the U.S. Air Force, he specialized in research on comparative respiratory physiology, comparative pulmonary responses to inhaled toxicants, and the human health hazards of materials inhaled in the workplace and the environment. During the past decade, his research has focused on disentangling the physical-chemical species causing health effects of complex mixtures of air contaminants, with emphasis on combustion emissions, and on the utility of animal studies for estimating human health hazards. He has au-

thored or coauthored more than 290 articles, chapters, books, and published technical reports and is on the editorial boards of *Inhalation Toxicology* and *Environmental Health Perspectives*. He has chaired and participated in numerous National Research Council (NRC), Environmental Protection Agency (EPA), and university advisory committees, including the Clean Air Scientific Advisory Committee. He has held offices in the Environmental and Occupational Health Assembly of the American Thoracic Society and the Inhalation and Respiration Section of the Society of Toxicology.

GREGORY P. MEEKER, M.Sc., is a research scientist at the U.S. Geological Survey (USGS) in Denver, Colorado, and a project chief for the USGS Earth Materials and Human Health Project. His current research focuses on detailed studies of the mineralogy and morphology of fibrous and asbestiform amphiboles including those that triggered a major EPA Superfund action in Libby, Montana. Mr. Meeker was a principle investigator in the USGS study of the dusts generated by the collapse of the World Trade Center and served as a member of the EPA World Trade Center Expert Technical Review Panel. Mr. Meeker is currently a member of the Science Advisory Panel for a study of air quality in Minnesota's taconite mining region being conducted by the University of Minnesota's Natural Resources Research Institute. He also served on two EPA technical panels to develop methods for the analysis of asbestos-contaminated vermiculite attic insulation. Other recent investigations include studies of naturally occurring asbestos in California and environmental studies of sedimentary materials deposited as a result of Hurricane Katrina. His research interests involve the application of microscopy and microanalysis to the fields of geochemistry, mineralogy, volcanology, and environmental geology. Prior to joining the USGS in 1989, he worked for Charles Evans & Associates in Redwood City, California, as a senior research analyst in materials analysis. He began his career at the California Institute of Technology in the Department of Earth and Planetary Sciences, where he studied meteorites and lunar materials with the electron microscope, electron microprobe, and ion microprobe. Mr. Meeker is a past president of the Microbeam Analysis Society, and has twice been a national tour speaker for that organization. Mr. Meeker holds a master of science degree in geology from California State University, Los Angeles.

ANDREA KIDD TAYLOR, Dr.P.H., is an assistant professor at the Morgan State University (MSU) School of Community Health and Policy. She has more than 20 years' experience in occupational and environmental health and safety. Before joining the MSU faculty, Dr. Taylor served a five-year term on the U.S. Chemical Safety and Hazard Investigation Board (CSB), a board established under the Clean Air Act Amendment of 1990 to investigate chemical accidents at fixed facilities, an appointment that she received from President Clinton with confirmation by the U.S. Senate. Prior to the CSB, she worked as an industrial hygienist and occupational health policy consultant for the United Auto Workers in Detroit, Michigan. Dr. Taylor serves as a member of the Beyond Pesticides/National Coalition Against the Misuse of Pesticides Advisory Board; she formerly served as a member of the U.S. Presidential Advisory Committee on Gulf War Veterans' Illnesses and as a health representative on the National Advisory Committee on Occupational Safety and Health (NACOSH). She has authored many publications, including articles that highlight minority workers, chemical safety, and disease and injury prevention. Her research interests are occupational and environmental health and safety interventions and policies, indoor air quality in public schools, minority workers, and the prevention of environmental exposure to pests and pesticides.

CONSULTANT

ERNEST E. McCONNELL, D.V.M., is president of ToxPath, Inc., a consulting firm in Raleigh, NC, that specializes in experimental toxicology and pathology. Much of his research experience has dealt with the pathological effects of various types of asbestos and man-made fibers used as asbestos substitutes. Before becoming a consultant, Dr. McConnell was director of the Division of Toxicological Research and Testing Program, National Toxicology Program at the National Institute of Environmental Health Sciences (NIEHS). He has served two terms as a member of the NRC Committee on Toxicology and on several NRC committees, including the Subcommittee on Manufactured Vitreous Fibers. He received his D.V.M. from Ohio State University and his M.S. in pathology from Michigan State University. He completed his residency in comparative pathology at the Armed Forces Institute of Pathology, Walter-Reed Army Medical Center.