Comments Received from Peer Reviewers on the NIOSH draft Document "Asbestos and Other Mineral Fibers: A Roadmap for Scientific Research"

The comments received from the peer reviewers of the draft NIOSH document "Asbestos and Other Mineral Fibers: A Roadmap for Scientific Research" are compiled below. The peer reviewers were asked to respond to 14 questions. Their general comments on the document are presented first, and their responses to each question follow in no particular order of author. To move to the comments on a specific question, point to the question with the mouse and right-click .

Question **Page**

General Comments

Comments
The NIOSH Roadmap has a fundamental problem, i.e., distinguishing between asbestos health effects and mineral fiber health effects. These seem to be lumped together, but are fundamentally different. Asbestos-related diseases are related to the very long thin fibers (less than 0.1-0.2 microns thick and more than 20-40 microns in length). These fibers are responsible for the asbestos-related diseases, yet the Roadmap does little to chart a course for future research. Moreover, there is little on the pathogenetic mechanisms published in the past. There is a plethora of material on cellular and organ system mechanisms of asbestosis , including animal and human studies including growth factors, oxidants, signaling, cytokines, NO and other mediators, and clinical disease. There are many mechanistic animal study options. There are a few good studies on genetic susceptibility. For the future, there needs to be further study on how asbestos fibers cause fibrosis, especially on the epithelial-mesenchymal transition (EMT). There needs to be a real focus on how asbestos works as a carcinogen. These should include effects on meiosis, and chromosomal effects. There needs to be studies on genomics and proteomics in the lung of asbestos models. There are very few studies on asbestos and transgenic mouse models. There needs to be a good mesothelioma model. Few studies approach early detection of asbestosis, lung cancer in asbestos-exposed, and detection of mesothelioma using biomarkers. NIOSH does have Health in its name. The focus on other mineral fibers is very distracting, since it gets into contaminants and this raises huge issues with businesses and whole industries who then face regulation. For the most part, these industries incur cost but have a very small, if any, disease burden in comparison to past asbestos industries. There are three cohorts of interest: 1) Libby, MT, and this one has had extensive clinical/epidemiological study, but less in terms of fiber exposures (tissues, air analyses); 2) Minnesota taconite where there has been very little study with 50-70 mesotheliomas reported in the press; and 3) the talc mining industry, where there has been a fair amount of research with very small increases in pneumoconiosis and cancer. The main focus in these other industries should be fiber characterization and toxicity determination. NIOSH should do the fiber characterization and prepare samples for scientists to perform the toxicity determination using human lung cell lines and murine models. IOSH needs to state, in its Roadmap, that this is a very important priority and should garner necessary res d be 10% of its budget. Furthermore, NIOSH should develop a series of RFAs for the scientific academic l to respond with innovative and creative approaches to the asbestos-related diseases using novel animal inations. NIOSH needs to develop an academic community across the country that brings the brightest m ce this type of expertise does not exist in-house. Lastly, NIOSH needs to emphasize interdisciplinary and humans as much as possible.
If the morphology of durable particles were the only variable that correlates with the potential to cause asbestos-related disease, then it is only a particular set of morphological characteristics that would separate biodurable, carcinogenic and fibrogenic particles from biodurable particles that are neither carcinogenic nor fibrogenic. What we know today suggests that this is unlikely to be the case and that morphology will not be the only foundation of a unified fiber theory. The morphological boundary may not be sharp, and there may be gradations of potency associated with a range of morphologies and minerals. Furthermore, the atomic structure, chemical composition, and surface properties may also be primary variables. These are the issues that NIOSH's research agenda must address; they are not simple problems. The testimony given by NIOSH at the OSHA hearings in 1991 "characterized the evidence as suggesting that neither mineralogic identity nor origin of the particle are critical factors in carcinogenic potential." In other words, NIOSH has argued in the past that morphology is the key to carcinogenicity and fibrogenicity with the implied assumption that as long as the fibers are durable chemical composition, atomic structure, and surface properties are irrelevant. Currently the morphological parameters for both carcinogenic and fibrogenic fibers are defined by NIOSH as >5µm

in length and 3:1 or greater in aspect ratio. These parameters define Regulatory Fibers (RF).

NIOSH applies the morphological argument to particles composed of serpentine, tremolite, actinolite, riebeckite, grunerite or anthophyllite. However, the Roadmap raises the issue of other fibrous minerals including erionite, fibrous talc, and fibrous mineral intergrowths, fibers with morphological characteristics similar to asbestos. How amphiboles unnamed in the standard, such as richterite, winchite, edenite, and arfvedsonite, among others, are to be treated when they are asbestos (and when they are not) is also an issue.[1]

NIOSH's explains that its reliance on morphology alone is based on the fact that 1) studies that have shown that the carcinogenic potential of mineral particles depends on dimensions and biopersistence, 2) the evidence for excess lung cancer attributable to cleavage fragments is equivocal, 3) the FD incorporates most asbestos fibers, and 4) asbestiform fibers and cleavage fragments of the same mineral occur together, and NIOSH cannot more precisely define asbestos fibers.[2]

To understand mineral toxicity in all of its forms, careful evaluation of the morphological parameters that describe carcinogenic potential and fibrogenic potential[3] will undoubtedly be important. However, even after more than thirty years of use, there is no toxicological basis for the Regulatory Fiber Definition.[4] Dr. Berman correctly points out that in the industries using asbestos "any metric of dust exposure could be correlated with risk." Dr. Berman also points out that the RF definition, in fact, shows a significant "lack of fit with tumor incidence." While a scientifically based fiber definition is needed, morphology alone will not form the basis of a unified theory of fiber toxicity.

Missing from the document is a plan for selecting a set of samples for testing that will inform broadly on toxicity. **The lack of a plan is a major oversight and a matter of serious concern.** Samples of individual minerals must be chosen as a set that contains a wide variety of particle morphology and surface properties that are developed by cleavage and by growth. A number of different minerals, both amphiboles and perhaps others, should be selected to represent a range of atomic structures. I urge NIOSH to work in close partnership with the United States Geological Survey (USGS) to identify and provide carefully selected samples to those who will perform animal and cell studies. Locations for epidemiological studies must be chosen with the same regard for the mineral particles forming the airborne particulate.

In my comments below, I also plead with NIOSH to describe minerals accurately and to employ mineral-related terminology rigorously. The correlation between health effects and properties of mineral particles is a classic interdisciplinary problem. Since NIOSH does not have mineral expertise in house, the USGS should be consulted regularly throughout the path along the Roadmap. They have the expertise to provide sound scientific advice an all mineral matters. NIOSH should take the comments submitted by the USGS as sound recommendations.

The importance of the research agenda described in the Roadmap was reflected widely in the comments received NIOSH. NIOSH is widely praised for bringing these issues forward, for reviewing the RF definition, and for developing a set of recommendations for the next steps in the research

[1] This issue was also raised by the Industrial Minerals Association-North America (IMA-NA), by Dr. Nolan, and by the American Society of Safety Engineers (ASSE). Lyall Mortimer and American Society of Safety Engineers asked that man made fibers also be included.

[2] In my comments that follow, I have particularly addressed the morphological characteristics of asbestos to assist NIOSH in addressing the problem of defining asbestos.

[3] These will likely be different.

[4] Dr. Berman, National Stone, Sand and Gravel Association (NSSGA), Georgia Pacific Gypsum, and R.T. Vanderbilt make the same argument in their comments to NIOSH.

agenda. I share this view, and offer my comments to NIOSH in an effort to assist NIOSH in their objectives. I appreciate the opportunity to do so.
Summary

The materials that are to be studied according to the Roadmap must be carefully chosen to provide comprehensive criteria for 'fibers of concern'. The comments of the National Asphalt Paving Association (NAPA) sum up the issues pretty well. "Fibers of concern need to be defined based upon sound, evidence-based and health effects science in relation to the chemical and physical chemistry properties."

I appreciate the considerable time and effort on behalf of Drs. Middendorf, Zumwalde and Castellan in putting together a well-written, clear and concise document that can be understood by a group of scientists in diverse disciplines in the mineral field. I also applaud the organizational skills of Dr. O'Brien in assembling a balanced and credible peer review group and supplying us with the reports and comments by stakeholders in a timely fashion. I am enthusiastic about NIOSH's rejuvenated interest in answering critical questions that still exist on mechanisms and health effects of mineral fibers "to serve as the basis for evidence- based public health policies for asbestos and other mineral fibers " (page i, statement from Dr. Howard, Director). However, I stress that a far more important goal should be to use the results of research outlined in the Roadmap (and additional areas of priority suggested by peer reviewers) to facilitate preventive and therapeutic approaches to asbestos-related diseases in individuals who, after occupational and environmental exposures to amphibole fibers (i.e. the Libby population) are at risk today. This should be a primary objective of fiber toxicity research but will also require clinical and epidemiologic studies on human susceptibility factors such as age, genetic polymorphisms, antioxidant status, etc., as well as an understanding of cofactors contributing to asbestos fiber toxicity.

Throughout the document and in the presentation by NIOSH scientists in Washington, DC, there was an emphasis on whether short fiber-like cleavage fragments (FLCF) should be included in the NIOSH definition of asbestos which was criticized as without a scientific basis by geologists offering comments and on the peer review committee. Based upon the body of data showing no carcinogenic effects of cleavage fragments in man, and the massive literature basis showing the lack of or minimal effects of short fibers on toxicity endpoints *in vitro* and carcinogenic/fibrogenic effects in animals (many of these papers were not referenced in the document), there should be more emphasis on other amphiboles (winchite, richterite), and durable fibrous minerals (erionite). Moreover, the NIOSH definition of "asbestos" , as recommended by geologists and mineralogists, should be more precise in accordance with the USGS mineral definitions which would include the Libby amphibole. The specified dimensions of > 5 microns length or more seem arbitrary. It is also clear that there need to be different standards and regulation for especially durable fibers in view of data in the literature over the last two decades, but this will require careful analysis and testing of standardized preparations of sized samples of chrysotile and amphibole asbestos as well as erionite, perhaps the most potent mesotheliomagenic fiber in humans, in human cells and inhalation experiments using rats and mice. NIOSH should take the lead on selecting, characterizing, and sizing these samples and providing them to qualified investigators in the scientific community. Dose-response experiments and studies to determine how these fibers change in dimension and chemistry after inhalation or uptake by human cells and their translocation and clearance over time are essential in assessing their pathogenicity in addition to mechanistic work on their molecular, cellular, inflammatory and pathogenic effects. Extensively mapping the many physical-chemical properties of "raw" fiber preparations in an attempt to determine what contributes to toxicity may be naïve in view of the fact that fibers may adsorb other pollutants when inhaled in various settings and are coated immediately with respiratory secretions which may modify their properties after inhalation.
It is unlikely that prospective epidemiologic studies will be informative to the goals of the Roadmap because of their expense and necessarily long time until completion. Are there sites where high exposures of "long" fibers are taking place currently or in the recent past?

The Roadmap did not effectively address a major exposure assessment need that NIOSH should be facing. I refer to exposures where asbestos fibers represent only a small fraction of the mixed dust occupational environment. This can be in mining or mineral processing, such as for vermiculite in Libby, MT, in rip-out of old asbestos pipe lagging, and in building demolition. With the drastic reduction in the use of new asbestos, this will represent an ever-increasing proportion of occupational exposure to asbestos. Clearly, the special exposure assessment needs that are associated with this issue warrant more discussion in the Roadmap.

A Final Comment – There is Need for a more Strategic and Holistic Approach.

The Roadmap recognizes that there are many unknowns and uncertainties that limit the abilities of NIOSH, and other interested parties, to determine the extent of the health risks associated with the inhalation of airborne mineral and vitreous fibers. However, the Roadmap attempts to address many of these on a piecemeal basis, i.e., it examines the ground under each of multiple "lamp-posts". It then seeks insights from: 1) hygienists, microscopists, and mineralogists on improved methods of exposure assessment; 2) toxicologists and molecular biologists on biological mechanisms and exposure-response relationships; and 3) epidemiologists on the characterization of quantitative risks to humans. Unfortunately, it provides no overall risk assessment framework that could guide each of the more-narrowly focused groups of investigators to identify and characterize the most critical needs for additional investigation. In the following paragraphs, I offer my own suggestions for a more strategic approach to the selection of critical research needs in these three broad areas.

Exposure Assessment: The severe limitations of PCM and TEM measurements of fiber concentrations are well known. PCM cannot identify fiber type or fibers thinner than ~0.25 *u*m. TEM cannot determine the lengths of fibers that cross grid lines. These include many of the long fibers that should be of primary interest in terms of carcinogenesis. In addition, TEM cannot well-characterize fiber bundles or fibers within compound particle aggregates. Furthermore, TEM is often used at magnifications that lead to excessive counting of fibers too short to be of health concern while characterizing too few long fibers. These limitations are important because there is already broad agreement among scientific peers in the fiber research community that the health risks resulting from the inhalation of fibers penetrating into the thorax are much more highly dependent on fiber length, width, and biopersistence than on chemical composition or crystal structure. In terms of fiber length, fibers <5 um in length pose little, if any, risk, while risk increases rapidly with length > 5 *u*m. In terms of width, fibers with widths >2 *u*m do not penetrate appreciably into thoracic airways, while the risks of mesothelioma are associated primarily with very thin fibers that can be translocated to the pleura and peritoneum. In terms of biopersitence, we know that chrysotile asbestos is considerably more soluble in the thorax than amphibole asbestos, accounting for its much lower risks in terms of mesothelioma, and that most synthetic vitreous fibers (SVFs) dissolve even more rapidly than chrysotile. We also know that SVFs and asbestos cleavage fragments break into shorter length segments *in vivo* much more rapidly than do asbestiform fibers. In consideration of these important factors, it was striking that the Roadmap did not seriously consider that the most relevant measurements of the health risks of fiber inhalation could be made by state-of–the- art SEM. SEM is equally able to identify fiber composition and crystalline form as TEM, and superior to TEM in terms of measuring the lengths of long fibers and characterizing fibers within bundles. Its only technical limitation is that fibers thinner than ~0.1 *u*m cannot be resolved. However, this may not be a severe limitation if it can be shown that few fibers this thin are longer than 5 *u*m, or if fibers this thin, with their very large surface-to-mass ratio, rapidly dissolve within the thorax.

Toxicology: In my view, the big-picture issues that can best be addressed by toxicological investigations are: 1) fiber-cell interactions as a function of cell size and fiber length; and 2) factors

other than fiber length in stimulating the release of cellular enzymes and mediators.

Epidemiology: As shown in Figures 1 and 2 in the Roadmap, both asbestos production and occupational exposure levels in the US are now extremely low. Thus, it seems to be absurd to expect that any prospective study of contemporary exposures in a previously unexposed working population could be productive. For any study of a previously exposed population with prior exposures at relatively high fiber concentrations to be useful, there would need to be an extensive archive of membrane filter airborne dust samples that could be analyzed for bivariate length and diameter distributions of asbestiform fibers, and this seems like a long shot, at best, and such an opportunity may only exist in another country. Thus, I conclude that the Roadmap recommendations for epidemiology are not worth pursuing.

I have read the Roadmap prepared by NIOSH's Mineral Fibers Work Group, as well as the public comments about the report. I found the Roadmap to be a well written and informative document that includes a useful summary of the scientific community's current thinking about the health effects of exposure to asbestos and mineral fibers. The NIOSH scientists who produced the Road Map deserve commendations for putting together a fine report.

Certainly, the Roadmap could be more comprehensive. Other reviewers have pointed out that more detail could be included in many sections. My understanding is that this is not a document that attempts to provide a comprehensive review of the scientific literature, but one that provides a summary in order to propose future directions. As long as this is acknowledged, I have no problem with it. My comments focus on the usefulness and value of moving forward with the roadmap.

1. Is this Roadmap Useful?

The first reports of asbestos-related disease appeared more than 100 years ago. In the decades since then, there have been tens of thousands of deaths attributable to asbestos. Scientists have published an enormous number of articles on the health effects of asbestos. I know of no occupational exposure that has been the subject of more scientific inquiry than asbestos.

As a result of the death toll associated with the exposure, and the accumulated knowledge of the health effects associated with exposure, the public health regulatory system in the United States generally operates under the presumption that all exposure to asbestos and related fibers should be prevented or at least minimized, since many types of asbestiform fibers have been associated with both malignant and non-malignant disease. Not all asbestiform fibers have been associated with these disease, but there is no convincing evidence that any asbestiform fiber type is not associated with increased disease risk in humans. As a result, the well-justified default regulatory position is that exposure to any fiber type is dangerous.

In examining the health effects of exposure to asbestos, the most valuable information comes from human studies. Animal studies are useful for understanding issues of mechanism, but cannot replace human studies in estimating risk of morbidity and mortality. In theory, the questions raised in the Roadmap, especially about the effects of exposure to fibers of specific dimensions or to fiber-like cleavage fragments, can be answered through epidemiologic studies of humans exposed to these materials. However, in reality, the proposed research cannot be undertaken. I am unaware of the existence of adequate cohorts, about whose exposure is well enough documented, to provide evidence on the carcinogenic potential of fibers of different dimensions or of fiber-like cleavage fragments. I did not see evidence in the public comments to the contrary. In some respects, this is a sign of the success of our regulatory system in reducing exposure; in any case, it is reality.

I look at the toxicologic and in vitro studies discussed in the Roadmap as ones that are useful primarily as compliments to epidemiologic studies. The lack of studies that measure risk in human populations renders any results found in the toxicologic and in vitro studies somewhat less useful. Since we have such strong evidence of the carcinogenicity of several types of asbestiform fibers (and no compelling human evidence of the lack of carcinogenicity of any type of asbestiform fiber), it would not be appropriate to conclude on the basis of toxicologic and in vitro studies that a fiber type was non-carcinogenic. If little were otherwise known about asbestos, non-epidemiologic studies on these questions would be of great potential use, and the results could be applied in regulatory settings. But that is not where the scientific literature is at present. We know a great deal about asbestos and its health effects, and the results of any study proposed in the Road Map would have to be interpreted within the context of the extant literature. Therefore, in the absence of adequate human studies on the health effects of exposure to fiber-like cleavage fragments, the results of positive studies using laboratory animals would be seen as confirmation of what is known, while the results of negative studies could not be assumed to show a lack of effect in humans.

2. Should These Studies be Undertaken?

Let's assume that the full set of studies described in the Roadmap could be undertaken (in other words, adequate cohorts existed to pursue the questions raised.) The Roadmap describes a series of studies that are both expensive and personnel-intensive. To go down the road described in the Roadmap, NIOSH would have devote a significant portion of its budget, and involve many of its top personnel in these activities. This, I believe, would be a serious mistake. As noted above, there are few if any occupational hazards better understood than asbestos. The marginal gain from undertaking the studies described (if it were possible to do so) would be modest; NIOSH could make a greater contribution to improving the health of American workers by focusing on other workplace hazards, for which much less information on health effects is known.

The NIOSH White Paper provides an excellent mainstream review of health effects of asbestos, and most of the mainstream issues in analysis. The scientific quality is high. However, NIOSH leadership has charged the Institute of Medicine Review of NIOSH Research Programs with looking back at NIOSH research programs for relevance and impact. This review is an opportunity to look forward using the criteria of the IOM framework. This review will initially address this reviewer's questions of the relevance and potential impact of the work proposed.

The most important reason for NIOSH research is identifying gaps in protection of people at work. For asbestos, a significant gap in protection arises because a significant risk of cancer persists at exposure levels below the limit of quantitation by the most widely used measuring techniques. Therefore, as NIOSH identifies in the roadmap, improved measurement methods in that range of exposure, taking into account asbestos-derived particles invisible by those methods is the highest priority of research. Risk extrapolations based on those new measurement methods should be derived, especially for the presently neglected small particles.

Regarding health effects research comparing mineral types, the alternative to a surge in activity would be to examine the impact of treating all fibrous minerals the same as asbestos, breathable fiber for breathable fiber, under current conditions. Asbestos exposure is by OSHA standards limited to the extent feasible, until better measurement techniques are accepted. Epidemiological studies among workers exposed to additional mineral or synthetic fibers are not likely to be sensitive or specific enough to support changes in allowable exposure levels. Lifetime exposure laboratory studies at best will establish a relative potency compared to asbestos fibers, after a large consumption of resources.

b. A reading of published data on occupational exposures to asbestos during brake, clutch and gasket repair, measured by PCM, is that sometimes measurements see 0.1 fiber/ml, but frequently asbestos

fibers are below the limit of quantitation and described as not detectable. While these exposures may be characterized as in compliance with the PEL, levels of 1/3 the OSHA PEL are at the benchmark for a significant risk.

This suggests that counting of "structures" according the AHERA clearance sampling protocol may be the appropriate method for evaluating and prioritizing the risks of such operations. [AHERA clearance sampling involves both aggressive generation of dust and the TEM counting method for "structures." These comments apply only to the analytical method of counting structures.]

The same consideration should be applied to worker exposures during asbestos abatement operations. Exposures below the limit of quantitation may pose a significant risk.

The roadmap could be improved with some discussion of the relationship between fiber counts and "structures." Although structures are an EPA feature, perhaps the majority of asbestos exposed workers at this time are engaged in asbestos abatement and familiar with those sampling methods.

c. The relationship between concentrations of "structures" and fibers should be explored retrospectively, perhaps through archived samples, and prospectively through demonstrations of typical operations. Where fiber levels are above the limit of quantitation, it's not necessary to resort to "structures," because a hazard has been identified. The concern is prioritizing risk where fibers are below the limit of quantitation.

An exposure response relationship for "structures" should be developed based on the proportion of "structures" observed or expected in the fiber based studies observing health risks.

d. The discussion of risk of fibers vs. cleavage fragments could be amplified with a discussion of new understanding the respiratory cancer hazard posed by granular durable particles. The Stanton Hypothesis derives from a time when asbestos was known to cause fibrosis and lung cancer, while silica was "known" to cause only fibrosis and not lung cancer. Now it is "known" that silica is a human carcinogen based on literally dozens of mortality studies; this effect has been duplicated in rats by inhalation. Other durable particles, including titanium dioxide – used as a "negative" control for inhalation studies – are also carcinogenic in rats and therefore "possibly" carcinogenic to humans. This reviewer is not familiar enough with the voluminous asbestos literature to dismiss the hazard of cleavage fragments in light of the hazard of the particles of similar size.

The Stanton hypothesis, perhaps enhanced by some account for bio-persistence, may remain applicable to mesothelioma.

e. Similarly, the discussion of risk of fibers v. cleavage fragments could be amplified by discussion of the new understanding of the hazards of nanometer particles. Do cleavage fragments penetrate into the systemic circulation? Perhaps an inhalation study in the laboratory could examine this in relatively short time and with relatively modest expenditure of resources.

f. Regarding the possibility of additional studies in people of specific fiber types or new materials, the quantitative measures of risks in paragraph a. above should be taken into account. The calculated risk rate for asbestos at 0.1 fiber/ml is right at the limit of detection for lung cancer in a large, high powered, well conducted study of lung cancer in people; that limit is a relative risk 50% above background. The exposure equivalent would be about 5 fiber/ml-yrs with appropriate latency. Studies not adequately powered to detect a hazard of a material of lesser potency or lesser latency only confuse the public health debate and waste resources.

g. Regarding laboratory studies of toxicity of various fiber types, it will be important to consider in advance how these results might be translated into information about human risk. A common measure of dose and therefore potency must be arrived at. For lung cancer, this reviewer has the impression that the rat is very resistant to effects of inhaled particulate in general, and asbestos in particular. That is, very high exposure levels are needed to produce an observable tumor yield, and therefore asbestos appears a carcinogen of low potency, in contrast to experience in people. However, the mouse and

hamster are almost completely resistant to inhaled particulate including asbestos.

As stated in the Roadmap, primary goals for NIOSH are to conduct research and make recommendations for the prevention of worker injury and illness. In this situation, NIOSH is re-evaluating its definition and recommendations for worker safety for asbestos and other mineral fibers. The main concerns raised in the Roadmap are 1) how to deal with fiber-like cleavage fragments from non-asbestiform analogs of asbestos minerals; 2) whether other fibrous minerals should be included in the policy definition (e.g., winchite, richterite, erionite); 3) if the analytical components of the NIOSH Asbestos Definition should be modified or updated; and 4) whether additional *in vitro, in vivo*, or epidemiological research is required to better understand the factors that contribute to the toxicity of asbestos fibers. There is the suggestion that it might be possible to identify a unified theory of fiber toxicity based upon the research proposed.

As requested of each of the peer reviewers, I will provide answers to the questions submitted in the letter of June 29, 2007. However, I wish to propose that given current events, other research priorities might take precedent over those listed in the Roadmap.

1. With the ongoing issue of banning asbestos in this country (Congressional Hearing "Examination of the Health Effects of Asbestos and Methods of Mitigating Such Impacts" June 12, 2007), it would seem that NIOSH should focus its efforts on understanding the health effects of materials that would be considered as substitutes for asbestos. Even though a stated goal of the Roadmap is to include other mineral fibers in the discussion and analyses (including man-made fibers or synthetic vitreous fibers such as refractory ceramic fibers, mineral wool, glass wool, fiberglass, etc.), this should become a primary goal of NIOSH.

2. As noted in the Roadmap, the occupational exposure to production and use of asbestos has declined in the past 20-30 years. However, other significant exposures to asbestos fibers continue in certain settings that include occupational and environmental exposures. These exposures are becoming more of a health issue in recent years and include short-term exposures to asbestos fibers that are part of dust from building collapse and demolition (WTC 9/11), asbestos exposures in abatement work, and asbestos contamination of other material (vermiculite). These latter occupational and environmental exposures will require further research to determine what short-term and long-term health effects may occur. This research would be conducted with collaboration with other government agencies: EPA, ATSDR, NIEHS.

3. NIOSH could also continue to provide guidance in diagnosing asbestos-related lung diseases in individuals with previous exposures. Given the number of cases of litigation in this country for asbestos-related diseases (asbestosis, pleural disease, lung cancer, mesothelioma), NIOSH could recommend diagnostic criteria for better identification and characterization of these diseases. These criteria would include B-readings of chest radiographs, CT scans of the chest, use of lung biopsy results, use of pulmonary function test results and exposure histories.

A general editorial note: I feel that the report is sorely lacking in illustrations, in particular photographs that would help the layman visualize the terminology used in the paper, such as asbestiform, cleavage fragment, nonasbestiform, etc. As they say, a picture is worth a thousand words. Without pictures and examples, the asbestos terminology can be especially difficult to visualize, but they become readily apparent with photographs.

Asbestos is a known carcinogen and inducer of fibrosis of the lung parenchyma and pleura. The Occupational Safety and Health Administration (OSHA) initially regulated its use in the United States in 1971 as an Emergency Temporary Standard and in June, 1972 promulgated a “final” standard designed to protect workers from the development of asbestosis. In 1986 and most recently in 1994,

revised standards were promulgated for the regulation of chrysotile, amosite, crocidolite, tremolite, anthophyllite, and actinolite asbestos. OSHA lowered the permissible exposure limit (PEL) from 5 f/cc in 1971 to 0.1 f/cc in 1994, noting in the most recent standard "… reducing exposure to 0.1 f/cc would further reduce, but not eliminate, significant risk."[1] With regard to its decision not to separate these fiber types for regulatory purposes, OSHA stated in 1986 that "… to summarize the data on risk differential by asbestos fiber type, human epidemiological studies have suggested that occupational exposure to amphiboles is associated with a greater risk of mesothelioma than is exposure to chrysotile….No clear risk differential for lung cancer or other asbestos-related disease has been demonstrated by epidemiological studies. Animal experiments, however, have indicated that chrysotile is a more potent carcinogen than amphiboles when administered by inhalation or intrapleural injection…"[2] This decision and its rationale were reaffirmed by OSHA in 1994.[1]

Thus, for more than three decades asbestos has been recognized and regulated as a hazardous substance with the potential to cause multiple exposure-related diseases and without known safe level of exposure. These exposure-related diseases include asbestosis, lung cancer, malignant mesothelioma, and gastrointestinal cancers. The use of asbestos has been banned by the European Union, Australia, Argentina, Chile, Iceland, and a number of other countries. There is widespread support for a similar ban in the United States. New-use-exposure in the United States results from work with and around a limited number of asbestos-containing products, including brake linings, roofing materials, and gaskets. Exposure to in-place asbestos occurs as a result of maintenance and demolition activities. We know how to prevent worker exposure where the potential for asbestos exposure is known – through worker education, product labeling, wet down, isolation, and respiratory protection. Unfortunately enforcement of regulations that require the use of such protective measures is spotty and inadequate.

To what end, then, is NIOSH and are we now, in 2007, considering the development and implementation of a complex, comprehensive, and expensive "roadmap for scientific research" on "asbestos and other mineral fibers?" Should we not instead be focusing our efforts on enforcing existing regulations to protect the health of workers?

This reviewer believes that we can and should be doing both. In my opinion, the Roadmap is important for reasons that include the following: 1) The use of asbestos in developing countries is widespread and increasing. 2) There is a need for better understanding of such issues as the toxicity of short fibers, the importance of biopersistence to toxicity, and interactive effects of mixed dust components such as asbestos and silica and amphibole and serpentine fibers. 3) There is a need for a better understanding of health risks associated with land development and residential occupancy of areas with naturally-occurring seams of asbestos, such as El Dorado County, CA.[3,4] 4) There is a need for better understanding of risks from background environmental exposures not associated with residence near an asbestos source. 5) The research should be relevant to determination of health risks associated with dust exposures in workplaces not known to contain asbestos or asbestiform fibers, such as the taconite mines in Minnesota, and to risks from talc mining. For the former, data are lacking; for the latter, data are conflicting.[5] And 6) the research contemplated may aid the development of pre-clinical indicators of asbestos-related disease that can be made readily available in the clinical setting and utilized for secondary prevention. OSHA enforcement of existing regulations and those that may be recommended as a result of this endeavor is beyond the scope of this review.

I echo the concerns of some of those who have provided oral and written comments to NIOSH when I point out that participants in research carried out under the auspices of the Roadmap must clearly state beforehand any potential conflict(s) of interest and, where such conflicts exist and are significant, be excluded from participation. The body of prior research in the area of asbestos-related disease is substantial and should not be victimized by future research that is tainted by bias.

Literature cited in this review is obviously quite limited. A comprehensive review of the relevant scientific literature as part of the Roadmap is one of the recommendations of this reviewer.

1. **Is the discussion of health effects of asbestos and mineral fibers a reasonable reflection of the current understanding of the evidence in the scientific literature?**

Comments
The Roadmap contains an excellent summary of the issues surrounding the definition of fiber, trends in asbestos uses and occupational exposures, asbestosis and mesothelioma trends, and NIOSH REL. There is little on mechanisms of health effects, which must be in the Roadmap if it is to be a document highlighting priorities. Health effects are not being studied by NIEHS, NHLBI, EPA, or other agencies, and have thus fallen through the cracks. There are significant sums of money in this field through trust funds and plaintiff lawsuits that the diagnosis and treatment of these diseases should have some Congressional credence.
In general, yes, but several more recent references need to be incorporated. For example, on page 5 it is stated "Results of some studies suggest that other diseases (e.g., laryngeal cancer, digestive system cancers, and immune disorders) are also associated with exposure to asbestos fibers [ATSDR, 2001]. This statement should be modified in accordance with the most recent panel report from the IOM (Samet J. et al., Asbestos: Selected Health Effects, National Academy of Sciences, Washington, DC, 2006). Also it is unclear why the number of malignant mesothelioma deaths in Fig. 4 are more elevated and have not peaked as have the US SEER data which should also be referenced. The statement on p. 7 , "A risk-free level of exposure to asbestos fibers has not been established " should be omitted or qualified especially in terms of the summary of dose-response epidemiologic, rodent and cell culture studies and conclusions presented in the HEI Report, "Asbestos in Public and Commercial Buildings', 1991. The statement (p. 9) "The testimony characterized the evidence for excess lung cancer risk attributable to fiber-like cleavage fragment exposure as "equivocal"." should be referenced with scientific publications to support it. 'Cleavage fragments' vs. 'fiber-like cleavage fragments' need clear definition. Moreover, throughout the document, the term asbestos is used without reference to what type of asbestos (p. 9, "During an exposure survey NIOSH identified airborne fibers of asbestos, but the mining company maintained that the mineral is not asbestiform". I also found the document biased in terms of either not including references at all for important statements, i.e. (p. 13) "Evidence from animal and some *in vitro* studies suggests that short fibers (e.g. less than 5 microns long) may have some role in fibrosis but are of a lesser concern that longer fibers for cancer development." Other statements were not in line with mainstream scientific conclusions nor published data , i.e. (p. 13) "Although the presence of the short fibers does not substantiate causality , the authors concluded that short, thin (chrysotile) asbestos fibers should be included in the list of fiber types contributing to the induction of human mesothelioma". These views are contrary to the conclusions at the EPA Workshop on Mechanisms of Toxicity, Chicago, 2003 and ATSDR meeting on effects of short fibers chaired by Dr. Lippman in NYC thereafter.
This question must be answered as though it were two separate questions. First, “Is the [Roadmap] discussion of health effects of asbestos a reasonable reflection of the current understanding of the evidence in the scientific literature?” To this question, the answer is generally yes, although there are several areas not addressed. The issue of the appropriateness of the linear model for estimating risk from low level exposure was raised by Mr. Guidotti. NIOSH should evaluate if additional research in the area is warranted. The studies examining the differences in the carcinogenicity of chrysotile-asbestos as compared to amphibole-asbestos were not treated in depth. Mr. Lemon, former NIOSH official, states that the potency for mesothelioma is less for chrysotile than for amphibole. This issue should be addressed by

the NIOSH Roadmap.[5] The second question, however, is much more complex. "Is the [RoadMap] discussion of health effects of mineral fibers (i.e., non-asbestos particles that meet the RF definition) a reasonable reflection of the current understanding of the evidence in the scientific literature?" To this, the answer is no. The epidemiological studies describing amphibole cleavage fragment exposures are incomplete. The studies on Homestake and Mesabi are not discussed although they are widely cited in comments as studies that inform on the issue of cleavage fragments. Furthermore, there are a number of epidemiological studies of cohorts from the R.T. Vanderbilt talc mine in New York State that have not been adequately analyzed. Dr. Castleman and R.T. Vanderbilt both point out that the talc there is asbestiform, although it is not asbestos. NSSGA and R.T. Vanderbilt also point out that the product from the Vanderbilt mine contains more than 50% tremolite in its cleavage fragment form. Surely the epidemiology of these New York State talc miners and the results of animal studies[6] and cell studies.[7] on the material from this mine should be considered carefully.[8] In fact, NISOH did not cite any study that shows an asbestos-like risk from fragments meeting the RF definition in the absence of asbestos, but did not state clearly that no such studies exist.[9] A general inadequacy of the literature review was also pointed out by Dr. Berman. The USGS questions the use of the Pan et al. reference to support an association between mineral particles found in the El Dorado Hills region and mesothelioma. These researchers did not consider time of residence in the region and the fact that part of the cohort had previous asbestos exposure. NIOSH should address this objection or remove this reference as informing about articulate from this area. In conclusion, amphibole asbestos is a known carcinogen. Certain populations of amphibole cleavage fragments have been shown to produce no excess in asbestos-related diseases. These populations provide evidence that there are amphibole populations that are carcinogenic and there are amphiboles populations that are not and they cannot be distinguished by the Regulatory Fiber Definition. Where to draw the boundary must be determined by a carefully drawn research protocol.
This is discussed in paragraph a. above. The discussion is a reasonable reflection of the current understanding in a qualitative manner. The quantitative issues raised in paragraph a. should be included. Somewhere the new understanding of carcinogenicity of particles generally, and nano-particles should be recognized.
Yes, but it is less than what is needed to fully appreciate the health risks associated with airborne inorganic fibers. It should also summarize the recent literature on the health effects of synthetic vitreous fibers (SVFs), which is highly informative on the issue of factors affecting the biopersistence of fibers in the thorax. This literature is relevant to both asbestiform amphiboles and serpentine minerals in terms of fiber dissolution *in-situ*, and to asbestos cleavage fragments in terms of breakup into shorter lengths.
Yes, the *Roadmap* is a "reasonable" reflection of the current understanding. A full treatise on the health effects of asbestos requires an entire book, such as a recent book by Dodson and Hammar (2006, *Asbestos—Risk assessment, epidemiology, and health effects*: Boca Raton, Florida, Taylor & Francis Group, 425 pages). A comprehensive report that summarizes the health effects and causal

[5] The question of chrysotile vs amphibole was also raised in the comments of Guidotti and Ahmed.
[6] Stanton et al., 1982; Smith et al., 1979
[7] Wylie et al., 1997
[8] Dr. Gibbs and Dr. Nolan's comments support this recommendation.
[9] This issue was raised by the NSSGA, Dr. Berman, Dr. Gibbs, and IMA-NA.

mechanisms ***of all mineral fibers*** has apparently not been written to date, which is one reason that NIOSH was compelled to produce the *Roadmap.* It seems a great deal to ask that the *Roadmap* must reference ***all*** of the landmark literature that is relevant to the health effects of asbestos and mineral fibers. Rather, I view the *Roadmap* as simply an outline designed to refocus the efforts of the scientific community. Follow-up work from the *Roadmap* should include development of a comprehensive list of the most relevant scientific literature, which should be compiled, evaluated and synthesized by a blue-ribbon panel. Public reviews of the *Roadmap* have recommended many references that could be added to the next draft to enhance the document's discussion of health effects. NIOSH will have to pick and choose from this list for the final draft of the *Roadmap*. However, to implement the research recommendations of the *Roadmap,* a select panel of experts should select the most important and relevant literature, not a public-wide selection process. I believe that the *Roadmap's* role is to summarize the lack of consensus within the scientific literature regarding mineral-fiber issues, while proposing a general plan to address the important scientific shortcomings that still exist; it has generally accomplished this goal.

Yes, the discussion of the known aspects of the health effects of asbestos is a reasonable reflection of the current understanding including the uncertainty regarding the health effects of fiber-like cleavage fragments. However, as mentioned above, the areas that need more complete discussion are the possible health effects of the synthetic vitreous fibers (SVF) or the man-made fibers such as refractory ceramic fibers (RCF), fiberglass, glass wool, mineral wool, etc. It appears from the literature that these asbestos substitutes may not exhibit the toxicity of asbestos regarding carcinogenicity or fibrogenesis; however, these materials do have some degree of toxicity that needs further evaluation with subsequent recommendations for worker safety. I know that NIOSH has a criteria document for RCF: "NIOSH Criteria for a Recommended Standard, Occupational Exposure to Refractory Ceramic Fibers" May 2006. Discussion should include that document and other relevant literature.

The discussion of known health effects of asbestos in the Roadmap is a reasonable reflection of current understanding of the evidence. Although the scientific literature cited is inadequate, the human health effects of exposure to asbestos are well known and include, as the Roadmap points out, asbestosis, malignant mesothelioma, lung cancer, and pleural plaques. Other reported health effects for which the literature is less abundant, such as gastrointestinal, laryngeal and kidney cancer, are mentioned only in passing and should be given greater consideration in light of the literature that does exist.[6-9]

I agree with Dr. Berman's recommendation that contradictory literature should be reconciled, to the extent possible. Such reconciliation, if carried out without bias, should help pinpoint specific knowledge gaps and aid in prioritization of research efforts in more controversial areas – such as the health effects of cleavage fragments, short fibers, mixed dusts, low level, and "background" exposures.

Health effects of exposure to mixed dusts warrants more attention in the Roadmap, as a number of those offering public comments noted. For certain occupations such as mining and construction work, workplace exposure is predominantly to mixed dusts. For asbestos miners, airborne dust contains mixed asbestiform fibers, asbestiform and nonasbestiform fibers, and cleavage fragments. The International Agency for Research Against Cancer (IARC) (1998) and Smith's (1996) general review of chrysotile and malignant mesothelioma have raised the question of synergy between amphibole fibers and chrysotile in the development of malignant mesothelioma.[10,11] More recently, McDonald (2001) has reported additive effects of amphiboles in a case-control study of fiber burden in the lungs of relatively young cases of malignant mesothelioma.[12] For workers in the construction trades, there is exposure to asbestos dust from the demolition of buildings with asbestos-containing material "in place" and from tunnel and underground construction work where asbestos-containing cement structures such as pipes are unexpectedly encountered. The cement contains not only asbestos but also

silica. Both are lung carcinogens and the health effects of simultaneous exposure to both deserves further study, as Dr. Egilman points out. Mr. Plumlee comments on the complicated nature of mixed dusts in the real world and raises appropriate questions about the toxicity of individual components.

2. Is the discussion of the current understanding of the analytical issues and the research needs for analysis of asbestos and mineral fibers appropriate and relevant?

Comments
No. The discussion was limited to PCM, PLM, and TEM. It provided an adequate description of the quite severe limitations of PCM (non-detects for thin fibers and no capacity to distinguish asbestos from other visible structures with aspect ratios >3). Also, it provided an inadequate discussion of an important limitation of TEM (seeing only partial lengths of long fibers that intersect grid bars or are hidden by grid bars). There was no discussion of state-of-the-art SEM, which can resolve all but the very thinnest fibers, can identify the fiber type, can measure the lengths of all long fibers, and can distinguish between asbestiform fibers and cleavage fragments. Furthermore, there needs to be a discussion of protocols that require the determination of the distributions of fiber lengths and diameters for hazard evaluation.
It was apparent from the discussion at the meeting on May 4, 2007 and the material submitted to the docket that this area requires further discussion for analytical tools including the role that Scanning Electron Microscopy would add to the identification and characterization of asbestos fibers as well as cleavage fragments. In terms of sampling strategies, it will be important to work closely with the other federal agencies (including the EPA) to arrive at some consensus for the characterization of air samples of particulates that include asbestos fibers and man made fibers. There continue to be differences in the terminology for particle size measurements between occupational and environmental scientists who study the health effects of particulates. The deposition of particles within the lung and airways depends upon several factors including the mass median particle diameter and the geometric standard deviation as well as the aerodynamic particle diameter. The terms PM_{10}, $PM_{2.5}$, etc. are used in the environmental literature whereas the occupational scientists often refer to the inhalable, thoracic, and respirable aerosol fractions.
The question of the measurement of low levels of asbestos is an important one. There is a significant variability in the detection limits of the PCM method among particle types. For example, PCM measurements of chrysotile-asbestos are lower than for grunerite-asbestos for the same fiber concentration due to differences in width and in visibility. Understanding true risk requires that a more accurate method of measurement be developed. [10] Mr. Laubenthal states that the "method does not work to provide statistically reliable data as employed in a majority of sampling situations" due to low fiber concentrations. NIOSH should address this point if it disagrees with his conclusion. Question 2 also addresses the analytical issues and research needs presented by mixed particle populations, such as those found in industrial mineral mines, mills, and products and in some non-industrial settings such as the El Dorado Hills, CA, region. In these environments particles other than asbestos dominate the population of airborne and bulk particles. The analytical problem becomes one of establishing the presence and/or assessing the abundance of very small amounts of asbestos, an issue inadequately addressed by the RoadMap. This is a pressing problem and would benefit from early attention on the research agenda.[11]

[10] ASSE, A. Oberta, T. Laubenthal, Dr. Brown and Dr. Berman support this recommendation.

[11] The NSSGA and the IMA-NA both stressed its importance in their comments.

Most importantly, however, the Roadmap does not adequately address what is known about the dimensional characteristics of asbestos, knowledge which must be incorporated into the solution of all analytical problems. In the following section I provide an overview of what is known. I have also addressed specifically several analytical issues that must be considered in using an analytical method based on electron microscopy.

1.) Asbestos dimensions

NIOSH states that there was "a lack of routine analytical methods for airborne exposure that can be used to accurately differentiate non-asbestiform cleavage fragments from regulated asbestos fibers that meet the dimensional criteria of a [RF] fiber when examined microscopically." This may have been true in 1971 when asbestos was first regulated under the asbestos standard, but today the data are available to correct this problem. IMA-NA point out that it is the knowledge of the true nature of asbestos by the analyst that most influences the reliability of asbestos identification. My experience supports this conclusion.

Many published studies describe in detail the dimensions of asbestos fibers, including those from occupational air monitoring and from the lung of asbestos workers. The Roadmap does not discuss them adequately, and their significance to the proposed research agenda appears to have been dismissed. Perhaps I am particularly sensitive to the limited treatment of this topic in the Roadmap because I have spent so much time working on it. In the paragraphs below, I have summarized the general characteristics of asbestos dimensions. It should be clear that enough is known already about asbestos fiber size distributions to describe them accurately.

The most distinctive dimensional characteristic of asbestos is the narrow width of its fibers.[12] Commercial asbestos is composed of mineral fibers that are less than 1µm in width with abundant fibers less than 0.5 µm.[13,14] The widths vary somewhat within and among mineral deposits, but the range is narrow. The widths of fibrils of the three most abundant forms of asbestos are similar: riebeckite-asbestos fibrils (fibrils are the small building blocks of all asbestos fibers) are about 0.05 to 0.2 µm in width, grunerite-asbestos and anthophyllite-asbestos are about 0.2 to 0.7 µm in width , and chrysotile is about 0.02-0.065 µm. [15]

[12] Wylie et al. (1993) summarized all published data on the width of asbestos fibers found in bulk samples, on air monitoring filters, and in lung tissue.)
[13] Fibrils wider than 1um are brittle (lack tensile strength) and cannot be used as asbestos (see Zoltai, 1981 for an excellent discussion).
[14] Wylie et al., 1993
[15] Polygonal serpentine fibers may have diameters up to 10,000A. (Baronnet and Devouard, 2005)]

[16] Warnock, 1984
[17] Lippmann, 1990
[18] Wylie, 1993
[19] Wylie., 1993
[20] NIOSH must also consider the difference between diameter and aerodynamic diameter, particularly as fibers increase in length beyond 5µm.

[21] Supported by the testimony of Drs. Lee, Berman, and Webber.
[22] The presentation at the May 7 meeting by RJ Lee and associates suggested that the capability is available.
[23] This point was supported by comments from A. Oberta
[24] Data based on fractal models of riebeckite-asbestos from Cape Province, South Africa. The regularity of the distribution of length enables estimates of the ratio of the number of fibers of one length to those of another. Data derived from equation: log number = -1.6log length + b. (Wylie, 1999).
[25] A point made by Dr. Berman, Dr. McConnell, and Dr. Lai,

Other types of commercial amphibole-asbestos used in building material and coatings also have narrow fibrils. Actinolite-asbestos has fibril widths of about 0.06-0.2 µm and tremolite-asbestos fibrils range from about 0.2 to 0.6 µm. At Libby Montana, where the asbestos was not commercial and the deposit was worked for vermiculite, mean widths are about 0.5A and the range is 0.2 to about 1µm.

These tiny fibrils form composite fibers. The fibrillar structure of asbestos fibers is readily apparent in asbestos-containing bulk material when examined by polarized light microscopy. These large, distinctively characteristic fiber bundles make identification of asbestos in bulk material relatively straightforward.

Studies of the lung burden of asbestos workers also report very narrow fibers. In general, mean widths of the lung burden populations are less than the mean widths of bulk samples of the same type of asbestos. These differences can be accounted for by the fact that bulk samples, even well dispersed, contain composite fibers made up of multiple fibrils, many of which could not be inhaled.

Martha Warnock measured 3723 fibers from lung tissue from 27 mesothelioma cases and identified them by TEM as crocidolite (riebeckite-asbestos), tremolite, anthophyllite, actinolite, chrysotile, amosite(grunerite-asbestos), or other.[16] More than 60% of the fibers were identified as either amosite (grunerite-asbestos) or chrysotile. The mean width of the entire population was 0.26 µm; for grunerite-asbestos it was 0.23 µm. and for chrysotile, 0.06 µm. Similar dimensions were observed by Warnock in asbestosis and lung cancer cases.

Berman et al. (1995) extensive and careful evaluation of the 13 different experiments in rats conclude that the fibers that contribute to tumor risk are <0.4 µm in width or they are bundles and aggregates of such fibers. Stanton et al. (1981), Lippmann (1988), and others find that fibers 0.8 µm or less in width are most likely to be carcinogenic. The penetrability of airborne fibers into the peripheral rat lung drops sharply with aerodynamic diameter above two, corresponding to a diameter of approximately 0.67µm.[17] These dimensions are consistent with the actual dimensions of asbestos fibers.

While long fibers are usually found in asbestos deposits, in all deposits of all types, short fibers are many times more abundant that long fibers and the range in fiber length is several orders of magnitude. The frequency distribution of fiber lengths follows the general form of the equation:

$$\text{Log number} = M \log \text{length} + b.$$

M is a negative number for all asbestos populations because number and length are inversely correlated. The magnitude of M and that of b are population specific. Similar equations approximate well the distributions of width and mass.[18]

The dimensional characteristics of asbestos fibers should be recognized in the Roadmap's discussion of asbestos and considered in establishing priorities for future research. For example let us take the question raised by NIOSH about whether or not 3 µm should be taken as a minimum width of asbestos. Published studies of asbestos populations demonstrate the scaricity fibers wider than 1 µm and studies of fibers found in lung tissue of humans exposed to asbestos rarely if ever report fibers wider than 1µm.[19] Of what relevance are 2 or 3 µm wide asbestos fibers in terms of fiber number? [20]

2. Revised Analytical Method based on Electron Microscopy

Mineral identification, determination of chemical composition, and accurate morphological descriptions of airborne particles would be facilitated by using electron microscopy.[21] Narrow fibers

are more visible by EM than by optical microscopy, and the variability in visibility of chrysotile and amphibole-asbestos in the membrane filter method (discussed below) would no longer be a problem. Electron microscopy adds the capability of chemical analysis, and TEM can provide structural information by electron diffraction. Based on my knowledge of phase contrast microscopy, little is to be gained by research on extending its resolution capabilities as a solution for routine air monitoring in a complex mixed dust or a low level exposure environment unless it is part of a two-tiered approach such as that suggested by R.J. Lee, in which only particles of 1 µm or less in width are identified by PCM, followed by electron microscopy if these exceed the exposure standard.

In many routine SEM's the visibility of chrysotile is not controlled by the resolution of the microscope but by the lack of contrast in mass between chrysotile and filter. The capability of the Field Emission SEM (FESEM) to visualizing individual chrysotile fibrils at the same level as a TEM should be carefully evaluated.[22]

There are also limitations in using TEM that were described by several of the individuals who spoke at the Forum, in particular the lack of ability to deal with fibers longer than TEM grid openings. In the Roadmap, there was no discussion of the problems that long fibers present in TEM, including the fact that long fibers are hidden by the grid bars used to support the sample. If an analytical method were to be developed that relied on TEM, this limitation must be considered.

Conversion of exposure assessment between TEM and phase contrast method fiber counts presents particular problems**.** The Roadmap assumes that the lower limit of visibility of asbestos fibers on air monitoring filters viewed by phase contrast microscopy is a function only of the resolution of the optical system and can be approximated by 0.25µm. This is an important assumption for comparing electron microscopy and phase contrast microscopy measurements.

V**isibility** depends both on resolution limit and the contrast in index of refraction between fiber and substrate. The assumption that the minimum width for visibility is 0.25 µm and that this assumption holds for all types of asbestos has not been tested. Work by Kenney et al. (1987) has shown that fibers of amosite as narrow as 0.125 µm are "visible" by phase contrast microscopy. Paraticles of crocidolite less than 0.25 µm would also likely be visible since both amosite and crocidolite have indices of refraction much higher than the clarified membrane filter. On the other hand, chrysotile has low visibility because of the lack of contrast in index of refraction, and it may be that chrysotile must be wider than 0.25 µm to be "seen". Equating exposure derived by analysis of air filters with phase contrast optical microscopy to that derived by analysis with TEM or FESEM requires that the assumption of width visibility of 0.25µm be examined carefully. It cannot be assumed.[23]

Differential Counting applied to PCM should be evaluated carefully. Inevitably, from a practical perspective, only an index of exposure can be used in any method. Let me illustrate the problem. If one were to count all riebeckite-asbestos fibers that were 1µm or longer, one would have to count about 13 fibers to count one 5 µm fiber and about 230 fibers to count one 30 µm fiber and almost 1600 fibers to find one that is 100 µm. [24] Since almost everyone who has studied the problem concludes that long fibers are the most hazardous,[25] some form of selective counting must be employed to evaluate the abundance of long fibers. As Dr. Berman points out, it is a misconception that including a greater range of particle sizes and shapes in counts is automatically health protective.

There seems to be scientific agreement that PCM is no longer the approach to identify narrow fibers, and that SEM is the way forward. NIOSH needs to support SEM technologies development and application to asbestos and other mineral fibers. NIOSH needs to support a variety of *in vitro* systems to order asbestos and other mineral toxicities. The RFA route is recommended for this.

Yes. Although I am not an expert in this field, I am convinced by testimony and the Roadmap that PCOM is archaic and TEM may be the only way to capture and evaluate very small thin fibers of

chrysotile. Since this technique is expensive and with apparent variable results from lab to lab, and SEM is being refined by others, perhaps research is needed to develop less expensive, reproducible methods for analysis of asbestos fibers. One might also rationalize that if there is little or no scientific evidence that short thin fibers are hazardous, expensive techniques such as TEM might not be justified. On the other hand, should large durable fibers that are not inhaled be quantitated for any reason?
There seems to be scientific agreement that PCM is no longer the approach to identify narrow fibers, and that SEM is the way forward. NIOSH needs to support SEM technologies development and application to asbestos and other mineral fibers. NIOSH needs to support a variety of *in vitro* systems to order asbestos and other mineral toxicities. The RFA route is recommended for this.
This is discussed in paragraph b. and c. above. The discussion is consistent with current understanding. However, the relationship between fiber counts and AHERA "structures" or cleavage fragments should be discussed.
The discussion is appropriate and relevant but inaccurate with regard to mineralogy based on comments submitted by Mr. Meeker and Mr. Virta and insufficient in the following respects. The discussion of the strengths and weaknesses of PCM and TEM is appropriate and relevant, as is the discussion of the weaknesses of existing exposure data based primarily on analysis using PCM (NIOSH Analytical Method 7400). The most important shortcoming of PCM is that thin short fibers are not counted. Further, the only chrysotile asbestos that is counted exists in the form of bundles that split longitudinally into fibrils following inhalation, thereby most likely increasing the dose of chrysotile to the lungs, as Drs. Lemen and Egilman point out. However, the use of scanning electron microscopy (SEM) as an analytical tool is not adequately discussed in the Roadmap, as pointed out by Drs. Lee and Strohmier; nor is there discussion of the combined use of PCM/SEM/TEM, as they recommend. An expanded discussion of both methods should be included in the Roadmap. The importance of standardization of analytical methods and oversight with regard to inter-operator and inter-laboratory variability needs more emphasis, and analysis of fiber burden in the lung should be added to the discussion. Presently there is no standardization of methods or reporting for fiber burden analyses. The Roadmap discusses the development and validation of sampling methods that would selectively sample thoracic-size fibers. Much is already known about deposition patterns of particles in the lung; and the relevance and necessity of using 3-D imaging or other models to further examine fiber deposition patterns within the lung is not adequately explained. Similarly, spending time further refining and expanding the capability of PCM does not seem like time well-spent. Better to spend time and resources studying complementary methods such as PCM/TEM/SEM and making those methods more widely available and less expensive. If PCM analysis reveals fiber exposure in excess of the PEL, exposure can be reduced by methods that include other wet down, isolation, ventilation, and respirator use pending results of electron microscopic analysis.
The discussion of analytical issues and the research needs for analysis of asbestos ***is*** extremely relevant. But, the coverage of analytical techniques in the *Roadmap* is a bit lacking. The use and limitations of PCM and PLM techniques are generally well explained in the *Roadmap*. However, the limitations of TEM techniques, aside from cost concerns, are not elaborated. For example, the very high magnification of TEMs restrict their field of view to portions of long fibers, rather than full views of lengthy fibers nor of clusters of fibers and particles; also, the small TEM fields of view tend to bias the analyst towards only the thinnest of fibers. The use of modern SEM methods is barely touched upon in the discussion, although SEM techniques have significant utility. In particular, many of the research questions proposed by the *Roadmap* will benefit from the use of modern SEM and electron microprobe analysis, in particular to observe the microscopic visual and chemical characteristics of

acicular mineral particles (such as determining the distinct features of asbestiform fibers vs. elongate particles vs. cleavage fragments).

An aspect of the discussion on analytical techniques that I find bothersome within the *Roadmap,* and in most other asbestos-related articles, is its tunnel-vision focus upon only the fibrous component in mixed-dust samples. As I elaborate in point 2 of my attached specific comments, a mixed-dust sample from a natural occurrence can contain a spectrum of amphibole morphologies, which can range in shape from equant (blocky) to prismatic to acicular to asbestiform. If a particular analyst or laboratory chooses to count and describe ***only*** the amphibole particles that meet their criteria of countable "asbestos" fibers, then the utility of the analyses is quite limited in evaluating the potential health effects of that dust. Particularly in research samples, the spectrum of acicular amphibole particles in a sample should be cataloged (length, width, surface feature information).

The matrix effects of asbestos-bearing rocks and soils are usually overlooked. Some of the accessory minerals and associated metals may contribute to the health effects of a nuisance dust, in addition to the mineral fiber component. The *Roadmap* can benefit future research by noting that matrix minerals and metals should be recorded and considered in forthcoming scientific studies and analyses.

3. Is the discussion of the current understanding of the epidemiological issues and the research needs for understanding the health effects of asbestos and mineral fibers appropriate and relevant?

Comments
As with health effects, the epidemiological literature that is cited is limited and contradictory findings have not been reconciled. Expansion and reconciliation, to the extent possible, are necessary to better identify gaps in knowledge and study populations that can be further examined. Most importantly, the Roadmap is fuzzy with regard to the types of epidemiologic studies that may be possible and are appropriate. Prospective studies of exposed populations are unethical and therefore should not be contemplated. Whether or not exposures can be reconstructed and re-examined as suggested by Dr. Berman is not at all clear. Real-world exposures are mixed, complex, and variable from one site to another and from one time to another at a given site. In addition, as Dr. Egilman points out, we have not been measuring thin fibers which are the most toxic and we have not been measuring short fibers about which there is considerable controversy. So accurate reconstruction seems a near-impossible task – at least with regard to exposures incurred during the manufacture of asbestos products and end-use of these products. Mining exposures can perhaps be reconstructed where the mine remains in existence and dust samples approximating the original can be obtained. There is no mention in the Roadmap of potential risk for malignant mesothelioma among iron ore miners. The Minnesota Department of Public Health has reported 52 cases of malignant mesothelioma among these miners in Minnesota (2007). Mr. Kelse references a study of the Reserve Mine employees in Minnesota as one of the "two most significant human cohort studies" that fail to support "same as" toxicity for exposure to nonasbestiform amphiboles. However, the Minnesota Health Department is sufficiently concerned that it has launched two additional studies of iron ore miners in the State. The dust that these miners breathe needs more definitive characterization and other potential sources of asbestos need to be examined before a conclusion can be drawn that dust in iron ore mines does not pose a risk. This issue deserves more explicit discussion in the Roadmap. Likewise, health effects of low level environmental exposure to asbestos from an identified source and "background" (no identifiable asbestos source) exposure need further investigation and are not sufficiently discussed in the Roadmap. Including reference to the study by Pan et al in the Roadmap was criticized by Mr. Virta on the basis of epidemiologic caveats. While it is true that the epidemiology of this specific study raised questions that could not be answered – two of the most important being lack of knowledge about possible occupational exposure to asbestos and duration of residence at the site, I believe it should not be discarded.[3] Strengths of the study are the large number of malignant mesotheliomas and the use of geocoding to estimate relative exposures by site of residence. At least one of the seams of ultramafic rock (El Dorado, CA) has been well characterized by the Environmental Protection Agency and the US Geological Survey (USGS). Chrysotile fibers were present; and tremolite morphology and aspect ratios were found to be "intermediate between what might generally be considered a population of commercial-grade asbestos particles and a population of cleavage fragments…", with "an aspect ratio distribution that has higher values and is clearly distinguishable from a cleavage fragment population but does not contain as many high aspect ratio particles as a commercial-grade asbestos population".[4] The data set used by Pan et al and geologic characterization of ultramafic rock seams could be expanded and utilized in future epidemiological studies of health effects of low level mixed dust exposure to asbestiform and nonasbestiform fibers and cleavage fragments.
This is addressed in paragraph f. above. The discussion is appropriate and relevant. The limit of direct observation for lung cancer of more than 1 per 100 attributable mortality should be added.

My background and expertise is as a geologist and mineralogist, so I have refrained from providing a detailed critique of the epidemiology portions of the discussion. However, I wish to re-emphasize that epidemiology studies that are related to ***natural deposits*** should, in addition to characterizing the mineral fibers, also include information on the mineralogy and geochemistry of the asbestos-bearing source rocks and soils.

Not Clear. There was some discussion in the Roadmap of studies of future epidemiologic studies that could advance our understanding of the influence of fiber characteristics on health risks. To be useful, any such study would need to provide data on fiber type (or fiber types if of mixed composition) as well as length and diameter distributions, and it was not clear that all or most of the possible future studies mentioned would meet this criterion.[Note: New analyses of archived membrane sampling filters based on old exposures can be useful, as Berman and Crump (1995) demonstrated in their work with TEM analyses of filters from the long series of chronic rat inhalation studies performed in prior years by Davis and colleagues at the IOM in Edinburgh. The results of the current NIOSH follow-up study of the archived sampling filters from the S. Carolina textile workers (Kuempel et al. [Abstract] 2006), when available as a full paper, could be especially interesting in terms of the fiber dimension distributions and, if possible, the role of tremolite fibers.]

In general, the answer to this question is yes with some exceptions. However, the RoadMap states that "a conclusion that exposure to fiber-like cleavage fragments does not cause cancer lacks certainty due to the limited quality of relevant human health and animal data." This statement echoes the comments of former NIOSH official, Richard Lemon who calls for "irrefutable evidence for safety." Irrefutable evidence for safety can never be obtained since it is impossible to prove a negative and no one would argue that breathing in large amounts of rock dust of any kind is safe.

The Roadmap discusses the epidemiology from a talc mine in New York, but does not include studies from Lead, South Dakota; Enoree, South Carolina; and the Minnesota taconite iron district.[26] These studies should be included and their relevance to the health effects of mineral "fibers" discussed, particularly their relevance to the "path forward".

Another problem not mentioned in the Roadmap is the inclusion in asbestos exposure data of rock fragments which meet the RF definition but which are not asbestos.[27] Such inclusion overestimates exposure to asbestos and may underestimate risk in epidemiological studies of workers exposed in a mixed dust environment such as a mine. The example given is the inclusion of antigorite (or lizardite) in the fiber count of chrysotile. Dr. Brown points out that in Canada an inverse relationship between exposure levels and risk for miners and millers was observed because rock fragment was included in the exposure of miners but not millers. This problem has also been described by Wylie and Bailey (1992).

The EPA has supported significant research on the characteristics of asbestos that correlate with toxicity, including both animal and human epidemiological studies. Berman and Crump (2003) have proposed specific fiber sizes of amphibole asbestos and chrysotile while recognizing that potency depends of fiber type. This approach was not treated in the Roadmap but it is highly significant and endorsed by the peer reviewers for EPA. It should not be overlooked.[28]

The need for addition epidemiological studies in industries with exposure to various types of elongated particles is appropriate and relevant. However, there is no clear plan or criteria for choosing the sites that would be most informative. Most information would be obtained if there were a wide range of dimensional characteristics of airborne mineral particles across these studies and if the mineralogical

[26] McDonald et al., 1988, McDonald et al., 1978, Brown et al., 1986, Higgins et al., 1983, Cooper et al., 1992.
[27] This was discussed by both NSSGA and Dr. Brown in their comments
[28] Georgia Pacific Gypsum comments point out this problem.

characteristics of the airborne particles are well described. The USGS strongly urges conducting experiments using the same mineral from different localities to evaluate the influence of small differences in chemical composition, oxidation state of iron, manganese, etc., trace elements, etc. Furthermore, the dimensional characteristics of fragments of the same mineral will be different in different localities. There are a number of mining localities where actinolite is found and it might be a good candidate for study. The USGS can provide advice to narrow a selection of potential sites based on the characteristics of the airborne particles. Finally, Dr. Berman suggests that much would be gained from a detailed reconstruction of the exposure to asbestos for cohorts for which epidemiological studies are currently available. He proposes characterizing samples from the mines and mills in a standard way and from these a better assessment of the ranges of particle sizes and shapes to which the workers were exposed can be obtained. I recommend that NIOSH consider Dr. Berman's approach carefully as it may provide data currently unavailable and may prove to be most valuable.
This seemed truncated in view of its central importance to the mission of NIOSH in protection and treatment of workers afflicted with asbestos diseases. I would hope for more development of themes such as the poor prognosis of asbestos-related diseases and needs for research on new preventive and therapeutic strategies especially in high-risk individuals.
Although the discussion of the epidemiology related to asbestos fibers appears appropriate, the discussion regarding epidemiology for man-made fibers is lacking. Regarding research needs, it would be difficult to envision future epidemiological studies that would evaluate the health effects of workers exposed to asbestos. At best, re-evaluation of previous studies could be done with improved characterization of the exposures. However, this seems to be of questionable value given the decreasing exposure to asbestos in general. As mentioned above, future needs are for evaluation of health effects to asbestos exposures that might occur in short-term situations (building collapses or demolition) or in abatement situations or to the asbestos that occurs as contaminant in other minerals.
The Roadmap contains an excellent review of the epidemiological issues. The Minnesota taconite industry needs an epidemiological study. There should be more pathological studies of tissues and fiber analysis. Warnock has found long thin asbestos in tissues. There are important findings on actual dissolution of chrysotile in lungs, with retention of tremolite and commercial amphiboles—this area needs an infusion of new insight and analysis through a RFA. Many hungry young pathologists should be enticed to enter this field. Reconstruction of South Carolina textile plant exposures and fiber characteristics should be very interesting.

4. Is the discussion of the current understanding of the toxicological issues and the research needs for understanding the health effects of asbestos and mineral fibers appropriate and relevant?

Comments
Yes, but not adequate. The discussion would have been adequate for a condensed summary. Toxicological studies involving fibers need to be conducted with carefully selected fibrous materials having suitable compositions and length and diameter distributions. I was troubled by the unqualified indication on page 33 that future inhalation studies would probably be conducted with chrysotile. There was no recognition of the importance of the source of the chrysotile, or how it would be prepared for the exposures. Would it be Quebec chrysotile (contaminated by tremolite) or Brazilian or

Zimbabwe chrysotile (with little, if any, tremolite)? Would it be milled (as in the UICC materials) so that it would have relatively little long fiber? I was especially disappointed that these potentially major determinants of fiber toxicity were not even mentioned.
There is little such discussion in the Roadmap. Normal human bronchial epithelial cells, type II alveolar epithelial cells, and human monocyte-derived macrophages or human alveolar macrophages can now either be obtained or grown in pure culture, and used to test for effects of asbestos and mineral dusts. NIOSH should create a specimen bank of asbestos and other mineral fibers characterized by width:length, asbestiform fibers, cleavage fragments, etc., carefully characterized by SEM and purity/impurity of samples for scientists to test with a variety of end points. End points could be genomics, proteomics, MAP kinase signaling pathways, or release of specific growth factors, cytokines, etc. Scientists should carry out studies looking at a whole variety of creative and innovative *in vitro* mechanisms of cell injury. This is not in the Roadmap; however, it is essential that NIOSH point the way, so that RFAs or internal studies could be planned for future implementation as funds become available.
Yes, in one sense. Appropriate and relevant questions are raised regarding which asbestiform fibers should be studied and whether nonasbestiform fibers, cleavage fragments, acicular and prismatic crystals should be included. The need for a better understanding of the relative importance of morphology vs. surface properties vs. chemical characteristics is discussed. No, in another sense. The database from which NIOSH is starting is inadequate and should be re-examined and expanded in light of public comments. Dr. Addison in his comments points out that the interpretation of results of a study conducted by Davis, Addison, et al (1991) on the differences in carcinogenicity of tremolite dust samples of differing morphology that is presented in the Roadmap in incorrect.[13] This inaccuracy should be corrected. The very important question of the relevance of animal studies to toxicity in humans is not adequately addressed, particularly in light of comments by Mr. Manuppello and Dr. Berman. However, reconstruction of past exposures in retrospective cohort studies is not an acceptable alternative as noted above. And as 3-D imaging models do not allow the study of toxic effects of asbestos fibers on the human lung, this method of toxicological investigation does not offer an acceptable alternative to animal studies at the present time. Thus, it seems that in vivo and in vitro studies will continue to be necessary to examine the toxicity of asbestos in its various forms, at least for the foreseeable future. There is insufficient attention given to the study of mixed dusts vs. pure samples. Drs. Egilman and Berman, Mr. Plumlee and others, commented on the importance of studying mixed dusts as that is what exists in the real world. It is important to examine whether there are additive or synergistic effects of amphibole and serpentine fibers, silicates and asbestos fibers, cleavage fragments and fibers. In my opinion, the Roadmap makes a mistake in assuming that biopersistence is critically important to toxicity. This assumption ignores the demonstrated toxicity and carcinogenicity of chrysotile asbestos, which is not generally considered to be biopersistent. The Roadmap and the research effort should address the issue of biopersistence and its role in toxicity and carcinogenesis as an *hypothesis* rather than a *known fact,* as it seems to do now. Not cited in the Roadmap is the important work of Dr. Arnold Brody demonstrating toxic effects of asbestos on the lung within a relatively brief period of time following inhalation in animal models. His work is relevant to, among other things, the question of the importance of biopersistence and should be included in the Roadmap. With regard to chrysotile, the results of studies by Sebastien, Suzuki, and Dodson showing that short chrysotile fibers are the predominant fiber type found in the pleura, pleural plaques, and mesothelioma tissue in studies of human populations are not discussed in the Roadmap.[14-16] These studies show a predominance of short chrysotile fibers and a paucity of amphibole fibers in the target organ of the

lung for mesothelioma, as Dr. Egilman and Mr. Hartley point out. Based upon a review of the relevant scientific literature, Dodson et al (2003) concluded that asbestos fibers of all lengths are toxic to the lung.[17] The significance of these findings deserves attention in the Roadmap and in the research endeavor. Also worthy of greater attention in both is the actual dose of chrysotile fibers delivered to the lung, given that chrysotile exists outside the lung in bundles, which are not counted by PCM, and then splits longitudinally into fibrils following inhalation, as pointed out in public comments by Dr. Lemen, Dr. Egilman, and others.

Given the lack of data regarding toxicity of cleavage fragments from asbestiform habits, of nonasbestiform particles with dimensions similar to asbestiform particles, and of short fibers, as well as the inherent shortcomings of the historically-relied-upon PCM method of qualifying and quantifying exposure, it would, in my opinion, be premature for NIOSH to exclude any of these from the Roadmap, the research agenda, or its regulatory recommendations.

Two separate issues would need further discussion: 1) all the factors that might contribute to the toxicity of asbestos and 2) what different factors might contribute to different aspects of toxicity. As has been shown in the literature and material supplied to the docket, other factors than size, shape and biopersistence may play an important role in the toxicity of asbestos. Surface properties of the asbestos fibers seem critical to the subsequent release of inflammatory mediators in tissue leading to injury and disease. This requires further discussion. Also, an issue that has not been discussed is the different mechanism or pathophysiology of asbestos that can lead to different outcomes. As is known, asbestos exposure has been associated with lung fibrosis (asbestosis), pleural disease (pleural fluid and pleural thickening/plaques), lung cancer, pleural cancer (mesothelioma), and possibly (according to the ATS) airways obstruction. What are the properties of asbestos that result in fibrosis compared to the factors responsible for cancer? How are the pathways for carcinogenicity different from fibrogenesis? Are there different mediators involved and are different properties of the fibers (size, shape, dose, surface properties) responsible for different actions of the fibers in tissue?

A stated goal for the Roadmap is to identify a possible unified theory of fiber toxicity. Although this is a laudable goal, it does not appear that such a unified theory will be forthcoming and more importantly, it is uncertain how helpful such a theory would be for risk assessment and worker recommendations for different fiber types.

The RoadMap states that there is an important need for particle populations of narrow length and width ranges for experimentation purposes. For many years experimentalists have wanted mineral populations with very narrow dimensional ranges but this goal has been illusive. Berman points out that populations with particles of particular length and width in differing proportions can be used to correlate particular dimensional categories with a particular biological response across multiple studies. Since it is not strictly necessary to have populations with narrow ranges in width and length, a more likely attainable goal would be to have samples that will produce the same results using an approach described by Berman. This approach has the potential to reduce the number of experiments needed and reduce sample preparation costs. Its utility should be evaluated by NIOSH.

Choice of the appropriate samples to answer the toxicological issues is a major issue that has not been addressed by the Roadmap but is essential for defining the research agenda. The samples must be chosen carefully and systematically. The Roadmap needs a plan for doing so.

One of the authors of Davis et al. (1991), John Addison commented that the Roadmap misstates the results of the study.[29] NIOSH should rewrite the section dealing with the Davis study, or justify its conclusion by addressing Addison's comments.

[29] This problem was echoed by NSSGA and the comments of R.J. Lee.

Biodurability Issues

Studies of amphibole and chrysotile durability in the human body are not mentioned in the Roadmap. Studies of riebeckite-asbestos, talc, olivine, quartz and chrysotile point out the effects of structure and chemical composition on biodurability.[30] Dissolution studies of riebeckite-asbestos have shown that it is likely to remain far longer than chrysotile in the lung. For example, a 1µm fiber of chrysotile should dissolve in 9 months vs. 6-13 years for riebeckite-asbestos of the same size under ideal conditions.[31] There are many lung burden studies that demonstrate that riebeckite-asbestos and other amphiboles are preferentially retained in the lung, supporting the dissolution studies.

If sufficient chrysotile is present and if conditions exist in the interior of macrophages or in other specific regions of the body where there are restrictions on the flux of fluids, it is possible that chrysotile saturation may occur and dissolution rates decrease. It may also be retained if it is coated. This area of research may be quite fruitful in understanding chrysotile's potential to cause mesothelioma and lung cancer.

Several of the comments provided to the Roadmap took up the issue of how long some critical number of fibers has to remain in contact and interact with a target tissue before disease develops. This appears to be a significant legal issue. If the time is short, as the lawyers who testified contend, then the issue of biodurability is not as relevant. The long latency period separating exposure and disease is taken as evidence for the requirement of biodurability, but could the damage be initiated early and only produce the disease long after the fibers have been removed? This question is important, and perhaps additional animal and in vitro mechanistic studies would provide insight into an appropriate measure of biodurability.

The major issues were touched upon- the need for dose-response studies in human target cells of asbestos-related diseases and animal inhalation experiments that replicate natural exposures with selected, well-characterized fiber preparations should be stressed.

This is discussed in paragraph d and e above. This discussion is not adequate without addressing the issues in those paragraphs.

Again, my background is as a geologist and mineralogist, not a toxicologist. NIOSH has received considerable input from doctors with many years experience in the study of asbestos toxicology. I defer to their expertise in regards to the specific issues of mineral-fiber toxicology. However, I can not emphasize enough that the toxicological samples and "standards" that will be used in future research must be very thoroughly characterized before they are applied to the test media. The asbestos standards used in past toxicological experiments are typically heterogeneous mixtures containing a variety of fiber dimensions intermixed with numerous accessory minerals and metals. The heterogeneity of the earlier-used asbestos "standards" may account, it least in part, to the seemingly contradictory results obtained from previous toxicology experiments. In order to produce a "gold standard" for use in inhalation studies, the character of the test material must be known in order to correctly interpret the study results. This important factor in study design—sample characterization—has not been discussed in the *Roadmap*.

[30] Werner et al., 1995; Hume and Rimstidt, 1992, Jurinski and Rimstidt, 2001

[31] Werner et al, 1995 Hume and Rimstidt, 1992.

5. Is the discussion of the path forward appropriate and relevant and is the ultimate vision a reasonable outcome for the proposed research strategy for asbestos and mineral fibers?

Comments
In general, yes. Regardless of the monies available and priorities, it is unlikely that one or more researchers not working cooperatively or with the same well-characterized mineral samples will generate conclusive and non-conflicting results unless NIOSH encourages collaborations between geologists, clinicians, toxicologists and molecular/cellular biologists in a coordinated Program Project-type approach. As emphasized above, epidemiologic studies are unlikely to provide data in a timely fashion.
The path forward is limited in scope and focuses on the possible identification of a unified theory of fiber toxicity. It is true that further investigation into the characteristics of fibers that contribute to the toxicity of carcinogenesis and fibrogenesis will be important. However, it is not clear how findings from such research will be translated into new and improved recommendations for reducing adverse health outcomes in workers.
Clearly, the goal of the *Roadmap*—"a unified theory of toxicity for thoracic-sized mineral fibers"—is appropriate and relevant, if perhaps overly ambitious. Numerous important issues remain controversial in asbestos-related science and regulation, such as identifying the primary attributes of mineral fibers that cause toxicity (particle morphology, length, width, diameter, and (or) chemical composition), the potency or lack of potency of "fiber-like cleavage fragments", sampling and analytical protocols, and dose response, as just a few examples. The very fact that so little consensus exists on the fundamental issues of mineral-fiber toxicity and risk management shows the need for a *Roadmap* for research. Many of these details within the draft *Roadmap* will be fodder for critique, but the general goals of this document are worthy. I applaud NIOSH for this attempt to gather the very large collective knowledge, scientific talents and resources of the federal government and its stakeholders and focus them towards this important, unresolved occupational and public health issue.
No. It provided only the barest elements of a path forward, and went off track by introducing the idea that there may be some commonality between inorganic fibers and engineered nanomaterials. Also, as mentioned in my response to Question #1, SVFs do not belong in some future analysis, but rather should have been front and center in this Roadmap . This Roadmap needs to be focused on the unique effects of long biopersistant inorganic fibers that cannot be effectively incorporated within lung cells or cellular component structures and processed as nuisance dust. While nanomaterials may also have unique interactions with lung cells because of their extremely small size and enormous surface/volume ratio, they are extremely unlikely to share common effects with long fibers longer than 10 to 20 *u*m.
The discussion of research strategies in the Roadmap is appropriate and relevant but needs to be expanded to include a more detailed discussion of such issues as relevance of animal models to human toxicity, whether reconstruction of historic exposures is possible and how that could be done, and strategies for examination of toxicity of mixed dusts. It is difficult for me to answer the second question, as I am not entirely clear from reading the Roadmap just what the ultimate vision is. On page v. of the Executive Summary there is the following statement: "….the ideal outcome of a comprehensive research program for asbestos and other mineral fibers would be the development of a unified theory of toxicity for thoracic-sized mineral fibers. A unified approach would specify criteria, such as a range of chemical composition, dimensional attributes (e.g., length range, diameter range, aspect ratio), and dissolution rate/fragility (biopersistence), for inclusion of fibers as potentially toxic." Reasons given for why this is an ideal outcome include 1) reduction in the need for comprehensive toxicity testing and epidemiologic studies of the effects of individual mineral fibers in the future, 2) facilitation of the determination of "the

potency of fibers for causing specific diseases and how that potency varies, depending on the particular combination of fiber characteristics and dose" (p.v, Executive Summary), and 3) the enabling of a "unified, coherent risk management approach for fibers" that could then be used to "minimize the potential for disease" (p.34, The Path Forward).

It seems to me that the ultimate goal should be (and perhaps is) to minimize the potential for disease in exposed workers and populations. With advances in analytical technology, the issues surrounding asbestos fiber toxicity have become more complicated, not less. The adoption of a "unified theory of toxicity" seems impractical if not impossible, given all of the variables discussed above, in the Roadmap itself, and by public commentators. Further, such a theory might actually increase the threat to the health of exposed workers by making it difficult if not impossible to obtain funding to carry out studies of the toxicity of new fibers or new uses of known fibers.

If the ultimate goal is to minimize the potential for disease, we have tools now that are effective in reducing risk. These are worker education and the mandated use of such methods as wet down, isolation, ventilation, and personal protective equipment, including appropriate respirators. One of the problems with this approach has been inadequate enforcement of existing regulations and inaccurate measurement of exposure levels and dose. Research efforts aimed at better understanding of health effects of exposures (e.g., mixed dusts, short fibers), improvement in *availability* of more sophisticated analytical tools to measure actual exposures, and improvement in design of respiratory protective devices, along with more stringent enforcement of existing regulations, might better serve the needs of exposed workers and the public. Research efforts should also be directed at the development and validation of pre-clinical biomarkers of disease, such as serum osteopontin levels, to facilitate secondary prevention.[18,19]

Mr. Meeker questions the advisability of such a unified theory on slightly different grounds. He notes that such a theory would be applicable to "a significant portion of the material covering the surface of the earth." He warns that "extreme caution" would be needed in applying the theory beyond basic research because of potential fall out related to "real or perceived environmental exposure" and the financial consequences to industry.

This is addressed in the introductory section

The path forward in the Roadmap emphasizes a unified theory for considering fibers as potentially toxic: criteria would include a range of chemical composition, dimensional attributes and dissolution rate/fragility. This is an exciting rational approach for which there already is evidence, viz magnesium and aluminum silicates that are very long (>20-40 microns) and very thin (<0.1 micron in width) and are biopersistent (erionite, crocidolite, chrysotile fibrils-although less persistent in tissue) might be good examples. Like many things in science, a unifying theory may not be achievable, and characteristics that could be studied and described might be as good as we can do. More importantly, NIOSH needs to focus on the way forward on the *in vitro*, animal, and human health effects of such fibers to evaluate mechanisms of health and toxicity response. This is not well done in the Roadmap.

Unifying fiber theory will never rest on dimensions alone, and the roadmap understates the role of mineral identity and the nature of mineral surfaces. As summarized by Hochella (1993), all of the following may play a role in the carcinogenicity of fibers:

- Surface and near-surface composition
- Surface atomic structure
- Surface micro-topography
- Surface charge and its dependence on pH and surrounding solution
- Dissolution rate
- Associated minor or trace elements

In addition to surface properties, there may be other factors that determine the potential of mineral

particles to injure tissue and that control access to particular tissue. The role of all of these factors must be a part of any theory of fiber carcinogenicity.

6. Is the terminology for minerals and fibers clear and precise enough to define the research? If not, what steps should NIOSH take to clarify the terminology?

Comments
No, I had difficulty and a different interpretation of fibers vs. particles and cleavage fragments. The term asbestos is apparently a commercial misnomer and should be changed to the correct names these minerals. The NIOSH definition of a fiber seems to be severely criticized by mineralogists and should be substantiated or changed according to the results of research generated by this Roadmap. 'Asbestos' should never be used with out a preceding definition of the type of asbestos, one problem I encountered when reading this document.
Yes, the terminology is clear, but it is not sufficiently precise. I do endorse the NIOSH policy of not being bound to criteria used by mineralogists, and to rely instead only on specific physical criteria (i.e., particles that meet specific dimensional criteria) and compositional criteria (chemistry) to define asbestos hazards. I also agree with NIOSH in not endorsing the exclusion of noncommercial minerals, such as richterite and winchite fibers. Such asbestiform fibers can clearly present in workplaces and environmental settings, and they have been causally associated with lung fibrosis and cancer. The imprecision problem is particularly evident in the Roadmap's overly cautious treatment of cleavage fragments of asbestos minerals. Asbestos cleavage fragments can potentially cause fibrosis and cancer if they are long enough, and thin enough. So can other fibrous minerals (e.g., erionite). Long, thin, vitreous fibers with sufficiently low *in vivo* dissolution rates can also cause fibrosis and cancer. What is needed, in order to provide sufficient precision for defining a hazardous fiber, is a description of the critical values for length, width, and biopersistence. NIOSH can and should address the need for such definitions by sponsoring a National Research Council committee that is charged with reviewing the extensive literature that already exists on these parameters, and comes to expert judgments on them, and on residual research needs. The NIOSH Roadmap can serve as a useful background document for such an expert committee.
No, as the public comments offered by representatives from the USGS point out. NIOSH should consult and work in tandem with the USGS in this regard.
The terminology is clear to the average occupational health professional, but not to the mineralogy cognoscenti. NIOSH needs to partner with the USGS on terminology and definitions for the Roadmap that are readily accessible to professionals in both the health and mineralological communities.
The reviewer is not conversant with mineralogy, and so can provide no independent review of these sections. Renaming the asbestos forms is not helpful to public health. Proliferating the names only opens loopholes for particular products. The mineral terminology itself is not systematic and conveys no more information about physical and biological properties.
This is one of the key issues for this entire research area: how best to define an "asbestos fiber". It has been well recognized that the current NIOSH definition for asbestos as used for regulatory purposes has policy and analytical components. The question now remains how best to refine the definition to include all materials that have a similar toxicity profile to the asbestos minerals now included in the definition (chrysotile, crocidolite, amosite, anthophyllite asbestos, temolite asbestos, and actinolite asbestos). I don't believe that using the mineralogist approach would be useful given the exhaustive list of minerals that might be included with some that may have no clinical relevance. However, beyond including all possible minerals, it is still unclear what would be considered to be the best definition of a "fiber" to include in the definition. It appears that the dimensions of aspect

ratio of ≥ 3:1 and a length > 5 m may be too inclusive and not that helpful in determining those fibers that cause adverse health effects. We can only hope that re-analysis of potentially toxic asbestos materials as collected in previous studies and those to be used in *in vitro* and *in vivo* studies using more advanced analytical tools (SEM) may be helpful in arriving at a more useful dimensional definition.

In my specific comments that are keyed to the text (attached), I've made a number of rephrasing suggestions for several passages in the text and in the glossary where the terminology requires correction or simplification. Also, I suggest that much of the mineralogical terminology would be more comprehensible with the addition of photographs and diagrams that illustrate the descriptive terms. The science and regulation of asbestos certainly has its share of jargon, which can be more readily illustrated with photographs and diagrams than with technical writing alone.

First, discussion of the health effects of asbestos and mineral fibers requires scientific rigor in the use of mineral terms. In a large measure, the lack of rigor in the application of mineralogical terminology in the regulatory and health effects literature in the past has resulted in the "confusion" about mineral fibers to which NIOSH refers. Because health scientist normally know nothing about minerals, and because mineralogists are not normally trained health professionals, and because understanding mineral-induced diseases is by its very nature interdisciplinary, all those involved must use terminology rigorously to facilitate understanding across disciplines.

Unfortunately the Glossary that accompanies the Roadmap contains unscientific mineralogical definitions which NIOSH substitutes for those of well established, rigorously defined mineral terms such as anthophyllite, tremolite, and so forth, terms that rest on an extensive body of highly regarded scientific work developed over the last 100 years. This glossary must be revised to conform to standard scientific definitions of all mineral terms. Please ask the United States Geological Survey to revise it. Examples of other problems in mineral terminology that should be reviewed by the USGS are given below.

1. Mineral names imply **only** a particular atomic arrangement of a fixed set of elements in particular proportions. Alone, they cannot be used to equate with a specific morphology because mineral habits vary. All such implications should be removed from this document**. If asbestos is meant, it should follow the mineral name, e.g., tremolite-asbestos; the document and all researches who write about asbestos should not use the term "asbestos mineral tremolite."**

2.) The discussion of amphibole nomenclature is inadequate. As happens in medicine or biology or any field of science, as knowledge is gained nomenclature evolves. Built on the extensive knowledge of amphibole chemistry and structure, the modern amphibole terminology was established by the International Mineralogical Association[32] and is recognized world-wide. There have been minor modifications since it was first established[33] and other modifications are possible[34]. At the present the IMA classification is **the** authoritative sources on amphibole nomenclature and the one on which regulations that name amphiboles must rely. The use of trade names ***in place of mineral names***, e.g., amosite for grunerite or variety names in place of mineral names, e.g., crocidolite for riebeckite, should be discontinued although it is reasonable to refer to crocidolite and amosite when characterizing commercial asbestos **products**.

If the regulatory definitions were to include all amphibole-asbestos, many nomenclature issues would be resolved. For example, it would remove the problem of regulating the winchite-asbestos at

[32] Leake et al., 1978
[33] Leake et al., 1997, 2004
[34] Hawthorne and Oberti, 2006

Libby, Montana. This position has been advocated by many mineralogists, including myself, and was supported by the comments of the USGS.

The term fiber

The Roadmap does not reflect the scientific literature on the origin of the RF definition of a fiber. It was developed during air monitoring studies conducted in British factories that utilized asbestos. A length of >5 µm was chosen to reflect an acceptable level of reproducibility by analysts using phase contrast microscopy.[35][36] It is not known why a 3:1 aspect ratio was chosen. Perhaps is was the recognition that asbestos found on an air monitoring filter as particles that were **3:1 or less** were unlikely to be inhaled. Five micron particles with an aspect ratio of 3:1 or less would range from large equidimensional particles to elongated particles wider than about 1.5 µm.[37] In either case such particles are unlikely to be inhaled because of their size. In the asbestos manufacturing and mining environments, a 3:1 aspect ratio could well have been considered to be crude limit on respirability of 5 µm particles. Whatever the reason 3:1 was chosen, it was arbitrary. It is not a scientific definition of a fiber, and it was not chosen because of any studies linked to health effects. The USGS states clearly that its use by NIOSH is improper. IMA-NA points out that the term 'fiber-like' is also a misnomer and misleading.

The Roadmap states that in the "scientific literature" mineral fibers include cleavage fragments. This is only the case in the regulatory literature, not in the mineralogical literature, for the reasons noted above. In mineralogical terminology, a mineral fiber attains its shape by growth; fibers are not and cannot be created by breaking minerals. The Roadmap should recognize that there is disagreement in the "literature" on the appropriate use of the term "mineral fiber".[38] I strongly suggest that the only way to resolve this conflict is to preface the word fiber with the term "regulatory" when what is meant is a particle meeting the RF definition.

[35] Addingley, C.F., 1966; Lynch et al., 1970
[36] Dr. Brown also commented that 5 µm was simply chosen for analytical efficiency.
[37] For example, a particle 20 µm long having a 3:1 aspect ratio would have a width of almost 7 µm.
[38] This point was made the USGS, IMA-NA, and the NSSGA.

7. Are the key issues identified that warrant further research and or synthesis? Has the literature been adequately cited to support the need for further investigation of these issues?

Comments
Overall, I believe the key issues that warrant new research have been addressed in the *Roadmap*. Many details and additional literature can be added, but I suspect that the intent of the *Roadmap* was to briefly outline the numerous complex issues that remain unresolved. As I noted in my answer to question 1, an entire book is necessary to detail all of the findings and uncertainties that surround asbestos and mineral fibers. A select panel will be necessary to compile the list of hundreds of relevant asbestos and mineral fiber papers and reports, evaluate their findings, and synthesize this knowledge. The *Roadmap* was a fine first-step in this process—an expert panel should be the follow-up
I believe that a key issue that warrants further research which hasn't been adequately identified or cited with literature is the safety of replacement man made fibers for asbestos. As mentioned above, this will be a critical issue in the field of asbestos research for the coming years. Also, the collaboration for asbestos research with other Federal Agencies (EPA, NIEHS, ATSDR) should be further defined.
No. The key issue is how do asbestos and other mineral fibers cause cancer? This is the key issue over the next 10-20 yr, and it is important that NIOSH play a role in this endeavor, since it is not being addressed by NCI, NIEHS, or EPA. NIOSH should take the lead and outline an approach. First, there should be mechanistic studies at the gene level beginning with target cells and genomics. Second, chromosome studies need to be developed on how fibers interact with chromosomes, and during meiosis. Third, murine models from the transgenic world need to be moved forward; these coinicide nicely with gene target studies from gene arrays. Fourth, biomarkers of detection of lung cancer and mesothelioma need to be developed for the tens of thousands with asbestos fiber exposure in past workplaces. NIOSH also needs to develop an agenda for fibrosis research. This should focus on the molecular mechanisms of EMT-epithelial mesenchymal transition using cell, animal, and human studies
Yes. However, I still think that more evidence for the need to emphasize short cleavage fragments is needed (if it exists). If these cleavage fragments are ubiquitous, how will they be regulated even if positive data are achieved? Why not focus on fibers that should be studied because of their known pathogenicity such as erionite and the Libby amphibole?
In Part. Many key issues that warrant further research and/or synthesis have been identified. The cited literature does provide a good basis for further investigation on these issues. However, the exposure characterization section of the Roadmap gave inadequate consideration to more widespread use of SEM in exposure assessments, and the toxicology discussion failed to address the role of macrophages in releasing enzymes and mediators when confronted with long fibers.
With regard to the first question, the answer is not clearly enough – particularly with regard to such issues as toxicity and carcinogenicity of short fibers, the importance of biopersistence to carcinogenicity, the additive and/or synergistic effects of individual components of mixed dusts, and the use of SEM as an analytical tool. With regard to the second question, the answer is no, as noted in comments above.
The Roadmap is really not about asbestos. It is about rock fragments that are elongated. The research probably will begin with fragments of minerals that can form asbestos, i.e., the amphiboles, but the intent is to extend it to all elongated particles that are durable. This is a big task. I doubt that NIOSH recognizes how big it is. Most rocks are silicates and most silicates can form elongated mineral particles. The Roadmap needs to place some priorities on this path forward and provide a plan for the range in characteristics of mineral particles that will be studied.

These are discussed above in the introductory material to this review.

8. Are the needs for epidemiological and toxicological studies balanced appropriately? If not, how should they be adjusted?

Comments
This reviewer doesn't believe epidemiological studies are likely to be fruitful. For epidemiology to be fruitful, populations of 1000 persons with over 15 f/cc-year exposures [0.5 fibers/cc for 30 years] to the target fiber with 20 years of latency would need to be found.
That there is a need for both epidemiological and toxicological studies is certainly discussed in the Roadmap. However, there is insufficient attention given to what the toxicological studies should look like and the way in which toxicological studies could or should be used to supplement knowledge that can not be obtained epidemiologically for practical (e.g., impossible to accurately recreate exposures) or ethical reasons.
It is not clear how future epidemiological studies could be conducted given the decrease in exposure to asbestos in the workplace. At best, re-analysis of the collected samples of asbestos materials from previous studies will be useful using more recently available technology (SEM). Then re-analysis of health effects with the newer analyses may be useful. This would be especially true of investigations into the role that cleavage fragments might have. I would assume that toxicological studies might be helpful in further identifying other factors of fibers that would contribute to inflammation/injury including the role for surface properties.
From my perspective, both are necessary
I differ to my medical colleagues in regard to this question
No. The specifications of the needs that were listed in the Roadmap, while not entirely inappropriate, were far too diffuse, and most of them were not focused on research objectives that are attainable with reasonable certainty, or in a timely manner. I do not dispute the criteria cited on pages 27 and 28 of the Roadmap for an adequate exposure assessment for an epidemiological study, but I cannot envision any circumstance for either a prospective or retrospective study with a sufficiently high level of exposure to fibers of known dimensional and biopersistence characteristics, and where there is access to a sufficiently large population, to yield statistically significant evidence of health effects. If there were such a population, it would be unethical to let them continue to be exposed. The only exception that I can see as being useful is limited to further analyses of archived filters from past population studies, as outlined in my response above to Question #3. In terms of the needs for toxicological studies, I strongly endorse the goals in Section 2.4 on *in vivo* animal studies, but dispute the judgment therein that "new recommendations on exposure indices cannot be developed in the short term". I urge that a much higher priority be given to carefully designed animal *in vivo* studies, which have the best prospects of providing valuable new information on the roles of fiber dimensions and biopersistence in fiber toxicity. These studies should be accompanied by coordinate *in vitro* exposure studies under culture conditions that produce results that parallel those observed in the *in vivo* exposure studies. Such additional *in vitro* studies can extend the range of exposure variables (length, width, and biopersistence) used in the *in vivo* studies. In terms of the description of multi-dose animal inhalation studies on page 33, I was disturbed by the apparently casual decision that the asbestos to be used would be chrysotile, without any justification or description of the particular source or its pretreatment, if any. Were the authors aware that most mined

chrysotile minerals contain tremolite, and that a small fraction of tremolite can govern its health effects? Also, are they aware that the UICC chrysotiles used in many past studies were too-finely ground, which reduced the effects as compared to the longer-fiber sample used by Davis and colleagues? Also, it should at least have been acknowledged that contemporary exposures to chrysotile in the US result more from rip out and demolition, rather than from exposure to raw chrysotile or commercially processed new material. I recommend that a more thorough discussion and rationale be provided for the choice of asbestos to be used in future studies.
Sort of. There are only so many opportunities for epi studies. The real challenge in the path forward is tox—this should be much more mechanistic and needs more cutting edge technology
No. I am not sure what a prospective epidemiological study will yield at current levels of fibers in the environment and workplace, but retroactive studies looking at archival dust samples or patient samples (if available) for fiber deposition and characteristics may be valuable if specific hypotheses are put forth

9. Are there other available or promising exposure assessment and analytical methods available that should be mentioned? What research objectives should be added to further develop and validate any promising methods you suggest?

Comments
This is not my field of expertise, so I cannot comment.
Scanning electron microscopy (SEM) is mentioned in the *Roadmap* only in passing (p. 22-23). SEM techniques should be investigated as a tool in routine sample analyses. Also, SEM and electron microprobe techniques have numerous applications in much of the mineral-fiber research that is suggested by the *Roadmap*. The *Roadmap* does not discuss specific analytical techniques for examining the durability/biopersistence or leach chemistry of mineral fibers. As noted in question 10 below, these chemical-compositional parameters may be very important factors in mineral toxicity. The public comments have noted several relevant papers.
SEM trumps PCM
I recommend using the Berman approach to reconstruct exposures of cohorts where epidemiological studies are already available. This may not be the only approach, but it would provide a much better understanding of the epidemiological data in terms of the details of the actual exposures. Using the RF definition, we have no details on dimensions and for the mines and mills, the exposures are likely to be to different types of particles. In most cases, only a reconstruction of exposure can be used to obtain the dimensional and mineralogical characteristics of the particulate exposure.
Correlation of fibers to AHERA structures in prominent current operations; correlation of fibers to AHEA structures in operations where epidemiology is available, followed by risk estimation from structures; similarly for animal studies.
Yes. As stated in my response to Question #2 above, state-of-the-art SEM would be preferable to either PCM or TEM for routine fiber counting and characterization, especially in exposures to mixed dusts where the fibers of concern are a small percentage of the exposure mixture. It should be made clear that the prime objective in making fiber concentration measurements is to determine the exposures to hazardous fibers, i.e., those that are long, thin, biopersistent, and of known mineral or vitreous composition
With regard to the first question, the answer is yes. As discussed above, at least one of these is SEM. The answer to the second question is beyond the scope of my expertise
The role for Scanning Electron Microscopy should be evaluated completely to help with characterization of asbestos materials including materials that include asbestos fibers or cleavage fragments as contaminants.

10. Should surface characteristics be specifically identified as a potentially important factor to be investigated for their contribution to fiber toxicity? Are there other fiber characteristics (in addition to dose, dimension, and durability/biopersistence) which should be specifically identified?

Comments
This question is beyond the scope of my expertise. However, the weight of the evidence in the public comments reviewed indicates that the answer to both questions is yes.
Intuitively, surface characteristics of inorganic particles should play a role in their interaction with our body systems. Thus, it seems worthy to mention mineral surface properties as another avenue of relevant research. Surface area, surface chemistry, and soluble chemistry (chemicals that are produced by the dissolution of the mineral particle) would seem to be important factors in the body's reaction to an inhaled particle. A medical panel could scour the literature for studies on the surface properties of mineral fibers to determine if applicable research already exists. In developing new toxicological standards, full characterization of the reference materials should be performed, including (as a minimum) documentation of the range of mineral particle morphologies and their populations (not restricted to the "countable" federal fibers), particle compositions (chemistry), and the surface properties of fibers that are typical of each component of the population. In order to understand the factors that cause or influence toxicity, the unique characteristics of the sample media—mineral shapes and sizes, compositions, biodurability, and surface properties—should be known to confidently evaluate the cause-and-effect relationships. In the inhalation studies, for example, it seems that only well-characterized sample media will lead to test results that withstand scientific scrutiny.
The Roadmap should be more cognizant of surface characteristics, esp. iron in ROS production. Beyond this, my mind is open.
Yes. As documented by Lippmann (1998) [Environ. Res. 46:86-106], the surface area of amphibole fibers is the best available index of their potential for causing asbestosis. Other than fiber length, width, and biopersistence, which are the most critical characteristics for cancer causation, I cannot identify another important variable.
Absolutely. Although the ability to generate free radicals is mentioned in the document, this can reflect the generation of many free radical species, metal content and charge, as well many alterations in surface chemistry. These studies on "raw" fiber preparations may be deceiving or meaningless unless they are coupled with studies on fibers after coating with biological fluids or studies on cells or tissues for evidence of oxidative markers of damage and antioxidant responses. Fiber size, charge and leaching of components may drastically affect oxidant generation by fibers - these experiments should be encouraged as well as evidence for *in vivo* signatures of oxidant injury by inhaled fibers. Equivalent surface areas of different fibers should be compared in these studies.
In principle, fiber characteristics are important for toxicity evaluation, that is, estimation of the potency of the material.
Unifying fiber theory will never rest on dimensions alone. There are already published studies that clearly show that dimensions are not the whole story and can never be the sole basis for a unified theory of fiber toxicity. The fact that quartz, a non-fibrous mineral, has been identified as a probably human carcinogen is a clear example. Dr. Nolan emphasized this point in his testimony, referring to the work of Hodgson and Darton (2000) who conclude that the relative risk for chrysotile: amosite: crocidolite is 1:100:500. These differences cannot be explained by dimensions. If NIOSH is to be successful in its ultimate objective to develop a unified theory, morphology, mineral identity, major and trace element chemical composition, oxidation state of metals, biodurability, and surface characteristics including atomic structure, topography, charge, chemical composition and surface specific dissolution rates must be examined independently for their relationship to carcinogenicity and

fibrogenicity.[39] If successful, these studies will greatly advance our understanding of the causes of disease that results from the inhalation of some mineral particles but not others.
It appears that surface properties are being investigated in various laboratories already. I am not aware of other fiber characteristics that will prove to be important for toxicity studies.

[39] This point was discussed in detail in the USGS submission and supported by the comments of Dr. Rubin, Dr. McConnel, Amar Nath and David Lai.

11. What different approaches can be used to minimize the use of animals in experimental studies? Are human 3D models sufficiently developed and validated to predict lung deposition and potential toxicity from exposure to mineral fibers and other elongated-mineral particles?

Comments
This question refers to large dose-finding and carcinogenicity studies, which are a thing of the past. The Roadmap needs to focus on murine transgenic mice and mechanisms of disease therein that can be performed with fewer numbers of animals and over a shorter time period.
As I have commented above, the approach advocated by Dr. Berman is most promising in minimizing the number of experiments that use animals. However, such an approach will require careful sample selection. I will leave comments on 3D models to others.
I do not recommend the use of human 3D models for fiber studies at this juncture. Although investigators at CIIT and other institutions have developed these for use with inhaled particles, they are not yet at the level of sophistication to study inhaled fibers and cannot demonstrate disease or account for important individual traits that might predispose persons to asbestos fiber-related diseases.
There are none. *In vivo* studies are the only ones that can provide strong evidence of *in vivo* toxicity. Models can be useful for estimating fiber deposition, but not of toxicity, which requires knowledge of clearance pathways and rates as well. The numbers of animals needed for *in vivo* studies is modest, and readily justifiable.
Minimizing animal use (rats) is not a public health goal.
I am not aware of any other approaches that would be useful.
I leave this question for the medical community to address.
The answer to the first question is provided above in my answer to question 4. In short, there appear to be no acceptable alternatives to the use of animals in experimental studies. The 3-D models appear to be sufficiently developed to predict lung deposition patterns (which are already predictable) but insufficiently developed for toxicity studies.[19]

12. Does the research agenda appropriately address the types of research needed to support public health decisions concerning worker health risks from cleavage fragment exposure? If not, how should it be revised?

Comments
If this is an important goal of this research, I am not sure how negative or positive data will contribute to these decisions, especially in view of the vast literature on the lack of short asbestos fiber effects
No. There was virtually no discussion of what research on biological responses to cleavage fragments would be done. In order to be able to answer this question, I would need to know what the sources of the cleavage fragments were, how the cells *in vitro* and the animals *in vivo* would be exposed, and for how long. The inclusion, in the Roadmap, of words indicating that cleavage fragments would be characterized in exposure-related studies, and in population based epidemiological studies was not particularly helpful in envisioning what analyses of these data could produce in terms of new insights on cleavage fraction risks. Therefore, the document needs to be improved by indicating the prospects of advances in knowledge to be gained by the proposed studies.
Cleavage fragments may already be over-emphasized. Tox studies on human cells *in vitro* are needed with well-characterized cleavage fragments.
The risk evaluation of cleavage fragments [AHERA structures] is the key issue. This reviewer thinks that a fruitful approach is retrospectively estimating the cleavage fragment exposure of previously studied populations for which fiber exposures have been estimated. Then, unit risks of cleavage fragments could be calculated as an upper bound of risk [as if there were no fiber toxicity.]
The research agenda described in the *Roadmap* addresses the issues related to cleavage fragments only in part. Defining "cleavage fragment" is not as straight-forward as question 12 implies; therefore, "cleavage fragment" exposure is not clear-cut. Please read my specific comment #2 that is linked to the document (attached
The research agenda does not appear to this reviewer to include a discussion of public health decisions concerning worker (or public) health risks from cleavage fragments or other types of mineral fibers. It does not specifically identify which public health decisions are important, how they should or could be made, or how the research agenda itself might feed into such decisions. The Roadmap should be revised to specifically identify important public health decisions that may depend on or be altered by the outcome of the research to be undertaken. This in turn might allow shaping or reshaping of the research agenda so that outcome feeds into the identified public health decisions. Such an effort should be undertaken in consultation with public health administrators and practitioners
As the USGS points out, cleavage fragments of amphiboles can have highly variable dimensional characteristics. The samples for cell and animal studies must be chosen carefully to represent the full spectrum of habit of cleavage fragments. The USGS should be consulted on the choice of samples. The choice of samples should not be left to the medical community. NIOSH should also provide samples that come from mines and mills where additional epidemiological studies will be conducted for animal and cellular studies so the results can be directly compared.
It is hoped that re-analysis of collected samples from previous epidemiological studies for cohorts exposed to non-asbestiform materials might prove helpful with newer analytical tools to better characterize the role that cleavage fragments might have in causing adverse health effects. It is not clear how useful toxicological studies might be in arriving at public health decisions for worker safety.

13. Are you aware of any available procedures or techniques that can be used to generate sufficient quantities of biologically relevant sized cleavage fragments for use in research?

Comments
This question suggests that NIOSH is looking for cleavage fragments that have the dimensions of asbestos. Long thin fibers do not form by cleavage. If I misunderstand, and NIOSH just wants cleavage fragments that meet the RF definition, that is a rather simple task. Crushing and sieving monomineralic samples of a variety of amphibole samples chosen so that they produce populations with as wide a range of shapes as nature provides should be sufficient. Amphiboles that are characterized by (100) parting in addition to (110) cleavage are likely to provide the most elongated particles. The type of grinding mill will have only minimal impact on the ultimate shape of the particles. A study by Wylie and Schweitzer (1982) of the effects of a variety of different mills and times of milling on the shape of wollastonite illustrates the variability.
No.
This question really should be whether cleavage fragments can be generated in the absence of fibers. This reviewer doesn't know.
I do not know of a routine procedure or technique that could rapidly produce large quantities of cleavage fragments. However, I believe that amphibole-rich rock samples appropriate for this research could be found and collected. Careful sample preparation, checked by sub-microscopic examination, could produce useable research materials. Sample collection and refinement may take several weeks or months, but I believe that research samples could be produced. More importantly, the desired characteristics of the research samples must be carefully considered ***before*** ideal rock sources are sought.
No, but it might be worthwhile to talk to scientists in the fiber glass industry.
No, at least in the usual sense. The question would have been better framed if it defined "sufficient".
No. But this should be part of the research agenda of the Roadmap.
No. This is outside my area of expertise.

14. Would the results of the research needs and research approaches identified in the draft Roadmap appropriately inform the development of more effective worker protection policies for asbestos and other mineral fibers? Would the proposed research strategy for asbestos and mineral fibers contribute to understanding whether there are specific characteristics (e.g., physical, chemical) that could be applied to mineral fibers and other elongated-mineral particles in developing worker protection policies?

Comments
I understand that is the hope for NIOSH that a unified theory of fiber toxicity might be developed as a result of the proposed research agenda. And with that unified theory, there could be the subsequent development of worker protection strategies that would be useful for exposures to current and future mineral dusts that could include various fibers. However, it appears unlikely that such a unified theory will be discovered. It is hoped that the research planned (as well as research ongoing at other academic and federal facilities) will identify the fiber characteristics that can be more closely associated with injury and inflammation in humans. With that newer information and a subsequent more refined definition for "asbestos fibers", then worker protection strategies should be forthcoming.
The answers to these questions were addressed to a large extent in my introductory remarks. To reiterate, the results of the research needs and approaches identified in the draft Roadmap could conceivably improve worker protection policies in several ways. The first is by the identification of toxic effects of mineral fibers, individually or combined, that would allow the development of new regulatory standards by OSHA. (The benefits that accrue to workers would then depend, of course, on enforcement of these regulatory standards.) The second is by development of practical analytical tools to accurately measure exposures. The third is by facilitating the development of more appropriate and usable respiratory protective devices. The fourth and by no means least, is to make possible substitution of less toxic fibers for more toxic fibers.
It seems likely that even if a portion of the ambitious research proposed in the *Roadmap* were successfully completed, then the information produced would contribute to more effective worker protection. The effectiveness of new contributions to understanding the cause-and-effect mechanisms should ultimately lead to greater worker and public protection. At the present, little consensus exists on some very basic aspects of mineral fiber science, particularly in regards to the analyses, risk assessment, and regulation of natural deposits. As examples: *i*) Different laboratories use different criteria in counting “asbestos” fibers in mixed-dust samples. Some laboratories use a strict coherence to the dimensional criteria for a “federal fiber”; that is, they count amphibole particles in the sample that have an aspect ratio of 3:1 or greater and a length greater than 5 µm. Other laboratories use morphological criteria to discount some of the elongate amphibole particles from their count, even if the particle meets the regulatory aspect ratio and length; they suggest that the particle appears to be a “cleavage fragment”, based on criteria such as non-parallel, striated or stepped sides. With such diversity and lack of coherence between labs in the routine analyses of natural samples (rock and soil), there can not be consistent application of the asbestos federal policies. *ii*) There is no consistency amongst the federal agencies in asbestos regulation policy. For example, NIOSH sets the recommended exposure limit (REL) at 0.1 fiber per cubic centimeter or air (0.1 fiber/cm^3) measured as a 100-minute time-weighted average; in contrast, MSHA applies a REL of 2 fibers/cm^3. OSHA excludes non-asbestiform tremolite, anthophyllite and actinolite from its asbestos standard, while NIOSH does not recommend an upper limit for amphibole fiber diameter, but rather applies the 3:1 rule.

Lack of coherence in asbestos public policy and counting rules reflect a lack of consensus in the science of asbestos. The very fact that considerable debate remains over causal mechanism(s) of mineral fiber toxicity and general disagreement on terminology, shows that there is more work to be done. Much carefully thought-out research remains in order to develop consistent federal policies regarding asbestos and mineral fibers, particularly in the realm of fiber-bearing rocks and soils. A unified theory of fiber toxicity seems today like a lofty goal, but this attempt to organize the needed research is certainly admirable and worthy. Currently, the widespread, unconsolidated efforts of asbestos research, often with contradicting agendas, has not served to advance asbestos science or public policy beyond the earliest attempts in the 1970s. Also, as the asbestos issues focus more on natural deposits, which are inherently more complex than processed man-made asbestos materials, it is even more important that the forthcoming research be carefully coordinated amongst multiple disciplines (medical, hygiene, analytical, public policy, and natural science experts). With an organized approach, the ultimate goal of the *Roadmap* is a worthy one—"a research program that will provide answers to current scientific questions, reduce scientific uncertainties, and provide a sound scientific foundation for future policy development".
The asbestos fiber industry is not extant, but there is a significant industry dealing with other mineral fibers. The Roadmap needs a better strategy to define toxicological criteria of these other mineral fibers in comparison to asbestos. These tox studies need to be done on human cells. The focus no longer is on worker protection or primary prevention, but secondary prevention, which is to identify disease risk on the many thousands exposed to asbestos and now awaiting their fate for developing lung cancer, mesothelioma, or asbestosis
I am not sure about this, but if fibers in industry or the environment were identified that fit the criteria of "toxic" properties of fibers to be identified in the Roadmap plan, and tests were discovered for rapid prediction of health effects, this would certainly allow evaluation of "new" potentially hazardous fibers.
In discussion of Zoltai's paper, the Roadmap states that the durability of amphibole in the lung depends on the mineral habit. Zoltai reports on one experiment with amosite and grunerite cleavage fragments that shows that the progress of dissolution may be different. However, the most important point of Zoltai's work is not that dissolution in the human body may be a factor differentiating cleavage fragments from asbestos fibers, but rather that the surface of asbestos fibers are different from the surfaces of cleavage fragments and these surfaces may play an important role in both the carcinogenicity and fibrogenicity of mineral fibers. There are observed differences in the biological activity of fibers composed of different minerals, e.g., talc fibers vs. erionite fibers that cannot be explained by solubility or size.[40] If the disease mechanism involves repeated injury to the mesothelial lining or to lung tissue, how does this injury occur? Perhaps erionite fibers are more effective in producing this injury than asbestos fibers and talc fibers are much less effective. The characteristics of fibers that result in tissue injury that cannot be related to size and shape need to be evaluated. This work has not been reviewed in the Roadmap. There is literature on the differences in the nature of surfaces of asbestos and cleavage fragments of amphibole, but this literature is not addressed. It is known that asbestos fibers have a greater negative charge than amphibole cleavage fragments and that amphibole asbestos fibers have well developed surfaces (100) that are not as common on amphibole cleavage fragments. There are different solubilities of different mineral surfaces. It is also known that amphiboles dissolve by releasing cations from certain sites and leaving in place tetrahedrally coordinated Si. Further, it is the case that Fe+2

[40] This point was discussed by Dr. Nolan

may oxidize, perhaps coating the fiber. Furthermore a number of scientists have maintained that properties other than size, shape and biodurability contribute to the biological activity of minerals.[41] Hochella (1993) provides an excellent discussion of the variability of surface chemistry, structure and reactivity of mineral surfaces that may affect biological activity which I summarized in my response to question 5. An evaluation of the surface of mineral fibers should be part of any research program that examines their toxicology.
This was addressed in the introductory paragraphs.
Possibly, but not likely. Some useful information would almost certainly be generated. However, In order to give a more useful answer, I would need to know how much money would be spent, how it would be allocated to specific research needs, and whether there would be an effective means of strategic oversight by a suitable group of peers.

[41] For example: Chamberlain and Brown, 1978; Feuerbacher et al., 1980, Flowers, 1980 ; Marchisio and Pernis, 1963, Schlipkoter et al., 1963, Brown et al., 1990, Weitzman and Graceffa, 1984, Weitzman and Weitberg, 1985