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# Report on the Expert Panel on Health Effects of Asbestos and Synthetic Vitreous Fibers: The Influence of Fiber Length

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## NOTE

This report was prepared by Eastern Research Group, Inc. (ERG), an ATSDR contractor, as a general record of discussion for the expert panel meeting on "Health Effects of Asbestos and Synthetic Vitreous Fibers: The Influence of Fiber Length." This report captures the main points of scheduled presentations, highlights discussions among the panelists, and documents the public comments provided at the meeting. This report does not contain a verbatim transcript of all issues discussed, and it does not embellish, interpret, or enlarge upon matters that were incomplete or unclear. ATSDR will use the information presented during the expert panel meeting to aid in developing scientifically sound public health evaluations for exposures to short fibers. Except as specifically noted, no statements in this report represent analyses by or positions of ATSDR or ERG.

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## List of Abbreviations

| | |
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| ATSDR | Agency for Toxic Substances and Disease Registry |
| BAL | bronchoalveolar lavage |
| DPPC | dipalmitoyl phophatidyl choline |
| EPA | U.S. Environmental Protection Agency |
| FEV1 | forced expiratory volume in 1 second |
| FVC | forced vital capacity |
| IARC | International Agency for Research on Cancer |
| NIOSH | National Institute for Occupational Safety and Health |
| PCM | phase contrast microscopy |
| PMR | proportional mortality ratio |
| RADM | rear admiral |
| RCF | refractory ceramic fiber |
| ROS | reactive oxygen species |
| SMR | standardized mortality ratio |
| SVF | synthetic vitreous fibers |
| TNF-$\alpha$ | tumor necrosis factor-alpha |
| $\mu$m | micrometers |
| WTC | World Trade Center |

## Executive Summary

Seven expert panelists reviewed and discussed the state of the science on how fiber length relates to toxicity of asbestos and synthetic vitreous fibers (SVFs)—an issue relevant to the Agency for Toxic Substances and Disease Registry's (ATSDR's) ongoing work at several sites where fiber contamination is found in or near residential neighborhoods. The expert panelists included epidemiologists, pathologists, physicians, hygienists, pulmonologists, and toxicologists. During a 2-day meeting in October 2002 in New York City, the panelists thoroughly discussed the physiological fate of structures less than 5 micrometers (μm) in length having aspect ratios greater than 3:1, health effects of asbestos and SVFs of the same dimensions, and research needs.

The panelists' main findings and recommendations are listed below. The remainder of this report summarizes the discussions and observations that led to these findings, and reviews the panelists' comments on many topics not listed in this executive summary. This report provides insights and advice on how to interpret exposures to asbestos and SVFs less than 5 μm in length based on panelist discussions; however, the contents of this report should not be considered ATSDR policy.

- **Factors that influence toxicity.** Health effects from asbestos and SVFs ultimately are functions of fiber dose, fiber dimension (length and diameter), and fiber durability or persistence in the lung (as determined by the mineral type, the amorphous or crystalline structure, and the surface chemistry).

- **Fibers or particles?** Some panelists questioned why structures less than 5 μm long, regardless of their aspect ratio, were referred to as "fibers." This report refers to structures less than 5 μm long as "fibers," while acknowledging that some expert panelists have reservations about this terminology.

- **Deposition and retention of short fibers.** The lung depositional patterns of fibers less than 5 μm long have been well established and depend almost entirely on fiber width. For short fibers with diameters between 0.1 and 1.6 μm, total lung deposition in healthy people will be between 10% and 20% of what is inhaled, with most of that deposition occurring in the deep lung; the fibers that do not deposit will be exhaled. For short fibers

with diameters less than 0.1 μm, a greater proportion will deposit and there will be a somewhat greater proportion of deposition in the proximal airways.

The short fibers can be cleared from the lung by various mechanisms, depending on where the fibers deposit. Fibers depositing on the surface of conductive airways (i.e., the tracheobronchial region) are efficiently cleared by the mucociliary escalator, generally within 24 hours. Many of the short fibers that reach the gas exchange region of the lung are cleared by alveolar macrophages, and the rate of clearance by phagocytosis has been found to vary with fiber length and to differ across mammalian species. One panelist, for instance, cited *studies of mice and rats* suggesting that phagocytosis clears short fibers from the alveolar regions of the lung within a few weeks following exposure. On the other hand, another panelist noted that researchers have established that alveolar macrophage mediated clearance in *human* lungs takes considerably longer (retention half-times of 400 to 700 days). Overall, panelists noted that rodents clear short fibers from their lungs approximately 10 times faster than do humans. Deposition and retention patterns may differ in people with impaired capacities to clear foreign material from their lungs. The extent to which short fibers preferentially translocate from the gas exchange region to the pleura is not well known.

- **Cancer effects of short fibers.** Given findings from epidemiologic studies, laboratory animal studies, and *in vitro* genotoxicity studies, combined with the lung's ability to clear short fibers, the panelists agreed that there is a strong weight of evidence that asbestos and SVFs shorter than 5 μm are unlikely to cause cancer in humans.

- **Noncancer effects of short fibers.** The laboratory animal studies, epidemiologic studies, and *in vitro* studies generally suggest that asbestos and SVF pathogenicity increases with fiber length, but there are several notable exceptions. In laboratory animals, for example, short asbestos and SVFs at sufficiently high doses have been shown to cause inflammation, pulmonary interstitial fibrosis, and pleural reactions; however, the doses needed to cause these effects in humans may not be relevant to environmental exposures. In humans, four epidemiologic studies (Churg et al. 1989, 1990; Nayebzadeh et al. 2001; Case 2002b) involving highly exposed workers found that pulmonary interstitial fibrosis is correlated with the amount of *short fibers* in the lung at death; some researchers have hypothesized that this apparent association is explained by long fibers breaking down into shorter fibers between exposure and the time at which lung samples were collected. Finally, at least two *in vitro* studies (Ye et al. 1999, 2001) have found that short fibers are at least as active as, if not more active than, long fibers on a surface area or mass basis for multiple endpoints (e.g., tumor necrosis factor-alpha [TNF-α] production, activation of TNF-α gene promoter activity); however, the relevance of these *in vitro* findings to health effects *in vivo* is not known. Taken together, the findings from the laboratory animal, epidemiologic, and *in vitro* studies suggest that short fibers may be pathogenic for pulmonary fibrosis, and further research is needed to clarify this issue.

- **Research needs and recommendations.** Throughout the meeting, the panelists identified data gaps and made recommendations for filling them. Some recommendations addressed issues specific to sites (e.g., Libby, Montana; Lower Manhattan) with concerns about short fibers in residential communities. These recommendations are listed in Section 4.1. The panelists' recommendations for general research projects follow, in no particular order:

  - Encourage increased use of sampling human lung tissue or other biological indices, such as sputum collection, in known or suspected human exposure situations to improve both qualitative and quantitative exposure assessment.

  - Conduct a laboratory animal study to characterize the extent to which fibers of all lengths translocate into the pleura, and whether the translocation preferentially occurs for fibers of any dimension or type. Some panelists noted that translocation of fibers into the pleura does not necessarily imply causation of pleural disease, the mechanisms and site of action of these mechanisms being unknown (Kane et al. 1996). One panelist indicated that some studies (e.g., Gelzeichter et al. 1996; McConnell et al. 1999) have already examined this issue, to a certain extent, for refractory ceramic fibers; and a follow-up study has recently been completed, but not yet published, for amphibole fibers.

  - Develop and adopt standardized environmental and biologic sampling and analytical protocols to ensure that samples collected from different sites for different purposes can be compared.

  - Perform personal exposure sampling, or an equivalent, to quantify what exposures result when household surfaces are contaminated with asbestos or SVFs; analyze samples using conventional fiber counting methods (i.e., counting only fibers longer than 5 μm), but archive a subset of filter samples for further analysis.

  - Further investigate the possible association between short fibers and pulmonary interstitial fibrosis in humans and the impact of short fibers in regard to pleural changes, such as pleural plaques and diffuse pleural fibrosis.

  - Design and conduct an *in vitro* study to characterize the influence of fiber length on cell proliferation, DNA damage, and cytotoxicity endpoints that can then be confirmed in animal studies.

## 1.0 Introduction

The Agency for Toxic Substances and Disease Registry (ATSDR) invited seven expert panelists to a meeting to discuss the current understanding of health effects related to asbestos and synthetic vitreous fibers (SVF) less than 5 micrometers (μm) in length—an issue that is related to the agency's ongoing work at many sites. The expert panel review took place in a meeting open to the public on October 29–30, 2002, in New York City. Discussions at the meeting focused on three specific issues: the physiological fate of fibers less than 5 μm in length, health effects of fibers less than 5 μm in length, and data gaps.

This report summarizes the technical discussions among the expert panelists and documents comments provided by observers. The remainder of this introductory section reviews the background on ATSDR's concern about fibers less than 5 μm in length (Section 1.1), the scope of this expert panel review (Section 1.2), and the organization of this report (Section 1.3).

### 1.1 Background

ATSDR conducts public health assessments to evaluate the public health implications of exposure to contaminants from hazardous waste sites and other environmental releases. A crucial part of these evaluations is understanding the toxicologic implications of environmental exposures. Recent events have highlighted a need for ATSDR to explore the potential of exposure to biopersistent fibers—specifically asbestos and some SVF—to cause health effects. For instance, ATSDR is currently assessing the implications of residential and community exposures to fibers from past industrial operations (e.g., vermiculite processing plants across the country), contaminants at hazardous waste sites, and dust in Lower Manhattan generated from the collapse of the World Trade Center (WTC) buildings. These sites are distinct in that contaminants have been found, or are suspected of being present, in residents' homes. Moreover, ATSDR has received concerns specifically about the public health implications of exposure to shorter fibers, particularly for materials found in Lower Manhattan.

ATSDR has therefore identified a need to understand the potential of fibers less than 5 μm in length to contribute to adverse health effects. As one part of addressing this need, ATSDR convened an expert panel to discuss and review the current state of the science regarding the influence of fiber length on health effects of asbestos and SVF. ATSDR will use the panel's findings to help develop scientifically sound public health evaluations for human exposures to small fibers.

## 1.2 Scope of the Expert Panel Review

The expert panel review involved many activities before the meeting (see Section 1.2.1), at the meeting (see Section 1.2.2), and after the meeting (see Section 1.2.3). The following subsections describe what each of these tasks entailed.

### 1.2.1 Activities Prior to the Expert Panel Meeting

ATSDR selected seven experts in toxicology, epidemiology, pathology, pulmonology, hygiene, and medicine to serve as panelists for the meeting. Every panelist is either a senior scientist, physician, or researcher with extensive experience in the aforementioned fields, as demonstrated by peer-reviewed publications, awards, and service to relevant professional societies. ATSDR selected panelists with a broad range of affiliations (e.g., academia, consulting, other federal agencies) in hope that the expert panel would offer a balanced perspective on the meeting topics. Furthermore, during its search for expert panelists, ATSDR asked all candidates to disclose real or perceived conflicts of interest. Appendix A lists the names and affiliations of the seven expert panelists selected for this meeting, and Appendix B includes brief biographies that summarize the panelists' areas of expertise.

To focus the discussions at the meeting, ATSDR prepared written guidelines (commonly called a "charge") for the expert panelists. The charge included several questions that the expert panelists discussed during the meeting. These questions addressed the physiological fate of fibers less than

5 μm in length, the health effects associated with these fibers, and data gaps. A copy of the charge is included in Appendix B. Several weeks prior to the expert panel meeting, every panelist received a copy of the charge, logistical information for the meeting, a preliminary bibliography of publications on asbestos and SVF, and copies of six publications relevant to the meeting topics (Bourdes et al. 2000; Churg et al. 2000; Davis 1994; Kinnula 1999; Morgan 1995; Ohyama et al. 2001).

In the weeks after the panelists received these materials, the panelists were asked to prepare their initial responses to the charge questions. Booklets of the premeeting comments were distributed the expert panelists, and made available to observers who registered in advance to attend the expert panel review. These initial comments are included in this report, without modification, as Appendix B. It should be noted that the premeeting comments are preliminary in nature. Some panelists' technical findings may have changed after the premeeting comments were submitted.

### 1.2.2 Activities at the Expert Panel Review Meeting

The seven panelists and approximately 50 observers attended the expert panel meeting, which was held at the Jacob K. Javitz Federal Building in New York City, New York, on October 29–30, 2002. The meeting was open to the public, and the meeting dates and times were announced in the Federal Register. Appendix C lists the observers who confirmed their attendance at the meeting registration desk. The schedule of the expert panel meeting generally followed the agenda, presented here as Appendix D. The remainder of this section describes the introductory presentations given at the meeting.

- *Introductory remarks from ATSDR.* The meeting began with Rear Admiral (RADM) Robert Williams (Director of ATSDR's Division of Health Assessment and Consultation and Chief Engineer for the United States Public Health Service) explaining why ATSDR had convened the expert panel. He first reviewed ATSDR's site-specific experiences with asbestos contamination since 1980: assessing roughly 150 sites at which asbestos was a contaminant of concern, evaluating approximately 50 sites at which completed or potential exposure pathways were found for asbestos, and issuing public health advisories for sites

where the public might come into contact with elevated levels of asbestos-contaminated materials. RADM Williams indicated that the available environmental data for these previous evaluations were typically the percent of asbestos in a waste material, as quantified by measurement methods that count fibers longer than 5 μm. For most of these sites, detailed information on fiber size distributions is not available.

More recent work on sites with asbestos contamination, RADM Williams explained, has led to a greater need to understand the role of fiber length on asbestos toxicity. He reviewed ATSDR's activities at two sites with public health concerns regarding asbestos exposure. First, RADM Williams presented findings from medical testing that ATSDR conducted on residents of Libby, Montana, where vermiculite mining and exfoliation operations occurred for more than 50 years. ATSDR found that 18% of the residents tested (which included workers at the former mine and exfoliation plant) had pleural abnormalities, which were most prevalent among people who had lived in the area longest and who had completed exposure pathways for asbestos. RADM Williams described ATSDR's ongoing public health actions to address asbestos exposure issues in Libby. Second, RADM Williams described ATSDR's recent activities evaluating asbestos and SVF in dust generated during the WTC collapse. Activities included reviewing results of asbestos samples, conducting limited sampling in residential properties, evaluating whether buildings could be entered for occupational purposes, and assessing the need for maintaining the "exclusion zone" in Lower Manhattan.

RADM Williams indicated that ATSDR's experiences with the Libby, WTC, and other sites have raised unique challenges regarding asbestos and SVF. At these sites, for example, fibers are being found in homes, rather than at waste sites and in the environment; children are being exposed; and analytical methods are now quantifying amounts of shorter fibers (less than 5 μm) than were typically characterized previously. As one step in helping the agency respond to these challenges, RADM Williams indicated, ATSDR convened the expert panel to review the current state of the science on health effects of asbestos and SVF, focusing on the role of fiber length. RADM Williams explained that ATSDR often uses the expert panel forum to seek scientific input on priority issues the agency is evaluating. He noted that the panelists were invited to present their individual opinions and were not asked to reach consensus on any issue, and representatives from ATSDR were present strictly to observe the proceedings.

- *Introductory remarks from the meeting chair.* Dr. Morton Lippmann, the chair of the expert panel meeting, provided additional introductory remarks. After reviewing the charge to the panelists and the meeting agenda, Dr. Lippmann indicated that the goal of the expert panel meeting was to review health effects associated with asbestos and SVF, with a special emphasis on fibers shorter than 5 μm. He explained that the focus on fibers less than 5 μm emerged from conventions previously used to evaluate asbestos exposures. Specifically, risk assessment decisions related to asbestos, Dr. Lippmann noted, have typically been based on optical measurements of fibers longer than 5 μm, and one goal of

the expert panel was to evaluate the toxicity of the shorter fibers that are not counted by the optical analytical methods. Dr. Lippmann also emphasized that the expert panel's discussions should have a public health focus, such that ATSDR could apply the findings from the expert panel to sites where community members are concerned about exposure to asbestos and SVF.

To illustrate recent concerns about asbestos and SVF, Dr. Lippmann described ongoing research being conducted to evaluate contamination by WTC dust in Lower Manhattan. He indicated, for example, that his research group and colleagues have collected and analyzed numerous settled dust samples and ambient air samples following the WTC collapse and are evaluating health effects among approximately 300 firefighters and several thousand residents of Lower Manhattan. These dust samples reportedly were composed almost entirely of particles larger than 10 μm in aerodynamic diameter, with only 1% of fine particles less than 2.5 μm in aerodynamic diameter. Dr. Lippmann also noted that asbestos fibers detected in the dust samples were primarily small (less than 5 μm), because building materials were crushed by the force of the WTC collapse. He indicated that the purpose of the expert panel review was to help ATSDR interpret the public health significance of short fibers, like those detected in the WTC dust.

Following these opening presentations, Dr. Lippmann asked the panelists to introduce themselves by stating their names, affiliations, areas of expertise, and past research experience. For the remainder of the meeting, the panelists gave individual presentations and engaged in free-flowing discussions when answering the charge questions and addressing additional topics not specified

***Are structures less than 5 μm in length fibers or particles?***

The expert panel meeting was convened to address the health effects of fibers less than 5 μm, but some panelists questioned the appropriateness of the relevant terminology. One panelist, for instance, noted that many scientists would classify structures smaller than 5 μm as particles, regardless of the structures' aspect ratios (see Dr. Case's premeeting comments in Appendix B). During his introductory remarks, Dr. Lippmann reviewed these concerns and noted that mineralogists, geologists, health scientists, and individuals in other disciplines may use different definitions of fibers and these definitions may be based on size, aspect ratio, and other properties. Section 2.4 presents more detailed information on the panelists' opinions on the most appropriate terminology. This issue is raised here to inform readers that this entire report uses the term "fibers less than 5 μm," while acknowledging that some panelists had reservations about suggesting that structures less than 5 μm are fibers.

in the charge. Observers were given the opportunity to provide verbal comments throughout the expert panel meeting. Representatives from ATSDR were observers at the meeting and did not engage in or direct the panelists' discussions.

### 1.2.3 Activities Following the Expert Panel Meeting

The primary activity following the expert panel meeting was preparing this summary report. A technical writer who attended the meeting prepared a draft of this report. The expert panelists were asked to review and comment on the draft report, ensuring that its contents accurately reflect the tone and content of the discussions at the expert panel meeting. The draft report was revised based on the panelists' comments. The panelists were then given the opportunity to review the revised report; and the final expert panel review report (i.e., this report) was submitted to ATSDR. Some panelists submitted written comments after the meeting; these are included in this report, without modification, as Appendix E. ATSDR was not involved in the preparation of this report.

## 1.3 Report Organization

The structure of this report follows the order of the panelists' discussions during the meeting. For instance, Section 2 summarizes the discussions on the first agenda topic (physiological fate of asbestos and SVF less than 5 μm in length), Section 3 summarizes comments on the second topic (health effects of these fibers). Section 4 presents overall conclusions and recommendations. These report sections document comments raised both by the panelists and the observers. Finally, Section 6 provides references for all documents cited in the text.

The appendices to this report include extensive background information on the expert panel review. This information includes items made available to all meeting attendees, as well as items

generated since the expert panel meeting (e.g., a final list of attendees). The appendices contain the following information:

- List of the expert panelists (Appendix A).
- The panelists' premeeting comments, the charge to the reviewers, and brief bios of the expert panelists (Appendix B).
- List of registered observers of the expert panel meeting (Appendix C).
- Agenda for the expert panel meeting (Appendix D).
- Written comments that panelists submitted after the meeting (Appendix E).

## 2.0 Comments on Topic 1: Physiological Fate of Asbestos and SVF Fibers Less Than 5 Micrometers in Length

This section summarizes the panelists' discussions on the physiological fate of asbestos and SVF fibers less than 5 μm in length. Two panelists—Dr. Lippmann and Dr. Oberdörster—were designated discussion leaders for this part of the meeting, during which the panelists responded to the three specific charge questions regarding physiological fate of small fibers (Sections 2.1, 2.2, and 2.3) and addressed topics not identified in the charge (Section 2.4). Panelists also commented on the toxicity of asbestos and SVF fibers; these comments are summarized in Section 3. This section also summarizes observer comments made after the panelists completed their discussions (Section 2.5). Overall, this section presents a record of discussion of topics mentioned during the meeting, and it should not be viewed as a comprehensive literature review on the role of fiber length in the physiological fate of inhaled fibers. Dr. Lippmann's post-meeting comments (see Appendix E) also summarize these discussions.

Although the panelists focused their initial discussions on fiber length, several panelists stressed that length is not the only factor affecting fiber toxicity. These panelists noted that toxicity is rather a complex function of the fiber dose, dimensions, and durability, as has been widely documented in the scientific literature.

### 2.1 Depositional Pattern in the Lung

The first charge question asked the panelists: "What is the expected physiological depositional pattern for less-than-5-μm fibers in the lung?" When responding, the panelists provided relevant background information on lung physiology, reviewed what researchers have established for depositional patterns of particles, and then addressed what is currently known about depositional patterns for fibers:

- *Background on lung physiology.* Before addressing the specific charge questions on how fibers deposit in the lung, one panelist first reviewed fundamentals of lung physiology, which largely dictate fiber dosimetry. He explained how air flows through the respiratory system: inhaled air enters the body at the nose or mouth, passes through the larynx and trachea, and eventually enters the lung in airways that branch numerous times before reaching terminal bronchioles. These airways are all conductive, meaning that they move air to the deeper portions of the lung where gas exchange occurs. The air flow velocity decreases as air moves into the more distant bronchi, because the cross-sectional area of the branched bronchi is greater than that of the parent airways. After passing through the terminal bronchioles, inhaled air enters into respiratory bronchioles, then alveolar ducts, and eventually alveolar sacs, where most gas exchange occurs. Movement of air in the respiratory bronchioles and alveolar sacs is dominated by diffusion, rather than by convective forces.

  This panelist noted that clearance processes in the conductive airways differ from those in the airways distal to the terminal bronchioles. In the conductive airways, mucus is secreted onto the airways' surfaces, and ciliated cells on the bronchi and bronchioles gradually move the mucus up to the throat, where the mucus is swallowed. This mucus clearance mechanism efficiently removes particles that deposited on the conductive airways, typically within about 1 day following exposure. The clearance mechanisms for particles that deposit in the respiratory bronchioles, alveolar ducts, and alveolar sacs operate on a much longer time scale (see discussion on "phagocytosis" in Section 2.2).

- *Depositional patterns for particles.* One panelist then reviewed the state of the science of how inhaled particles tend to deposit in the respiratory tract. For both fibrous and non-fibrous particles, the deposition pattern is dictated largely by the particles' aerodynamic diameter. The aerodynamic diameter, another panelist noted, is equivalent to the geometric diameter of a unit density sphere that has the same terminal settling velocity in still air as the particle in question.

  The discussion leader then noted that researchers have long established that airborne particles with aerodynamic diameter larger than 10 μm typically do not pass the larynx, and the particles that enter the lungs deposit by one of three mechanisms—impaction, sedimentation, or diffusion (Brownian motion). The relative importance of these mechanisms is a function of the particle size. The largest particles that enter the lung, for example, have the most momentum, which causes them to have a greater tendency to deposit on airways by impaction as air flow changes direction at bronchial airway

branches. Smaller particles,[1] on the other hand, are less likely to deposit by impaction and therefore are typically carried by convective forces further into the lung.

Any particle that enters the respiratory bronchiole will likely deposit either by sedimentation or Brownian motion; impaction is relatively unimportant in regions where the air flow velocity is low. Sedimentation and diffusion tend to be the more dominant mechanisms in the small lung airways for particles, which diffuse in air much slower than gases. One panelist noted that sedimentation is the dominant deposition mechanism for particles with aerodynamic diameters greater than roughly 0.8 μm, while smaller particles are increasingly subjected to diffusional deposition in the airways. Particles depositing in the respiratory bronchioles, alveolar ducts, and alveolar sacs will remain in these regions of the lung until cleared by other mechanisms (see Sections 2.2 and 2.3).

- *Depositional patterns for fibers.* One panelist described depositional patterns of fibers, noting how their elongated shapes caused fibers to deposit differently in the lung than particles. The main difference between fiber and particle deposition is that fibers can be intercepted by airway surfaces, while particles generally cannot. For instance, as long fibers move through small airways, the end of a fiber might contact (and deposit on) an airway surface, even in cases when the fiber's center of mass is on a flow streamline in the center of the airway. Interception can therefore cause enhanced deposition of fibers, when compared to particles; and interception becomes an increasingly important deposition mechanism for longer fibers.

  This panelist indicated that many researchers have evaluated the depositional patterns of fibers in the lung. He cited the following studies as examples:

  - Studies using hollow airway cast models from human lungs have demonstrated that the extent of fiber interception varies with fiber length. Specifically, interception has been shown to be relatively unimportant for fibers less than 10 μm in length (Sussman et al. 1991). This panelist indicated that these shorter fibers will likely act like particles in the lung, because the one deposition mechanism unique to fibers is unimportant.

  - Other studies using these models have reported that fibers with aspect ratios greater than 10 behave aerodynamically like unit density spheres with diameters three times the fiber width (Stöber et al. 1970; Timbrell 1972). Interception accounts for the fact that longer fibers have proportionally greater deposition in the conductive airways than shorter fibers.

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[1] Two panelists had different opinions on the particle sizes that should be cited in this sentence. One panelist indicated at the meeting that particles with aerodynamic diameters less than roughly 2 μm would be expected to be carried by convective forces further into the lung. Another panelist, when reviewing a draft of this report, recommended that the size cut-off for this sentence be 0.8 μm.

For fibers less than 5 μm in length, Dr. Lippmann indicated, the information available on particle deposition and longer fibers suggests that fiber diameter likely has the greatest influence on deposition patterns. He noted that fibers less than 5 μm in length will have diameters less than 1.66 μm, assuming the aspect ratios are at least 3:1. This panelist estimated that 10% to 20% of short fibers with diameters between 0.1 and 1.6 μm will deposit in the lungs of healthy people.

Another panelist reviewed findings from multiple publications to illustrate how the four mechanisms—impaction, sedimentation, diffusion, and interception—affect fiber deposition patterns. First, this panelist summarized results of a lung modeling study (Asgharian and Yu 1988), which predicted the relative importance of the four deposition mechanisms as a function of fiber diameter. For all fiber dimensions considered, diffusion (Brownian motion) accounted for an increased amount of deposition as air traveled further into the lung. Further, impaction, interception, and sedimentation were relatively unimportant for the thinnest fibers (those with diameters of 0.01 μm), yet accounted for most of the predicted deposition pattern for the larger fibers (those with diameter of 10 μm). Second, he reviewed the extent to which fibers are filtered from inhaled air in the nose versus the mouth, as predicted by mathematical models. The model predicted that, for all fiber dimensions considered, nose breathing is considerably more effective at filtering airborne fibers than is mouth breathing. In fact, appreciable filtration for mouth breathing was predicted only for fibers at least 1 μm in diameter. Overall, these comments highlight that researchers have already predicted how fiber dimension (both length and diameter) affect depositional patterns in the lung (see Dr. Oberdörster's premeeting comments in Appendix B for references to relevant peer-reviewed publications).

- *Role of laboratory animal studies in evaluating depositional patterns in humans.* The panelists acknowledged that laboratory animal studies have provided additional insights on how fibers deposit in the lung, but the panelists noted that inter-species differences in lung airway structure limit the utility of the animal data. One indicated, for instance, that laboratory animal studies have the advantage of being able to characterize lung fiber burdens at different time frames following highly controlled dosage conditions. On the other hand, he added, airway branching patterns in humans are nearly symmetrical, while rats (and most other mammals) have asymmetrical branching patterns. Such differences in branching patterns influence the cross-sectional air flow profiles, which in turn affect fiber deposition behavior. Consequently, lung deposition patterns in laboratory animals are expected to differ from those in humans.

Another panelist showed how modeling results of lung deposition patterns support this expectation. Based on predictions of a mathematical lung dosimetry model developed by the International Commission on Radiological Protection, this panelist illustrated differences between rats and humans in estimated deposition fractions of fibers in alveolar regions. His figure indicated that the predicted deposition fraction in humans was greater

than that in rats for all fiber lengths considered, and this difference was most striking for longer fibers. Specifically, the model predicted that virtually no fibers with aerodynamic diameters of 3 μm and aspect ratios of 10:1 deposit in the alveolar region of rats, while more than 25% of these same fibers are predicted to deposit in the alveolar region of humans. Such predictions, this panelist noted, raise questions about whether rats are good models for humans in terms of fiber deposition in the lung.

## 2.2 Lung Clearance and Biopersistence

The second charge question asked the panelists: "What is known about clearance/biopersistence of less-than-5-μm fibers in the lung?" The panelists identified several mechanisms by which asbestos and SVF are removed from lung tissue. As Section 2.1 explains, fibers depositing on the conductive airways are cleared, typically within 1 day, by mucociliary transport; this clearance mechanism is not discussed further here. The panelists' comments focused primarily on phagocytosis and dissolution, but panelists considered several additional factors when discussing lung clearance. All of the panelists' comments are summarized below; Section 2.3 addresses clearance of fibers by migration to other tissues.

- *Phagocytosis.* Reviewing general lung clearance mechanisms, one panelist indicated that alveolar macrophages engulf and can eventually remove foreign materials (e.g., fibers, particles, bacteria) that reach the alveoli. Phagocytized material can then move to the ciliated airways, which would eventually clear the material up to the throat, or they can move into the pleura, lymphatics, or other tissues (see Section 2.3). Typical human macrophages have dimensions between 14 and 21 μm.[2] Consequently, alveolar macrophages can fully engulf fibers less than 5 μm long and remove them from the alveoli, but they are incapable of fully engulfing longer fibers. The extent of phagocytosis, therefore, clearly depends on fiber length, and may also depend on additional factors, such as surface properties of the inhaled fibers.

  The panelists noted that removal of asbestos and SVF from the alveoli by phagocytosis generally takes much longer than removal of these materials from the conductive airways by mucociliary transport—an observation that is supported by findings of lung clearance studies in rats (Coin et al. 1994). Specifically, the study reported how the half-life for lung

[2] Noting that rat alveolar macrophages have dimensions roughly between 10.5 and 13 μm, a panelist indicated that phagocytosis in rats is less effective than in humans at clearing fibers between 13 and 20 μm.

clearance in rats varied with the length of chrysotile asbestos fibers. For fibers approximately 20 μm long, the estimated half-life for clearance (by all mechanisms combined) was 100 days.[3] One panelist also presented data on time frames for lung clearance of fibers in humans, noting that the estimated half-life for alveolar macrophage clearance was estimated to be between 400 and 700 days; the panelist noted that these estimates apply to poorly soluble spherical particles of low cytotoxicity and to short fibers which can be engulfed by alveolar macrophages. He added that long fibers that cannot be phagocytized and that do not dissolve or break will not be cleared from the lung.

As one exception to the previous observations, one panelist noted that phagocytosis is not an effective clearance mechanism in "overload" conditions, or when high exposure doses overwhelm the lung's clearance mechanisms. The panelists questioned whether the environmental exposures that ATSDR typically evaluates would ever cause overload conditions, though they noted that overload conditions may be observed in some occupational settings or in unexpected accidental or emergency situations.

- *Dissolution.* Asbestos and SVF not only can be physically removed from the lung via phagocytosis, but can be chemically removed, or at least altered, by dissolution. A panelist indicated that the extent to which dissolution occurs depends largely on the fiber composition and the pH of the medium in which the fiber is located, and does not appear to depend on fiber length. Dissolution behavior can change when fibers are engulfed by macrophages, because pH varies considerably between the phagolysomes in the alveolar macrophages (pH = 4.5–5.0) and the extracellular fluid (pH = 7.4). Researchers already have documented the relative solubility of different fiber types (see Dr. Lockey's premeeting comments in Appendix B), which can be useful in characterizing the relative biopersistence of different fiber types.

- *Influence of fragmentation.* Asbestos and SVF fibers can fragment in the lung after being inhaled. Fragmentation is technically not a clearance process, because the fragmented fibers still remain in the lung. However, fragmentation can enhance clearance if the fragments formed are more easily cleared by phagocytosis than the original fiber. One panelist noted that glass and asbestos fibers fragment differently. Asbestos fibers, for example, tend to fragment longitudinally into thinner fibers of the same length. Therefore, an asbestos fiber that is too long to be engulfed by a macrophage tends to fragment into thinner fibers that are also too long to be engulfed by a macrophage. Glass fibers, on the other hand, tend to fragment transversely into shorter pieces that can more easily be cleared by phagocytosis.

- *Influence of co-exposure to other contaminants.* A panelist reviewed results from a mixed-dust exposure study in rats (Davis et al. 1991) to illustrate how co-exposures to other

[3] This half-life estimate likely understates the clearance half-life for amphibole fibers of the same length, one panelist noted, because more recent studies have shown that chrysotile fibers are cleared more readily from the lung than are amosite fibers of the same dimension.

contaminants affects fiber retention in the lung. In the study, groups of rats received different combinations of exposures: chrysotile asbestos and titanium dioxide, chrysotile asbestos and quartz, amosite asbestos and titanium dioxide, and amosite asbestos and quartz. Exposure concentrations for the chrysotile asbestos, amosite asbestos, and titanium dioxide were all 10 $mg/m^3$, while the exposure concentration for quartz was 2 $mg/m^3$. The animals were dosed for 1 year and lung tissues were analyzed for fiber retention after 2 years. The study found that co-exposure with titanium dioxide and quartz had no effect on lung retention of amosite fibers. For chrysotile fibers, on the other hand, co-exposure with titanium dioxide increased lung retention of the fibers (as compared to exposure to chrysotile alone) and co-exposure with quartz decreased lung retention of fibers. This panelist indicated that this study suggests that non-fibrous particles could affect fiber retention characteristics, though he acknowledged that the exposure concentrations used in the study are not relevant to typical environmental exposures.

- *Influence of physical structure: amorphous versus crystalline material.* The panelists briefly discussed how the physical structure of fibers (amorphous or crystalline) affects biopersistence and toxicity. One panelist noted that a laboratory animal study examined this issue by comparing lung samples from rats exposed for 3 months to amorphous silica to samples from rats exposed for 3 months to crystalline silica (Johnston et al. 2000). The study found that significant amounts of crystalline silica remained in the rat lungs 3 months after exposure ceased, while the lung-retained amorphous silica was near background levels. The panelist indicated that this trend suggests that the amorphous silica is more soluble than crystalline silica in the lung.

- *Populations that may have impaired capacity to clear fibers in the lung.* One panelist identified populations that may be susceptible to fiber-related health effects due to impaired capacity to clear fibers deposited in the lung. These populations included people with medical conditions (e.g., primary ciliary disorders, cystic fibrosis, asthma) that affect lung clearance mechanisms. Further, smokers with damaged cilia along the conductive airways may have impaired ability to clear fibers from the lung. Finally, some common pharmaceuticals are known to slow mucociliary transport (e.g., atropine), while others can enhance this transport (e.g., sympathomimetics).

- *Relevance of sputum samples.* When discussing lung clearance, the panelists discussed the utility of analyzing sputum samples to characterize the distribution of retained fibers. One panelist explained that, in at least one study, concentrations of asbestos in sputum, when compared to cumulative exposure estimates, were more predictive of radiological changes in the lungs of workers at vermiculite mines and mills (Sebastien et al. 1988). Though these and other findings suggest that sputum samples can provide useful insight into asbestos exposures, the panelists indicated that implementing a sputum sample study has a potential drawback. While smokers can produce voluntary sputum samples relatively easily, non-smokers often cannot. Induced sputum samples can be collected from non-smokers to characterize past exposure, and bronchoalveolar lavage has also been used for

this purpose. Both of these sampling techniques are invasive and require informed consent, and have a consistently better yield than simple sputum collection. More than 50 such studies conducted in North America, Europe, and Japan have already been published.

## 2.3 Migration of Fibers Deposited in the Lung

The third charge question asked the panelists: "What types of migration are expected within the body for less-than-5-μm fibers?" Both in their premeeting comments and during the expert panel review meeting, the panelists offered various perspectives on how fibers of different lengths migrate within the lung and from the lung to other organs. One panelist, for example, indicated that fibers with diameters less than 0.5 μm can penetrate through lung epithelia and be transported through lymph channels to lymph nodes, blood, and distant organs. However, most of the discussion focused on the extent to which small fibers translocate into the pleura. Three reviewers' perspectives on this matter follow:

First, one panelist indicated that several researchers have attempted to characterize the distribution of asbestos fibers in samples of human pleura. Although it has been reported that only short chrysotile fibers (average length <0.2 μm) translocate to the pleura, this panelist found these studies to be of questionable quality because they lacked matched controls or sampled tissue (such as tumors) other than the pleura. This panelist then reviewed two preliminary studies of fiber translocation, one in humans (Boutin et al. 1996) and the other in goats (Dumortier et al. 2002), which were based on more robust methods using controls. He noted that one study found that 22.5% of fibers detected in the pleura were longer than 5 μm and that the pleural samples had far greater amounts of amphibole asbestos fibers than chrysotile asbestos fibers (see Dr. Case's premeeting comments in Appendix B). The studies did not examine how fibers translocate to the pleura, though the findings suggest that lymphatic drainage paths may play an important role.[4]

[4] A panelist also noted that lymphatic transport has been demonstrated to occur in laboratory studies of dogs that were dosed with amosite asbestos by intrabronchial instillation (Oberdörster et al. 1988). Analyses of post-nodal lymph collected from the right lymph duct found fibers only of shorter dimensions: the maximum length of fiber detected was 9 μm, and the maximum diameter was 0.5 μm.

The authors of these studies hypothesized that the translocated fibers might contribute to formation of pleural plaques and mesothelioma.

Second, another panelist summarized the findings from a study of rats exposed via inhalation to kaolin-based refractory ceramic fibers with geometric mean length of 4.5 μm (Gelzeichter et al. 1996). The study reported that the fate of the fibers depended on fiber length: fibers in the pleural tissue 32 days[5] after exposure had a geometric mean length of 1.5 μm and geometric mean diameter of 0.09 μm, while fibers in the parenchymal tissue were much larger with geometric mean length of 5 μm and geometric mean diameter of 0.3 μm. Thus, the study indicates that very thin fibers smaller than 5 μm—fibers that would not be counted by conventional phase contrast microscopy (PCM) asbestos sampling methods—are capable of translocating to the pleural tissue (see Dr. Lockey's premeeting comments in Appendix B).

Third, a panelist reviewed findings of a rat inhalation study that investigated whether co-exposure to non-fibrous particles affects translocation of fibers to the pleura (Davis et al. 1991). The study found more amosite asbestos fibers translocated to the pleura in rats that were co-exposed to non-fibrous particles (quartz or titanium dioxide), as compared to rats that were exposed to amosite asbestos alone. The panelist noted, however, that the exposure doses of titanium dioxide (10 $mg/m^3$) might have overloaded the rat lungs and impaired alveolar macrophage clearance processes. If the observed fiber translocation to the pleura was caused by these overload conditions, the relevance of this study to environmental exposures is questionable.

The panelists noted that the extent to which fibers translocate to the pleura is not fully understood, but is likely an important consideration when evaluating pleural plaques, diffuse pleural thickening, and mesothelioma. For instance, if fibers must actually enter the pleura for these outcomes to occur (a hypothesis that has not been verified), then understanding fiber

[5] When reviewing a draft of this report, one panelist noted that 32 days is a relatively short period of time to examine translocation of fibers into the pleura. He indicated that it may take longer for long fibers to reach the pleura, especially if direct penetration is required for the long fibers to enter the pleura (as compared to lymphatic transport for shorter fibers).

translocation into the pleura is critical. If, on the other hand, fibers localized toward the lung periphery beneath the pleura can cause disease, perhaps through chemical mediators that cross into the pleural space, then translocation of fibers is less important. Therefore, without a more detailed understanding of the mechanisms of toxicity for pleural reactions and other outcomes, the significance of fiber translocation into the pleura is not fully known. The panelists revisited fiber translocation issues when discussing the role of fiber length, if any, in causing pleural abnormalities.

## 2.4 Open Discussion Among Panelists

After summarizing the panelists' responses to the three charge questions, the discussion leaders invited the panelists to provide comments on additional topics relevant to physiological fate of inhaled fibers. The panelists raised the following issues:

- *Terminology: fibers or particles?* One panelist had reservations about calling structures with lengths less than 5 μm fibers. He explained that mineralogists, geologists, and health scientists generally do not consider such structures to be fibers, regardless of the aspect ratio; such structures would instead be considered particles. This panelist noted that regulators have established a precedent for distinguishing between fibers and particles: the Occupational Safety and Health Administration, for instance, regulates structures smaller than 5 μm as particles not otherwise regulated, rather than as fibers. For these and other reasons (see Dr. Case's premeeting comments in Appendix B), this panelist had concerns about the terminology ATSDR used to characterize the structures with dimensions less than 5 μm. As noted previously, this report refers to structures less than 5 μm as fibers, and the concern about using this term has been documented.

- *Importance of the distribution of fiber lengths.* Noting that all mineral fiber exposures always involve inhalation of a wide distribution of fiber sizes, one panelist questioned the utility of focusing exclusively on fibers less than 5 μm in length. To illustrate this concern, he showed a graph depicting the fiber size distribution (in terms of length and diameter) in an ambient air sample collected at Libby. The graph showed that a clear majority of fibers

were less than 5 μm, as is often observed in occupational and environmental exposure situations.[6] The sample also included many fibers approximately 15 μm long, though in considerably smaller amounts than the short fibers. In such cases, the panelist cautioned about focusing exclusively on fibers smaller than 5 μm, even if they account for the overwhelming majority of the dose, because the smaller amount of longer fibers contribute more to overall toxicity.

To illustrate this issue further, the panelist presented data on the distribution of fiber lengths measured in surgical lung tissue samples from six miners and four cement plant workers who were exposed to asbestos fibers (primarily chrysotile) and non-asbestos fibers (Case et al. 2002a). The men were hospitalized with various lung diseases, which were mostly not related to their asbestos exposures. In these individuals, the majority (71%, by fiber count) of lung-retained chrysotile asbestos fibers were shorter than 5 μm, with lesser amounts (25%) of chrysotile asbestos fibers between 5 and 20 μm, and even lesser amounts (4%) of chrysotile asbestos fibers longer than 20 μm (Case et al. 2002a). A similar pattern was observed for the lung-retained non-asbestos fibers, with an even greater number of fibers shorter than 5 μm (85%) and none longer than 20 μm. Based on these results, this panelist reiterated that characterizing how toxicity varies with fiber length is critical, because retained doses can vary considerably between different fiber length intervals. The panelists revisited this topic when discussing whether a critical fiber length exists below which adverse health effects from environmental exposures would be unlikely (see Section 3.4).

- *Comments on fibers detected in Libby.* When evaluating the influence of fiber length on dosimetry, the panelists briefly discussed the significance of ambient air measurements in Libby, and asked Dr. Aubrey Miller (EPA) to summarize relevant data. Referring to trends among ambient air sampling data, Dr. Miller indicated that typically more than 60% of airborne fibers at the site are less than 5 μm long and therefore would not be counted by PCM testing for regulatory purposes. A panelist added that two asbestos amphibole minerals not currently regulated by the Occupational Safety and Health Administration (winchite and richterite) are included among the fibers in these samples. Dr. Miller noted that some Libby residents who were not occupationally exposed to asbestos and who had no household contacts with occupationally exposed individuals have developed pleural abnormalities, which raises questions about which fiber types are contributing to this disease. The panelists discussed this matter further when reviewing the current state of the science on human epidemiologic studies (see Section 3.1).

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[6] During this discussion, one panelist cautioned about distinguishing environmental exposures from occupational exposures and instead encouraged scientists to focus on the exposure dose, regardless of whether it was experienced in an occupational or environmental setting. To illustrate this concern, he noted that some "environmental exposures," such as those experienced by Libby residents, might exceed "occupational" exposures in well-regulated work places.

- *Dose metric issues.* The panelists briefly discussed how the available dose metrics—mass, number, and surface area of fibers—correlate with toxicity. A panelist noted that one study (Timbrell et al. 1988) reported that surface area correlated best with pulmonary fibrosis scores and therefore might be the best dose metric for that endpoint. This panelist said this finding is consistent with toxicologic studies of non-fibrous particles, which also indicate that surface area correlates better with pulmonary fibrosis than do other dose metrics. Another panelist questioned whether surface area of retained fibers is an appropriate dose metric, noting that such a selection implies that short fibers (i.e., fibers less than 5 μm in length), if inhaled in substantial quantities, can be equally toxic as very long fibers. This issue was not resolved, but a panelist noted that surface area of fibers might be more predictive of certain endpoints (e.g., lung fibrosis) while other dose metrics may correlate better with carcinogenic endpoints.

- *Research needs.* While discussing the physiological fate of fibers in the lung, the panelists identified several research needs. One panelist, for example, suggested that a laboratory study comparing dosimetry of fibers less than 5 μm to that of non-fibrous particles less than 5 μm could provide insights into lung deposition and clearance of shorter fibers. Another panelist advocated research that characterizes dosimetry for a series of fiber length intervals, rather than focusing entirely on fibers shorter than a given threshold length (i.e., 5 μm), because people are ultimately exposed to airborne fibers of varying lengths. One panelist suggested that studies consider the relevance of susceptible populations, but other panelists indicated that research on susceptible populations should be conducted after key studies on healthy populations have been completed. The panelists discussed additional research needs later in the meeting (see Section 3.5).

## 2.5 Observer Comments and Ensuing Discussions

After the panelists finished addressing the first topic area, observers were invited to provide comments. The panelists were not required to respond to the observer comments. However, some comments led to further discussion among the panelists, as documented here. The observer comments are summarized in the order they were presented:

### Comment 1: David Bernstein, consultant in toxicology

Dr. Bernstein presented findings from a chronic inhalation study that investigated the influence of fiber length and biopersistence on toxicity in rats. The study was conducted for the European Commission, but findings from the study have not been reported in the peer-reviewed literature and a written summary of the study was not provided to the expert panelists. Dr. Bernstein indicated that this study found that long fibers were more

biopersistent than short fibers. He further noted that exposure to fibers up to 20 μm long were found to be uncorrelated with toxic response, and only those fibers longer than 20 μm were correlated with toxicity. These findings were reportedly derived by comparing a toxic endpoint at 24 months following exposure to the distribution of fiber lengths retained in the rats' lungs. The toxic endpoint considered was collagen deposition at bronchoalveolar junctions—a precursor to pulmonary fibrosis. Dr. Bernstein claimed that the panelists can draw from this study's findings to make definitive statements on the toxicity of fibers shorter than 5 μm.

> **Panelists' Discussion:** When discussing this study, one panelist asked if preferential deposition of long fibers is expected to occur at the bronchial-alveolar junctions, and Dr. Bernstein said yes. This panelist noted that the apparent correlation between fiber size and toxicity might simply result from studying an endpoint where short fibers do not preferentially deposit. Another panelist encouraged Dr. Bernstein and his colleagues to publish these results.

Dr. Bernstein also presented data from an animal study on biopersistence of chrysotile fibers mined in Brazil. He explained that chrysotile fibers have a somewhat unique molecular structure, because more magnesium atoms are in the fiber surface; in amphibole fibers, on the other hand, these atoms are more concentrated internal to the fiber, away from the surface. Due to this unique structure, Dr. Bernstein argued, the chrysotile fibers are more readily dissolved in the lung. He reported that long chrysotile fibers (>20 μm) have a biopersistence half-life of only 1.3 days, while amphibole amosite fibers of similar length have a half-life of 466 days. He also showed a series of images depicting the fate of different length fibers in the lung as a function of days following exposure. Dr. Bernstein did not provide a reference for the data he presented.

> **Panelists' Discussion:** One panelist took exception to these studies, noting that his colleagues have published a study (Finkelstein and Dufrense 1999) indicating that chrysotile fibers longer than 10 μm have an estimated half-life of *8 years* in the lungs of Canadian miners. Further, he noted that a study of South Carolinian textile workers exposed to chrysotile fibers (Case et al. 2000) also supports a chrysotile half-life much longer than 1.3 days. That study found that the lung content of chrysotile fibers longer than 18 μm increased proportionally with the workers' cumulative exposure, suggesting that these longer fibers are more persistent in the lungs of occupationally exposed individuals than Dr. Bernstein's data imply.

**Comment 2: Jay Turim, Sciences International, Inc.**

Mr. Turim encouraged the panelists to consider the findings of two studies. First, he referred the panelists to a publication (Berman et al. 1995) that re-evaluated data from previous laboratory animal experiments in rats. This study reported that 99.7% of the potency for mesothelioma was due to asbestos fibers longer than 40 μm, with only 0.3%

of the potency attributed to fibers shorter than 40 μm. Mr. Turim suggested that the panelists consider these findings when commenting on the carcinogenicity of short fibers.

Second, Mr. Turim reviewed a recent study (Brown et al. 2000) in which two groups of rats inhaled formulations of different refractory ceramic fibers (RCF1 and RCF1a). The fiber formulations were reported as having approximately the same number of long fibers, but the RCF1 formulation contains much more non-fibrous particles than does the RCF1a formulation. In the study, the rats were exposed for 3 weeks (6 hours per day, 5 days per week), and were followed up for 1 year after exposure ceased. Mr. Turim noted that the lung retention of long fibers did not differ between the two exposure groups, even though the study authors reported that macrophage clearance processes were severely impaired in the rats exposed to RCF1, due to lung overload conditions. Mr. Turim also indicated that the study provides evidence that RCF (and SVFs, in general) behave differently from asbestos fibers in the lung, because the short RCF fibers were largely removed despite the impaired macrophage activity. Finally, because the study found more persistent inflammatory response, as gauged by bronchoalveolar lavage (BAL) analysis, in the rats dosed with the RCF1 mixture, Mr. Turim argued that the study shows that the presence of non-fibrous particles must be considered when evaluating the toxicity of SVFs.

> **Panelists' Discussion:** One panelist addressed this comment, noting that some aspects of the RCF study were not entirely clear to him. For instance, he did not think the publication adequately explained how lung clearance of short fibers could be similarly effective in the two groups, when macrophage activity was severely impaired only in the rats dosed with RCF1a. Further, he noted that the differences in toxicity between RCF1 and RCF1a were actually relatively minor, based on his interpretation of the BAL data and the histopathology results. Moreover, the panelist indicated that a follow-up study by the same group has found the non-fibrous FCF particles to be of high toxicity (Bellmann et al. 2002; Brown et al. 2002).

**Comment 3: Jenna Orkin, 911 Environmental Action Concern**

Ms. Orkin asked the panelists to comment on environmental contamination resulting from the WTC collapse, which blew contamination downwind toward downtown Brooklyn, where she lives. Concerned about ongoing exposure to WTC dust, Ms. Orkin indicated that she recently had a carpet sample from beneath a window in her house analyzed for fiber contamination using ultrasonication. She indicated that this analytical technique can detect about 100 times more asbestos fibers than can be found by ASTM MicroVac methods. Ms. Orkin noted that experts have reported that, for ASTM MicroVac samples, 1,000 structures per square centimeter is considered typical for rural homes and 10,000 structures per square centimeter typical for urban homes. However, she said that experts will not specify a safe level of structures measured by ultrasonication.

Ms. Orkin indicated that EMSL Analytical analyzed the carpet sample from her home and found "80,000 structures per square centimeter of asbestos." Seven chrysotile fibers were in the sample, including five long fibers. She indicated that the ultrasonication instrumentation eventually clogged, which she was told might mean that the contamination levels in the sample could not be measured because they were higher than the measurement sensitivity. Ms. Orkin asked if the panelists would comment on the data she presented, such as the exposure levels she and her family members might have experienced.

**Panelists' Discussion:** Three panelists and an EPA observer responded to the comment. One panelist noted that regulatory agencies have not established "safe limits" for measurements of asbestos fibers on fabrics. This panelist acknowledged that he was unfamiliar with the measurement method identified in the comment, but he did question why any sampling or analytical instrument would clog when analyzing a sample with only seven chrysotile fibers. Another panelist said the key issue for this scenario is characterizing the inhalation exposure, but he noted that no one has established how to estimate airborne exposure levels from asbestos levels in isolated carpet samples. Finally, noting that amphibole minerals make up 7% of the Earth's crust, a third reviewer suggested comparing the sampling results from the Brooklyn residence to measurements using identical methods in other locations that were not impacted by WTC dust.

Dr. Miller (EPA) indicated that EPA struggles with issues like those raised in the comment at many sites: What levels can be considered safe in homes? What fibers should one count when establishing these levels? When should regulatory agencies recommend abatement? He acknowledged that these decisions are beyond EPA's current regulatory guidelines.

**Comment 4: Bertram Price, Price Associates, Inc.**

Dr. Price's comment addressed asbestosis in Libby, Montana—a topic the panelists had questions about during their earlier discussions. Dr. Price indicated that ATSDR's recent study of Libby residents identified 12 cases of asbestosis: 11 among former mine workers, and 1 in a family member of a former mine worker. He said these findings illustrate the impact of dose on asbestosis, and he cautioned against attempting to distinguish environmental exposures from occupational exposures. Commenting on the influence of fiber length, Dr. Price noted that researchers have established a dose-response gradient between exposures to long asbestos fibers and asbestosis, though he acknowledged that the past studies used measurement techniques that did not count fibers shorter than 5 μm.

**Panelists' Discussions:** No panelists addressed this comment.

**Comment 5: Suresh Moolgavkar, University of Washington**

Dr. Moolgavkar's comments also addressed asbestos-related disease among residents in Libby, Montana. Dr. Moolgavkar noted that ATSDR has conducted two epidemiologic studies on Libby residents—the second was necessary after the agency realized that some death certificate data were inadvertently omitted from the initial report. He indicated that the second study reported that lung cancer mortality in Libby was higher than expected when compared to the state of Montana and the United States, while the first study found no excess. Regarding asbestosis, Dr. Moolgavkar summarized the available data on asbestosis cases (see Dr. Price's comment, above), and noted that asbestosis is linked to the most highly exposed individuals, regardless of whether their exposures were environmental or occupational.

Dr. Moolgavkar then commented on results from multiple mortality studies published on occupational cohorts of Libby mine workers (Amandus and Wheeler 1987; McDonald et al. 1986, 2002). He found no indication that asbestos from the Libby mines is more toxic than is predicted from cancer risk calculations using asbestos unit risk data from EPA's Integrated Risk Information System. Dr. Moolgavkar mentioned this to question the suggestion among the panelists that Libby asbestos is more toxic than asbestos from other sites (see Section 3). In fact, Dr. Moolgavkar noted, radiological examinations documented in the previous mortality studies found no evidence (based on prevalence of lung abnormalities) that Libby asbestos poses a greater health risk than asbestos from other sites.

> **Panelists' Discussions:** One panelist indicated that he agreed with the comment, in terms of lung cancer outcomes and lung parenchyma abnormalities, but he noted that mesothelioma cancer risks may in fact be uniquely higher at Libby. Specifically, the risk of developing mesothelioma among asbestos miners in Libby, as gauged by the proportional mortality ratio (PMR), is greater than that experienced by crocidolite asbestos miners in South Africa and Australia (see Section 3.1.1 for a more detailed summary of this argument).

Dr. Moolgavkar questioned this response, arguing that the PMR is not a good metric to use. He indicated that one would expect to see an elevated PMR if the Libby cohort had a strong "healthy worker effect."

> **Panelists' Discussions:** The panelist who addressed this issue agreed with this response, but noted that there is no evidence of a "healthy worker effect" among Libby miners, as demonstrated by the large number of accidental deaths in the cohort. This panelist defended use of the PMR for mesothelioma because it is a rare disease, and use of other cancer risk metrics (e.g., the standardized mortality ratio) might not be appropriate.

## 3.0 Comments on Topic 2: Health Effects of Asbestos and SVF Less Than 5 Micrometers in Length

This section summarizes the panelists' discussions on the role of fiber length in health effects from asbestos and SVF fibers. The meeting agenda (see Appendix D) lists the specific topics that the panelists addressed and identifies the discussion leaders for these topics. This section organizes the panelists' comments as follows: cancer effects (Section 3.1), noncancer effects (Section 3.2), mechanisms of toxicity (Section 3.3), general comments and interpretations (Section 3.4), and recommended research (Section 3.5). Section 3.6 summarizes observer comments made after the panelists completed their discussions. Some panelists submitted post-meeting comments to summarize their findings. These are included in Appendix E for the following topics: review of epidemiologic data (see Dr. Lockey's comments), review of laboratory animal studies (see Dr. McConnell's comments), and review of mechanistic studies (see Dr. Mossman's and Dr. Wallace's comments).

When evaluating health effects, panelists were asked to review findings from key studies that examined the role of fiber length on toxicity, whether *in vivo* or *in vitro*. Accordingly, this section should not be viewed as a literature review of all toxicity studies for asbestos and SVF; rather, it documents results from key studies that examined impacts of fiber length.

Although the panelists focused their initial discussions on fiber length, several panelists stressed that length is not the only factor affecting fiber toxicity. These panelists noted that toxicity is rather a complex function of the fiber dose, dimensions, and durability, as has been widely documented in the scientific literature.

## 3.1 Cancer Effects

This section summarizes the panelists' comments on the role of fiber length on cancer effects. The section is organized into three different types of studies: human cancer mortality studies (Section 3.1.1), studies of lung-retained fibers in humans (Section 3.1.2), and laboratory animal studies (Section 3.1.3). Within each section, comments are organized by type of fiber (asbestos or SVF) and type of cancer (lung cancer and mesothelioma).

### 3.1.1 Data from Cancer Mortality Studies

The panelists' comments on cancer mortality studies from occupational cohorts follow:

- *Asbestos.* One panelist indicated that no studies have evaluated cancer outcomes associated with fibers shorter than 5 μm, because no occupational cohort is exposed exclusively to such fibers. For insights into carcinogenicity of the short fibers, he reviewed findings reported for two occupational cohorts that were exposed predominantly (though not exclusively) to short asbestiform minerals:
    - The panelist first reviewed a study of workers at reserve mine deposits in Minnesota (Higgins et al. 1983). The workers at this site were exposed to cummingtonite-grunerite, a mineral related to amosite, and the vast majority of fibers were reportedly less than 10 μm in length. The study found no increase in overall mortality or mortality from respiratory cancers, but the panelist indicated that the average latency for the cohort was 14.7 years after initial exposure, with a maximum of 24.6 years, or a relatively short latency for development of cancer.
    - Second, this panelist reviewed studies of gold mine workers in South Dakota who also were exposed to cummingtonite-grunerite asbestiform material. He indicated that an initial study of this cohort (Gillam et al. 1976) found increased mortality from malignant respiratory disease among workers with at least 5 years of exposure. A follow-up study of this same cohort (McDonald et al. 1978), which considered workers who had worked for 21 years or longer, found no such increase, but did report increased risks of silicosis and tuberculosis. Average exposure concentrations for this site were 4.82 (±0.68) fibers per cubic centimeter, with 94% of airborne fibers being less than 5 μm in length.

This panelist indicated that these two studies were the closest approximation he could find to occupational cohorts exposed only to fibers shorter than 5 μm, and neither showed evidence of increased cancer mortality. He advocated follow-up studies of these cohorts in view of the passage of more than 20 years since the original publications to investigate carcinogenicity of short fibers more fully.

During this discussion, one panelist reviewed cancer mortality data published in two studies for an occupational cohort of Libby miners (McDonald et al. 1986, 2002). These studies considered 406 men who worked in the mine for at least 1 month prior to 1963; the more recent study, therefore, considers an average latency of period of more than 30 years from first exposure. This panelist noted that both studies reported elevated mortality rates for lung cancer, mesothelioma, and non-malignant respiratory disease (including asbestosis[7]). Of particular note, the panelist indicated that the more recent follow-up study (McDonald et al. 2002) suggests a PMR for mesothelioma of 6.7%—otherwise stated, 1 out of every 15 deaths identified in the follow-up study was from mesothelioma. He found this PMR significant because it is higher than those observed among most other cohorts studied, including crocidolite miners in South Africa and Australia.

- *SVF.* One panelist reviewed cancer mortality studies of occupational cohorts exposed to SVFs, including glass fibers, mineral wool, and RCFs. The panelist first noted that no studies have been conducted on occupational cohorts exposed exclusively to fibers less than 5 μm long, again because no cohorts appear to be exposed only to short fibers. However, he noted that cancer mortality at fiber glass and mineral wool production facilities has been extensively studied, both in the United States and Europe. He summarized these studies for different materials:

  - For fiber glass, the panelist noted that the studies did not find increases in respiratory cancer to be related to fiber glass exposures.

  - For rock wool and slag wool, the panelist indicated that studies of production facilities in the United States found no evidence of increased risk for respiratory cancer. At production facilities in Europe, on the other hand, initial studies have demonstrated increases in respiratory cancer, but no clear information to indicate that the increased cancer risk was specifically related to fiber exposure. A subsequent case-control study indicated no relationship between cumulative rock or slag wool exposure and lung cancer (Kjaerheim et al. 2002). The International Agency for Research on Cancer (IARC) authors did not conclude that the increased cancer was related to the exposures to rock or slag wool.

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[7] One panelist, when reviewing a draft of this report, indicated that death certificate data typically use a single code for all non-malignant respiratory disease. He added that asbestosis probably accounts for a minority of these deaths when compared to chronic obstructive lung disease.

- For RCF, which are more durable fibers than the other SVFs, the panelist indicated that no cancer mortality data have been published for occupational cohorts exposed to RCF. This panelist noted that a recent study of a relatively small cohort of plant production workers has not demonstrated increased respiratory cancer risk for RCF, nor any identified mesothelioma, but he acknowledged that the study had limited statistical power for detecting an increased risk. Results from this study have been accepted for publication in a peer-reviewed publication (Lemasters et al. 2002).

The panelist who summarized these results also specifically noted that there is no indication of a relationship between exposure to SVFs and mesothelioma. Though a small number of mesotheliomas have been reported for workers at SVF manufacturing plants, these cases have since been explained by other factors (e.g., probable prior exposure to asbestos, incorrect diagnoses).

### 3.1.2 Data from Human Studies of Lung-Retained Fibers (Cancer)

Additional insights on the influence of fiber length on cancer outcomes was presented for studies that analyzed the amounts and sizes of fibers retained in the human lung. In these studies, lung-retained fiber is used to characterize exposure. The panelists identified limitations associated with such studies, most notably that the measurements of lung-retained fibers (typically at autopsy) are static and do not characterize when exposure occurred or temporal variations in exposure. Moreover, because lung-retained fibers can break or partially dissolve after exposure, it is possible that the length distribution of fibers observed after death is different from the length distribution of fibers in the original exposures. The panelists provided the following comments on available studies of lung-retained fibers:

- *General comments.* One panelist provided general comments on fiber accumulation and human disease. First, the panelist indicated that people are exposed to fibers of varying length, with shorter fibers generally accounting for the majority of exposure (by fiber count); a similar pattern—a majority of shorter fibers—is consistently observed in the lung-retention studies. Second, because asbestos fibers with widely varying lengths are detected in lung tissue samples from all populations, this panelist concluded that the human lung, under continuing exposure conditions, is not capable of completely clearing fibers of any length to background levels—a finding that is not replicated in inhalation

studies conducted in rats.[8] He demonstrated lung accumulation by displaying data from multiple studies (e.g., Sebastien et al. 1980; Case et al. 2000), which showed that all types of asbestos fibers (including long chrysotile fibers) accumulate in the lung with cumulative exposure.

- *Mesothelioma.* The panelists then commented on three case-control studies that examined the distribution of fiber lengths in people who died from mesothelioma (and most with matched controls). All three studies showed that risk of mesothelioma was considerably higher for individuals with larger amounts of long fibers retained in their lungs:

  - The first study (McDonald et al. 1989) examined lung tissues from 78 Canadian men and women who died of mesothelioma, as well as 78 lung tissues from age-, sex-, and hospital-matched controls. The lung samples were from pathologists' stock, without information on what parts of the lung the samples were collected from. Relative risk for developing mesothelioma was reported for different fiber types and lengths (<8 μm and >8 μm). The study found that the risk of mesothelioma was significantly related to concentrations of amphibole fibers longer than 8 μm and that fibers shorter than 8 μm accounted for none of the cancer risk.

  - The second study (Rogers et al. 1991) examined lung tissues from Australians who died of mesothelioma. Based on "the best fitting additive relative risk model," the study reported that mesothelioma risk was greatest for crocidolite asbestos fibers longer than 10 μm, followed by amosite asbestos fibers longer than 10 μm, and then by chrysotile fibers less than 10 μm. The authors suspected that the relative risk for chrysotile fibers less than 10 μm resulted from longer fibers breaking into shorter fibers.

  - The third study (Rödelsperger et al. 1999) evaluated lung tissue samples from 66 German individuals who died from mesothelioma and 66 matched controls. The study reported that "...a clear dose-response relationship up to an odds ratio of 99% has been demonstrated for the lung tissue concentration of total amphibole fibers longer than 5 μm." The study provided few details on the cancer risk associated with short fibers.

- *Lung cancer.* A panelist indicated that no lung-retention studies in humans have attempted to examine relationships between the length distribution of retained asbestos fibers and lung cancer. He suspected that studies have not been conducted due to the high attributable risk from smoking. This panelist noted that many studies have reported the total concentration of asbestos fibers for lung cancer in lung samples, but none of these evaluated the role of fiber length.

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[8] When reviewing a draft of this report, another panelist indicated that animal studies have found that animals are also not capable of completely clearing fibers of all lengths to background levels.

### 3.1.3 Data from Laboratory Animal Studies (Cancer)

The panelists identified several laboratory animal studies that illustrate the influence of fiber length on carcinogenicity, and made general comments about the relevance of these studies to humans. Panelists specifically referred to the following three studies when discussing how fiber length has been shown to relate to lung cancer and mesothelioma in laboratory animals:

- In the first study (Davis et al. 1986), no malignant cancers were observed in 42 rats exposed via inhalation to a short-fiber amosite mixture, while eight malignant cancers were reported in the 40 rats exposed to the long-fiber amosite mixture (30% of fibers longer than 5 μm and 5% of fibers longer than 10 μm).

- In the second study (Davis and Jones 1988), seven malignant cancers were observed among rats exposed via intraperitoneal injection to a "short" chrysotile fiber mixture, while 22 malignant cancers were observed among those exposed to the "long" fiber mixture. Cancers in the former group, however, have since been attributed to contamination of the "short" fiber samples with longer chrysotile fibers (Lippmann 1994).

- In the third study (Wagner et al. 1985), rats exposed to mixtures of erionite fibers that were mostly shorter than 5 μm did not develop mesothelioma, while every rat exposed to the longer erionite fiber mixtures developed the disease. One panelist found certain aspects of this study surprising, such as the fact that all of the rats exposed to long fibers died within 15 months, even though mesothelioma typically is not lethal in rats, and that

***General strengths and weaknesses of laboratory animal studies***

The panelists provided several general comments on the utility of laboratory animal studies for understanding toxicity of asbestos and SVFs. Benefits of animal studies include the ability to (1) conduct highly controlled experiments using well-defined exposure levels and (2) evaluate health outcomes and lung-retention levels at many different time frames following exposure. Extensive lung tissue sampling and other highly invasive tests in humans, on the other hand, are only feasible at autopsy. However, panelists identified key factors that must be considered when interpreting laboratory animal studies. These factors include differences in life span, macrophage size, and airway branching patterns; relevancy of high dose and administration methods (e.g., peritoneal injection); and failure to address certain human exposure conditions (e.g., smoking). Overall, the panelists generally agreed that laboratory animal studies can provide useful insights into toxicity to humans, provided the studies are interpreted in the proper context regarding their relevancy to humans.

the histopathological slides showed very intense pleural reactions. The panelists revisited this study (see Section 3.4) when discussing how chemical composition and surface properties might affect toxicity.

One panelist synthesized the findings from these and other relevant laboratory animal studies. This panelist first noted that the rat is an adequate model for cancers in humans, because the rat has been shown to develop both mesothelioma and lung cancer, though he acknowledged that these cancers are not as aggressive in the rat as in humans.[9] He added that the laboratory animal studies have allowed researchers to observe the progression of disease for both lung cancer and mesothelioma. Regarding the administration method, this panelist indicated that the inhalation studies were more relevant to human exposures. He noted that fiber administration by intrapleural implantation and intraperitoneal injection does not represent human exposures for several reasons (e.g., extremely large doses are administered in very short time frames, alveolar macrophage and mucociliary transport clearance mechanisms are bypassed, and the fibers inserted into the pleura might not be capable of reaching these tissues following inhalation exposure).

Overall, this panelist believed that laboratory animal data using all administration routes have shown that short fibers of any type are less potent than long fibers, both for mesothelioma and cancer, but the relative potency has not been quantified.

## 3.2 Noncancer Effects

This section summarizes the panelists' comments on the role of fiber length on noncancer effects and is also organized according to the different types of studies: occupational studies (Section

[9] The panelists noted differences in asbestos-related cancers in rats and humans. One panelist said that lung cancer in rats tends to be bronchioalveolar, and develops in the distal lung, while lung cancer in humans largely tends to occur in proximal areas of the lung. He wondered if differences in fiber deposition patterns (due to differing airway sizes and branching patterns) might explain differences in where lung cancers develop in rats and humans. Another panelist cautioned against expecting that lung cancer would develop in the same parts of the lung in rats and humans, primarily because of the confounding factor of cigarette smoking in humans.

3.2.1), studies of lung-retained fibers in humans (Section 3.2.2), and laboratory animal studies (Section 3.2.3). Each section is further organized by noncancer endpoint. Although many different endpoints were discussed (e.g., irritation, nephrosis), the majority of discussions focused on pulmonary interstitial fibrosis and pleural abnormalities (e.g., pleural plaques, pleural thickening, and calcification).

### 3.2.1 Data from Occupational Studies

Overall, the discussion leader for this topic area indicated, there is limited evidence of noncancer toxicity being associated with fibers less than 5 μm in length, with two exceptions. First, he indicated that very high doses to short fibers, especially those that are durable in intracellular fluids, may have the propensity to cause interstitial fibrosis. Second, he noted that exposure to short, thin durable fibers may play a role in development of pleural plaques or diffuse pleural fibrosis if the dose is high enough. The following paragraphs review the discussion that led to these summary statements:

- *Asbestos.* One panelist noted that no epidemiologic studies have examined populations exposed only to short asbestos fibers, because actual exposures are inevitably to a broad distribution of fiber lengths. To address this issue, the panelists commented on data reported among Libby residents, particularly the prevalence of intense bilateral pleural fibrosis in community members—some of whom reportedly did not work in the local vermiculite mine or processing plant, and did not live with mine or mill workers. One panelist was particularly concerned about the role of short fibers, noting that a very large portion of fibers in the homes are too short or too thin to be counted by conventional PCM sampling methods. He added, however, that some researchers have speculated that short (<10 μm), thin (<0.4 μm), durable fibers, particularly tremolite asbestos, may preferentially deposit on the pleural surface and therefore be associated with pleural plaques. This panelist emphasized that the relevance of short, thin fibers and the risk for pleural abnormalities has only been speculated, and needs to be further investigated. The panelists also wondered if the intense pleural effects observed in the Libby cohort might be associated with the unique mineralogy of the Libby asbestiform fibers. Pleural plaques have been associated with environmental exposures in areas where tremolite fibers naturally occur (e.g., in certain regions of Greece, Cyprus, Turkey, Canada, the Czech Republic, Romania).

  Some discussion focused on the extent to which pleural effects are associated with occupational versus environmental exposures. Two panelists cautioned against attempting

to classify exposures in this manner, because some individual exposures were difficult to assess. For instance, some residents might not have worked at the mine or the mill or lived with mine or mill workers, but could have been highly exposed through routine contacts with these individuals in other settings. These panelists recommended that the discussion focus strictly on dose, regardless of the contributions from occupational and environmental exposures.

- *SVF.* One panelist indicated that the available epidemiologic studies provide no indication of increased mortality from nonmalignant respiratory disease among occupational cohorts exposed to SVF. He then summarized morbidity data for several cohorts. The summary focused on SVF production workers. Although SVF "end users" (e.g., insulators, pipe fitters, heating/ventilation workers) have also been evaluated, these studies are commonly confounded by potential asbestos exposures. Overall, this panelist concluded that the available occupational studies indicate limited overall toxicity associated with SVF exposure, with the exception of RCF exposure being associated with pleural plaques. This conclusion was based on the following observations:

  - For exposures to SVFs (all types), one panelist noted that multiple studies have found that SVF exposure among current or former smokers is associated with small additional decrements in forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV1). He added that similar decrements in spirometric parameters are observed among other non-specific dust exposed industrial working populations, suggesting that the effect is not specific to SVFs.

    This panelist also reviewed studies, albeit limited ones, of skin irritation. These have reported irritation being related to mechanical effects of large diameter fibers (~5 μm in diameter), with increased irritation observed in hot, humid climates. Eye, upper respiratory, and lower respiratory irritation has also been reported in case studies among people accidentally exposed to high fiber concentrations, and these irritation effects are generally transient.

  - For fiber glass and mineral wool, this panelist noted that the available studies (e.g., Hughes et al. 1993), though limited in number, provide no indication of chest radiographic, interstitial, or pleural changes among production workers. The panelist added that studies have suggested an increased mortality risk from nonmalignant renal disease (e.g., nephritis, nephrosis) in occupational cohorts exposed to mineral wool, but not among those exposed to fiber glass; he questioned the biological plausibility of these outcomes.

  - For the more durable RCFs, the panelist indicated that occupational exposures have been associated with pleural changes, primarily pleural plaques. The pleural plaques were observed among approximately 3% of the production workers, but were found to be correlated with duration of RCF exposure, time since initial

exposure, and cumulative RCF exposure. The panelist added, however, that the available studies have not found RCF exposure to be associated with a statistically increased risk for pulmonary interstitial fibrosis.

- During this discussion, Dr. Ralph Zumwalde (NIOSH) informed the panel that, in the late 1970s, NIOSH studied the health implications among more than 2,000 miners who were exposed to an attapulgite clay that has fiber-like characteristics (Waxweiler et al. 1988). The clay "fibers" were less than 5 μm long, with diameters of approximately 0.1 μm. Dr. Zumwalde noted that this study, which he recalled found excess lung cancer among whites, might be useful in ATSDR's overall evaluation of short fibers. The increase in lung cancer deaths, however, was not associated with latency, duration of employment, or attapulgite exposure, and there was no increase in mortality from nonmalignant respiratory disease.

Overall, the relevance of short asbestos and SVFs to noncancer disease in humans was not entirely known. For the SVFs, only the durable RCF was found to be associated with pleural plaques; exposures to RCFs were not associated with pulmonary fibrosis, and exposures to fiber glass and mineral wools had no indication of chest radiographic, interstitial, or pleural changes. For asbestos fibers, no studies have examined the effects of exposures exclusively to short fibers. Given data collected in Libby, Montana, however, some panelists questioned whether short fibers might play a role in the observed cases of pleural plaques and diffuse pleural fibrosis; but others cautioned against inferring that the risk results from exposure to short fibers, given that the Libby samples contained significant numbers of long fibers as well.

### 3.2.2 Data from Human Studies of Lung-Retained Fibers (Noncancer)

Two panelists reviewed publications (case-control studies, a study recently submitted for publication, and a case report) that examine the influence of fiber length retained in the lung on the grade of pulmonary interstitial fibrosis, which is reported on a scale from 0 to 12. A summary of these studies, organized by fiber type, follows:

- *Findings for tremolite asbestos.* One panelist indicated that a study of tissues from chrysotile asbestos miners and millers reported an inverse relationship between fibrosis grade and length of tremolite fibers retained in the lung (Churg et al. 1989). In other

words, the most severe fibrosis was observed among those with smaller (on average) tremolite fibers in their lungs. Another study (Nayebzadeh et al. 2001) and a study recently submitted for publication (Case et al. 2002b) examined fibrosis grades for different length intervals of tremolite fibers: 0–5 μm, 5–10 μm, and 10–20 μm. Both studies found the highest average fibrosis grade occurred among those with the lowest tremolite fiber length interval, or for those with average tremolite fiber length less than 5 μm.

- *Findings for amosite asbestos.* One study (Churg et al. 1990) examined lung tissue samples from a small group (<20) of shipyard workers and insulators selected from litigation cases. This study also found an inverse relationship between fibrosis grade and length of retained asbestos fibers (amosite fibers, in this case).

- *Findings for total asbestos fibers.* One panelist summarized a study (Timbrell et al. 1988) that evaluated lung tissue samples at autopsy from workers exposed in different asbestos mines. Data were collected both for retained asbestos fibers and fibrosis score. The fibrosis scores were then correlated with lung-retained asbestos characterized by three different metrics: number of fibers, mass of fibers, and surface area of fibers. The correlation was best when the surface area of retained fibers was used as a dose metric. This panelist added that the surface area dose metric has correlated well with pulmonary inflammatory responses in other animal inhalation toxicity studies that examined inflammation, including fibrosis, following exposure to particulate contaminants that are poorly soluble with low chemical reactivity. The panelists referred to this study, which did not examine the role of fiber length, several times when discussing appropriate dose metrics.

- *Findings for aluminum oxide fibers.* One panelist reviewed data from a case report (Churg et al. 1993) on an individual with diffuse interstitial fibrosis who was occupationally exposed to aluminum oxide fibers. The lung-retained fibers in this case were predominantly 3–4 μm long and 0.01 μm in diameter. The panelist indicated that these findings raise questions about the significance of short, thin, durable fibers in the lung, though he acknowledged that conclusions should not be drawn from a single case report.

Several panelists commented on the trends among the aforementioned studies. Two panelists, for instance, noted that the trend of shorter fibers possibly being more toxic, at least in terms of interstitial fibrous, is counterintuitive. Two other panelists, on the other hand, noted that these findings suggest that, for interstitial fibrosis, the surface area of retained fibers may be more important than the fiber length, because larger amounts of short fibers would have considerably greater surface area than smaller amounts of long fibers. Finally, some panelists wondered if the apparent inverse relationship between fiber length and fibrosis score might be explained by long

fibers breaking down into shorter fibers between exposure and the time that lung samples were collected.

### 3.2.3 Data from Laboratory Animal Studies (Noncancer)

This section reviews the panelists' discussions on noncancer outcomes from asbestos and SVF exposure identified in laboratory animal studies. Before addressing this topic, one panelist summarized how the mammalian lung responds to exposures to inert materials, whether fibrous or particulate: once an inert material deposits in the lung beyond the conductive airways, it will either dissolve or be engulfed and cleared by alveolar macrophages; if the dose exceeds the lungs' capacity to clear the material, natural defense mechanisms may act, leading to fibrosis. Section 3.3 presents more details on the mechanisms involved in these steps. Specific comments on noncancer effects in laboratory animals, organized by endpoint, follow:

- *Inflammation, pulmonary interstitial fibrosis, and pleural reactions.* The panelists presented several observations when summarizing findings from laboratory animal studies on noncancer effects in the lung and pleura. First, two panelists noted that many laboratory animal studies have found pulmonary interstitial fibrosis following exposures to both fibrous material and non-fibrous particles. The sequence of events leading to the fibrosis was described (see Dr. McConnell's premeeting comments in Appendix B). When doses reach high enough levels, pleural reactions (e.g., localized acellular fibrotic changes) were observed, but one panelist questioned if the dose levels needed to elicit the pleural responses are relevant to environmental exposures in humans. Another panelist noted that the animal studies suggest that the pleural effects do not occur unless fibers are present in the pleura. When discussing interstitial fibrosis outcomes, one panelist said the long fibers appear to be more fibrogenic than the short fibers, though he stressed that short fibers alone are capable of generating fibrogenic responses if the dose is sufficiently high. The panelists' premeeting comments include specific references to studies that reported relative toxicity of short and long fibers for noncancer outcomes (see Dr. Mossman's premeeting comments in Appendix B).

  Reviewing specific studies, one panelist indicated that the intensity of noncancer responses in laboratory animals varies from one fiber type to the next. He noted, for example, that hamsters exposed to amosite asbestos had an increased incidence of pleural fibrosis, while hamsters exposed to comparable amounts of chrysotile asbestos did not; pulmonary fibrosis was evident, however, in both groups of hamsters. The panelist suspected that the different outcomes resulted from either the amosite fibers being more

durable (less soluble) in the lung or the amosite fibers being more likely to translocate to the pleura.

One issue that generated significant discussion was the extent to which interstitial fibrosis progresses in laboratory animals and the relevance of disease progression to humans. One panelist noted that, in every animal study he has conducted and reviewed to date, interstitial fibrosis is progressive only when asbestos exposure is ongoing. After asbestos exposure ceases, he noted, no overt signs of progressive fibrosis are apparent, although this has not been quantified in a definitive way. The inflammatory responses, microgranulomas, and bronchiolization also tend to decrease. This panelist added that fibrosis does not appear to progress and macrophage response tends to decrease when the exposure ceases, even though long asbestos fibers remain in the animals' lungs. He interpreted this trend as suggesting that short asbestos fibers in the original dose might play a role in stimulating an initial inflammatory response in the rats. Another panelist suggested that the lack of fibrosis progression, even in the presence of long fibers, might suggest that the retained fibers have been rendered inert (in comparison to the freshly inhaled fibers), possibly by being coated with biological fluids. In other words, he wondered if the freshly inhaled fibers are more likely to elicit cellular responses than fibers that have been in the lung for an extended period of time.

Though not questioning the comments on fibrosis progression in animals, two panelists emphasized that the trends discussed above are not observed in humans. Citing their experiences evaluating shipyard workers and chrysotile miners, these panelists noted that fibrosis and pleural changes have progressed in humans, even after asbestos exposures ceased. Reasons why fibrosis might progress differently in rats and humans were not discussed.

Commenting further on disease progression, one panelist indicated that certain noncancer effects and lung cancer appear to have consistent patterns in all animal studies he has reviewed, including studies of asbestos exposure and studies of exposure to non-fibrous particulate. Specifically, this panelist said he had not found any study in which a rodent had lung cancer, but did not have interstitial fibrosis; and he had never seen rodents with interstitial fibrosis in the absence of inflammation. These observations led the panelist to infer that lung cancer would not be expected to develop at doses that do not induce fibrosis or inflammation. He stressed that this inference is based solely on observations from previous animal studies and does not in any way suggest that fibrosis is a precursor to lung cancer—an issue that came up during the observer comments (see Section 3.6). He also added that this relative sensitivity of noncancer endpoints may not necessarily be observed in humans.

- *Irritation.* One panelist noted that laboratory animal studies have not studied the extent to which asbestos and SVF irritate the skin and eye. He added that histopathological studies of the nasal cavity, pharynx, larynx, trachea, and conductive airways have not identified

evidence of irritation, though he acknowledged that the histopathological techniques might not have detected certain responses (e.g., increased mucus production). He cautioned that these results do not necessarily suggest that humans will not experience fiber-induced irritation in the nasal cavity, larynx, and upper respiratory tract, because the rat studies did not consider populations with impaired mucociliary clearance, as might be observed in smokers. Finally, this panelist indicated that ingestion studies in rats and hamsters have shown no evidence of irritation in the gastrointestinal tract.

### 3.3 Mechanisms of Toxicity

This section reviews the panelists' comments on mechanisms of toxicity, primarily as presented by the two designated discussion leaders, Dr. Mossman and Dr. Wallace. After identifying several general advantages and disadvantages of *in vitro* studies, the discussion leaders reviewed current theories on mechanisms of toxicity for a wide range of fibers and analogous non-fibrous particles. This section reviews key points from those presentations. Emphasis is placed on what has been established or hypothesized regarding the relative toxicities of short and long fibers. For more detailed information on mechanisms of toxicity, refer to Dr. Mossman's and Dr. Wallace's post-meeting comments in Appendix E.

- *General comments on the utility of* in vitro *studies.* To initiate discussions, one panelist listed several strengths and limitations associated with *in vitro* toxicity studies. First, she indicated that *in vitro* studies, when compared to laboratory animal studies, offer a far more controlled setting for examining mechanisms of toxicity and dose-response behavior for specific cell types. She acknowledged, however, that interpreting trends among studies using widely varying doses and multiple cell types can be complicated. Moreover, the *in vitro* studies are all limited in duration, typically lasting a few days, due to the limited life spans of isolated cells in the *in vitro* environment. Consequently, the *in vitro* studies cannot characterize dissolution, macrophage clearance, and other processes that occur over longer time scales. Finally, this panelist noted that doses to *in vitro* samples cannot readily be extrapolated to human inhalation exposures.

- *Role of reactive oxygen species (ROS).* One panelist reviewed a widely accepted theory of how generation of ROS might explain asbestos-related toxicity. She indicated that alveolar macrophages, as they attempt to digest foreign fibers and particles, produce an "oxidative burst" and release ROS. (Other cell types that contact asbestos fibers also release ROS.)

These ROS can initiate sequences of events that have been shown *in vitro* to lead to outcomes such as genotoxicity, cytotoxicity, and cell proliferation.

This panelist highlighted two key observations regarding ROS. First, *in vitro* studies have shown that alveolar macrophages generate more ROS when attempting to digest longer fibers, while shorter fibers can be engulfed completely by macrophages (and other cell types) with no visible damage to the cells. Second, she noted that ROS can form highly reactive hydroxyl radicals via a reaction that is facilitated by the presence of iron. Therefore, long, iron-containing fibers, like several amphibole asbestos fibers, are capable of generating an intense "oxidative burst," which might explain their greater potency, when compared to fibers that do not contain iron. Finally, this panelist noted that researchers can prevent pulmonary fibrosis in animals by administering free radical scavengers or other substances that interfere with ROS formation and reactions—a finding that argues strongly for ROS having a causative role in inducing asbestos-related fibrosis.

Overall, this panelist noted that many aspects of the ROS theory help explain how fiber length and, to a lesser extent, mineral content relate to toxicity and why shorter fibers are substantially less toxic than longer ones. She presented results from several *in vitro* studies (e.g., Ohyama et al. 2001) that confirm that longer fibers generate a greater "oxidative burst" when they are not ingested by alveolar macrophages.

- *Effects on cell signaling events.* The panelist then described current research that has characterized effects of asbestos- and fiber-related cell signaling events. She explained that these events originate when fibers interact with cell surfaces, after which the cells activate transcription factors that mediate various outcomes which can be measured *in vitro*, such as cell proliferation, cell transformation, and cell death. She noted that cell proliferation is an important step in development in both malignant and nonmalignant disease.

The panelist then described studies examining how selected signaling pathways are affected by asbestos and glass fibers of different lengths. She summarized studies that demonstrated activation of transcription factors and cell proliferation. First, the panelist reviewed a study (Ye et al. 1999) in which mouse macrophage cell lines were challenged with two formulations of fiber glass mixtures, one with average length of 6.5 μm, the other 16.7 μm. These challenges caused production of tumor necrosis factor-alpha (TNF-α), a cytokine involved in inflammation and fibrosis, which in turn caused activation of nuclear factor-κB. Gene promoter activation induced by the short fibers was found to be between one-third and one-half what was observed for the long fibers.

Second, the panelist reviewed *in vitro* studies that examined specific aspects of cell proliferation. Although cell proliferation relates to cancer outcomes, she emphasized that development of mesothelioma and lung cancer is a multi-stage process with a long latency period, which cannot be captured in the short time frame of an *in vitro* study. The panelist identified many studies (see Appendix E) demonstrating that longer fibers are more apt to

cause cell proliferation than are short fibers, whether from tracheal explant studies (e.g., Sesko and Mossman 1989) or intratracheal models in rats (Adamson and Bowden 1990).

- *Studies of asbestos genotoxicity.* The panelist indicated that researchers have been studying the genotoxicity of asbestos, both *in vivo* and *in vitro*, for more than 20 years. These studies examined a wide range of endpoints (e.g., cell transformation, chromosomal aberrations, gene mutation) in various matrices. The panelist focused, however, on a series of studies conducted to examine the role of fiber length on cell transformation and cytogenetic effects (Hesterberg and Barrett 1984, 1985; Hesterberg et al. 1986). These studies demonstrated that long, thin fibers are most potent for both types of effects, and the shortest fibers examined (less than 1.7 μm long) had no indication of tumorigenic potential. These findings, she noted, indicate that longer fibers are again more toxic, with some suggestion that fibers below a certain length threshold may not be carcinogenic at all.

- *Observations regarding mechanisms of toxicity from non-fibrous particulates.* One panelist addressed mechanisms of action for non-fibrous particulates having compositions similar to those in asbestos and SVFs. First, he indicated that non-fibrous crystalline silica is strongly pathogenic for fibrotic lung disease, while two polymorphs of crystalline silica—quartz and cristobalite—have recently been classified as carcinogenic (IARC 1997). In contrast, amorphous silica (more akin to SVFs) has not been shown to cause lung cancer or mesothelioma in rodents (IARC 1987). Exposure to the crystalline silica polymorphs can directly damage cells, resulting in intracellular generation of reactive oxygen species and a cascade of events (e.g., synthesis and release of cytokines, cell proliferation, secretion of collagen into the extracellular space) similar to the those evoked by asbestos fiber. *In vitro* studies have shown that silanols (hydroxyl groups on the crystalline surface) are associated with the initial damage to cells: loss of surface silanols caused the crystalline silica to exhibit less damaging activity, and subsequent formation of silanols restored the silica's toxicity (Pandurangi et al. 1990). These and other studies (see Appendix E) suggest that surface chemistry plays a role in silica's toxicity.

  This panelist noted that an important but generally ignored component for physiologically representative *in vitro* bioassays is that particles and fibers depositing in the lung initially contact the aqueous "hypophase" lining on the terminal airway and airsac surfaces. The hypophase layer is rich with micellar dispersion of surfactant, composed largely of lipids and lipoproteins. Of particular note, the hypophase can be simulated *in vitro* with dipalmitoyl phophatidyl choline (DPPC) dispersed in physiological saline. Silica particles and other materials deposited in the lung have been shown to adsorb the surfactant, which extinguishes short-term cytotoxicity—another observation indicating that the toxicity of particles in the lung is affected by surface chemistry. This panelist noted that the alveolar hypophase contains more than enough surfactant to coat and neutralize the entire surfaces of respirable particles, even in most high dust exposures (Wallace et al. 1975).

Although the volume of surfactants in the alveolar hypophase is sufficient to coat respired particles completely (even in high dust exposures) and thus is theoretically capable of extinguishing the particles' toxicity, this panelist indicated that the toxicity can be restored when other cellular mechanisms remove the protective surfactant cover. Specifically, macrophages can engulf surfactant-coated particles, where they are subject to phagolysosomal enzymatic digestion which can remove the surfactant film and thus restore toxicity. Some study has shown that the surfactant film is more readily removed from crystalline silica than it is from kaolin, which suggests a mechanism by which quartz may be more toxic than kaolin; however, experimental study has not demonstrated that particle de-toxicification and re-toxicification explains the relative toxicities of these materials. Thus, surfactant coating of foreign particles deposited in the alveolar space again appears to play an important role in toxicity. The influence of surface chemistry has also been observed in quartz particles having alumino-silicate surface contamination; for such particles the surface contamination can delay for months or perhaps years the expression of fibrogenic activity.

Finally, this panelist noted that researchers might glean greater understanding of the main site of asbestos fibrogenic activity from theories reported for crystalline silica. He explained that a series of studies (e.g., Bowden et al. 1989) suggests that fibrosis results from a sequence of events following interactions between crystalline silica and interstitial cells, rather than interactions with alveolar macrophages. Specifically, it is hypothesized that interactions with the interstitial cells control the stimulation of exacerbated collagen synthesis by pulmonary fibroblasts; whereas, interactions with macrophages are hypothesized as being responsible only for an inflammatory response (not fibrosis) evoking neutrophil influx to the alveolus. This panelist suggested that further research on the mechanisms of fibrogenic toxicity for asbestos should consider interactions with interstitial cells, rather than focusing largely on responses initiated by interactions with alveolar macrophages.

- *Comparisons between fibrous minerals and crystalline silica particles.* This panelist noted that the available *in vitro* studies do not explain comprehensively how asbestos fibers and crystalline silica particles differ in inducing fibrosis. Although they identify several endpoints that asbestos and crystalline silica have in common, the studies cannot predict why asbestosis appears as a diffuse fibrosis, while silicosis appears in localized nodules.

  However, some research provides insights on differences between how long fibers, short fibers, and particles contribute to cytotoxicity. Specifically, an *in vitro* study (Liu 1994) examined whether surfactant coating inhibits the cytotoxicity of asbestos. (As the previous bulleted item indicates, similar studies found that surfactant coating virtually extinguished the short-term toxicity of crystalline silica particles.) In the study, Chinese hamster lung cells were tested for micronucleus induction after being challenged with surfactant-coated chrysotile asbestos. The study considered how induction differs between long fibers (average fiber length of 101 μm) and shorter fibers (average fiber length of 11.6 μm). It

found a slight, but not significant, decrement in cytotoxic endpoints for the long fibers and a considerable, statistically significant decrement for the shorter fibers. The findings suggest that surfactant coating is less effective at impairing toxicity for longer fibers.

Although the studies on crystalline silica underscored the role of surface chemistry in eliciting toxic responses, changes in the surface composition in chrysotile asbestos were found to have no significant effect on *in vitro* genotoxic activity (Keane et al. 1999). Specifically, fibers that had been mildly leached to remove near-surface magnesium atoms exhibited comparable genotoxicity to fibers that were not treated with the leaching solution.

Based on his review of these and other studies, one panelist suggested that more than one mechanism of toxicity may operate for asbestos and SVF, and the roles of the individual mechanisms might depend on fiber length. He explained that "frustrated phagocytosis" and its ensuing events clearly appear more relevant to long fibers (i.e., long fibers are much more likely to be only partially engulfed by alveolar macrophages), while a toxicity mechanism mediated by surface properties of phagocytized material (e.g., restoration of fiber toxicity in the intracellular matrix) would be more relevant to short fibers. In other words, part of the short fiber toxicity might be related to mechanisms involving surface chemistry, which were described in the previous bulleted item. This panelist added, however, that additional mechanisms could contribute to toxicity. As one example, he indicated that asbestos fibers penetrating the cell or cell nucleus may exercise modes of direct genetic or epigenetic damage. Whatever the mechanisms of direct fiber damage or stimulation of the cell surface, he noted, several components of the consequent intracellular response have been well defined. Appendix E provides additional detail on the responses that have been characterized, and the influence of fiber length on these responses.

- *Recent advances in fiber preparation methods.* One panelist noted that researchers at NIOSH have been developing a fiber size classifier (separator) that permits *in vitro* or perhaps limited *in vivo* experiments with sets of fibers of fairly well-defined length (Baron et al. 1994). The dielectrophoretic classifier reportedly can separate fibers from an airstream and produce about 1 mg/day of a given size interval. The panelist indicated that this preparation method recently was used to generate the following categories of fiber size intervals:

| Cut | Fiber Length | | Fiber Diameter | |
|---|---|---|---|---|
| | Average (μm) | Standard Deviation (μm) | Average (μm) | Standard Deviation (μm) |
| 1 | 32.7 | 23.5 | 0.75 | 0.50 |
| 2 | 16.7 | 10.6 | 0.49 | 0.27 |
| 3 | 6.5 | 2.7 | 0.44 | 0.22 |
| 4 | 4.3 | 1.0 | 0.40 | 0.15 |
| 5 | 3.0 | 1.0 | 0.35 | 0.14 |

This panelist noted that the preparation technique may now allow researchers to investigate the influences of fiber length more rigorously. Some panelists noted that the distribution of fiber lengths in the first "cut" is quite broad, but other panelists indicated that the subsequent "cuts" were more narrowly distributed.

One panelist illustrated the utility of the fiber preparation technique by reviewing findings from a recent publication. In initial studies with these size-classified materials, NIOSH research compared fibers from "Cut 2" and "Cut 3" (see table above) for their induction of the cytokine cascade cellular responses (Ye et al. 1999). The longer fiber sample was more active when dose was measured as fibers per cell, but the shorter fiber sample was equally or more active when dose was characterized on a surface area or mass basis. One panel member noted that this was of interest in the context of the previously presented "counter-intuitive" histopathology reports (see Section 3.2.2) associating fibrosis with short fiber exposures.

## 3.4 General Comments and Interpretations

While discussing the influence of fiber length on asbestos and SVF toxicity, the panelists made several general comments and interpreted observations from the laboratory animal, human, and *in vitro* studies. This section summarizes these general comments and interpretations, while Section 4.1 reviews the panelists' individual summary statements provided at the end of the meeting.

- *Evaluating toxicity based on the "reasonable certainty of no harm."* When discussing asbestos and SVF toxicity, the panelists discussed the terminology they should use to characterize the hazard of fibers less than 5 μm long. One panelist recommended that the panelists consider whether the short fibers have a "reasonable certainty of no harm," drawing from the language promulgated in the Food Quality Protection Act. Given that dose-response data for humans or animals uniquely exposed to fibers less than 5 μm is largely not available, most panelists agreed that the terminology proposed was appropriate for their conclusions. They also noted that separate conclusions should be drawn for different endpoints, using a weight-of-evidence approach that draws from all types of data, including dosimetric, toxicologic, epidemiologic, and *in vitro* testing.

- *Do fibers shorter than a certain length have a "reasonable certainty of no harm"?* The panelists debated whether summary statements could be made regarding whether fibers of certain length intervals have a "reasonable certainty of no harm." Two panelists suggested that environmental exposures to fibers shorter than 5 μm would likely be free of

carcinogenic effects. Other panelists, however, felt uncomfortable making such judgments for noncancer effects (e.g., pleural abnormalities), especially considering the evidence summarized in Section 3.2. Refer to Section 4.1 for the panelists' individual summary statements regarding the influence of fiber length.

- *Why arbitrarily establish critical fiber lengths?* Because humans are always exposed to fibers with a wide distribution of fiber lengths, one panelist wondered if ATSDR or environmental agencies could develop a universal algorithm that quantifies health risks associated with different types of fiber mixtures. For instance, an algorithm might include different relative toxicity factors for different fiber length intervals (e.g., 0–5 μm, 5–10 μm, 10–20 μm, and so on). Such data could then be applied to the distribution of fiber lengths measured in the environment to assess site-specific risks. This panelist acknowledged that the relative toxicity data do not appear to be available to support this approach, but he noted such a universal algorithm would be far less arbitrary than completely ruling out fibers having dimensions below a certain level. He added that such an algorithm can eventually account for other factors (e.g., biopersistence) that are also known to affect toxicity. In short, this panelist indicated that it is theoretically possible to express health risk as a function of fiber dose, dimension, and durability, though he noted that one would need additional research into dose-response and extensive inputs from biostatisticians to develop such an algorithm.

- *Other influences on toxicity.* While recognizing that the focus of the meeting was on how fiber lengths affect toxicity, the panelists noted that many additional factors determine the toxicity of a fiber mixture. Examples of other factors include dose, fiber composition (mineral type), physical state (amorphous or crystalline), surface area, and surface properties. The panelists cited several examples of why length alone might not adequately predict toxicity. First, the panelists noted that the cancers observed in the study of rats exposed to erionite (Wagner et al. 1985) could not be explained by fiber length alone; they suggested that the unique findings of this study might be best explained by unique surface chemistry or the mineral's relatively large internal surface area (2.5 $m^2$/gram). Second, the panelists noted that fiber durability likely explains why asbestos fibers and SVFs of the same length are not equally toxic. Due to these and other observations, a panelist noted, ATSDR might overlook other important factors that influence toxicity if it focuses exclusively on fiber length.

## 3.5 Research Needs

The panelists identified several research needs when discussing the influence of fiber length on health effects. In general, the panelists encouraged thorough planning of any future study, emphasized the need for having well characterized exposures, and advocated involving

researchers from multiple disciplines (e.g., epidemiologists, physicians, toxicologists, mineralogists). All research needs mentioned during this session of the meeting are documented here:

- Several panelists indicated that further study should be conducted among the residents of Libby, Montana, to understand the effect of fiber length on toxicity. One suggestion was, through the cooperation of the community and consent of residents, establishing a protocol to analyze lung and pleural tissue from community members who die, regardless of the cause of death. Another suggestion was to track the progression of the observed pleural disease.

- Given the health outcomes observed in Libby, one panelist encouraged focusing future research in laboratory animals on understanding fiber dose-response behavior for the visceral and parietal pleura. Such studies could use fibers from Libby to examine how doses to the pleura and progression of toxic responses vary with fiber length and between fibers and non-fibrous particles. Another panelist added that a well-constructed study can investigate multiple toxic endpoints.

- For added insights on toxicity of short fibers, possibly those from Libby or Lower Manhattan, the panelists suggested conducting an *in vitro* study using several cell types (e.g., rat pleural mesothelial cells, tracheal epithelial cells) to examine multiple endpoints that can be confirmed in animal models, such as cell proliferation and cytotoxicity.

- One panelist suggested that future study of environmental exposures could focus on residential development in areas with increased levels of naturally occurring tremolite asbestos (e.g., the Sierra foothills in California), but he added that a high level of cooperation from the local community would be essential to the success of any such study.

- To assess human health effects associated with exposures to short fibers, one panelist recommended follow-up study of two cohorts of miners, one in South Dakota and one in Minnesota, who were exposed predominantly to short cummingtonite-grunerite fibers. Further study would take into account a longer latency period and might reveal insights on the role of fiber length in toxicity.

- Several panelists encouraged NIOSH to continue to re-analyze personal exposure samples collected on membrane filters in the 1960s and 1970s from textile workers in Charleston, South Carolina. This suggestion followed an observer comment that informed the panel of NIOSH's planned work on this project.

## 3.6 Observer Comments and Ensuing Discussions

Observers were given two opportunities to provide comments on the second day of the meeting. The panelists were not required to respond to the observer comments. However, some comments led to further discussion among the panelists, as documented here. The observer comments are summarized in the order they were presented:

**Comment 1: John Hadley, representing the North American Industrial Manufacturers**

Mr. Hadley summarized selected IARC publications regarding the toxicity of SVFs. First, he noted that IARC has accounted for the influence of fiber length in one of its 1997 monographs (IARC 1997). Specifically, IARC classified palygorskite (attapulgite) fibers longer than 5 μm in "Group 2B," or "possibly carcinogenic to humans (limited human evidence; less than sufficient evidence in animals)." On the other hand, IARC classified palygorskite (attapulgite) fibers less than 5 μm in "Group 3," or "not classifiable." Mr. Hadley added that IARC researchers recently published an article on rock and slag wool production workers (Kjaerheim et al. 2002) indicating "no evidence of carcinogenic effect on the lung of rock and slag wool under exposure circumstances in the production industry during the last four to five decades."

**Panelists' Discussions:** No panelists addressed this comment.

**Comment 2: David Bernstein, consultant in toxicology**

Dr. Bernstein asked the panelists to provide more information on the lung-retention studies (e.g., how much of the lung was sampled, what parts of the lung were sampled, how representative are the samples of fiber loading in the entire lung).

**Panelists' Discussions:** One panelist summarized details of the lung-retention sampling performed in studies he authored, and he suggested that observers refer to the original publication for additional details. In one study, this panelist indicated, samples from the periphery and the central parenchyma were collected systematically from longitudinal sections of the entire lung. He noted that preferential sampling (e.g., diseased locations) did not occur, and he added that the study addressed concerns about sampling bias by collecting larger amounts of samples from a given lung.

**Comment 3: Aubrey Miller, EPA**

Dr. Miller asked the panelists to comment on research opportunities to examine why certain health outcomes (e.g., pleural abnormalities) are being observed in Libby, but have not been reported (and perhaps not examined) in other mining communities with generally similar doses as gauged by conventional fiber sampling methods (PCM). He wondered if research should be conducted in other mining communities to search for pleural abnormalities or if it should focus on understanding what makes the Libby experience unique.

**Panelists' Discussion:** One panelist indicated that extensive research has already been conducted to characterize mining communities in Quebec. He noted that the fibers have been well characterized and health effects thoroughly studied and identified key differences between these sites. For instance, there are far more asbestosis cases in Quebec miners, but the panelist noted that this might result simply from the larger size of the work force in Quebec. The proportional numbers of, and SMR for, lung cancers among workers are in fact twice as high among the vermiculite miners in Libby than among chrysotile miners and millers in Quebec. Additionally, there is more evidence of pleural disease in the Libby cohort.

**Comment 4: Mark Maddaloni, EPA Region 2**

Mr. Maddaloni asked the panelists to discuss residential cleanup issues associated with WTC dusts in Lower Manhattan, where fibers in dust samples are largely (80% to 90%) shorter than 5 μm and the asbestos fibers found are almost entirely chrysotile. He was specifically interested in dose-response data for short asbestos fibers and whether the panelists could establish a dose level for short fibers that constitute "a reasonable certainty of no harm."

**Panelists' Discussion:** Several panelists commented on this matter. One panelist, for instance, emphasized that focusing on fibers less than 5 μm is an arbitrary decision. He noted that residents are ultimately exposed to a complex mixture of fibers of many lengths. Further, this panelist indicated that virtually all dust and air samples contain large amounts (perhaps 80% to 90%) of short fibers, and the fact that WTC dust is composed largely of short fibers is not unusual. He indicated that, at most sites, concentrations of long fibers and concentrations of short fibers are correlated. Due to this correlation, this panelist argued, when measurements suggest that low levels of long fibers are present, one can have a "reasonable certainty of no harm" not only from the long fibers but also from the short fibers, because they are found in proportional amounts. Some panelists suggested that EPA consider using threshold limit values to evaluate the exposure levels.

Panelists expressed differing opinions on how to evaluate exposures. One panelist suggested that exposures to WTC have decreased considerably from the large amounts found immediately after September 11, 2001. One panelist, however, noted that the presence of fibers in household dusts presents an opportunity for ongoing exposure; he added that this exposure scenario differs from what has been evaluated in the literature among occupational cohorts of adults.

**Comment 5: David Bernstein, consultant in toxicology**

Dr. Bernstein commented on laboratory animal studies conducted for the European Commission. In these studies, rats were administered fibers both by inhalation and by interperitoneal injection. Though he agreed with the panelists' comments that inhalation administration is most relevant to human exposure, Dr. Bernstein cautioned against disregarding the data from interperitoneal injection studies, which have addressed the issue of fiber length. For example, he said recent data from the interperitoneal injection studies has shown that fiber length correlates better with cancer risk in rats than does the dose. Dr. Bernstein added that these studies found that the dose for short fibers had to be increased by orders of magnitude to elicit the same carcinogenic responses as observed for long fibers.

**Panelists' Discussions:** No panelists addressed this comment.

**Comment 6: Joel Kupferman, New York Environmental Law Project**

Mr. Kupferman urged the panelists, when discussing the WTC site, to not assume that exposures have ceased because much of the dust has settled. He noted that asbestos still remains throughout Lower Manhattan: in homes, in fire trucks, and in ventilation systems. He mentioned that dusts from some fire trucks have contained as much as 5% (by weight) asbestos. Mr. Kupferman asked the panelists to consider the fact that asbestos exposure is still occurring.

**Panelists' Discussions:** One panelist noted that the observer raised an important point. He added that researchers can investigate the exposure potential of these settled dusts through "comprehensive air sampling," during which time surfaces are disturbed to simulate actual work or home exposure situations. The panelists revisited this issue when making their final recommendations (see Section 4).

**Comment 7: Ralph Zumwalde, NIOSH**

Dr. Zumwalde suggested that, when recommending research needs, the panelists not only consider long-term projects that would help characterize dose-response, but also projects that might help ATSDR make prudent public health decisions in the short term. Regarding the short fibers, he asked the panelists to discuss research needs to characterize possible links between short fibers and inflammation and fibrosis (e.g., how do fibrosis grades in animals compare to those in humans? are rats an appropriate model for these endpoint?).

**Panelists' Discussions:** One panelist noted that several human studies have examined relationships between asbestos exposure (as gauged by lung-retained fibers) and fibrosis grade, but two panelists noted that comparable studies in which the length distribution of fibers was known have not been performed in animals.

**Comment 8: Suresh Moolgavkar, University of Washington**

Regarding the panelists' comments on progression of fibrosis, Dr. Moolgavkar cautioned the panelists about assuming that fibrosis is an intermediate endpoint for lung cancer, because these two endpoints result from very different pathogenic processes. Noting that toxicologists have long assumed linear dose-response relationships for cancer and threshold dose-response behavior for noncancer effects, he argued that low exposures levels might pose a risk (albeit small) for lung cancer and perhaps no risk for fibrosis.

**Panelists' Discussions:** One panelist agreed that fibrosis and lung cancer develop from different pathogenic processes. He explained that the animal studies he has conducted and reviewed involving fibrous and particulate materials all suggest that lung cancers are not observed in the absence of fibrosis. He emphasized that this does not mean that fibrosis is on a causal pathway for lung cancer, but rather demonstrates different dose-response behavior for the two outcomes, namely that fibrosis outcomes in animals appear to occur at lower doses than do cancer outcomes.

**Comment 9: Jay Turim, Sciences International, Inc.**

Mr. Turim asked the panelists to clarify comments made on disease progression.

**Panelists' Discussions:** One panelist responded, explaining that he has not observed overt progression of interstitial fibrosis *in animals* after asbestos exposures cease. He added that inflammatory response, microgranulomas, and bronchiolization tend to decrease after fiber exposures ceases, even for amosite. He said this has been observed both in rats and hamsters. This panelist acknowledged that these findings from laboratory animal studies may not be relevant to humans. Addressing this final point, two panelists indicated that progression of fibrosis has "absolutely" been observed *in humans* after cessation of exposure.

## 4.0 Conclusions and Recommendations

This section reviews the panelists' individual conclusions (Section 4.1) and summarizes remarks from the final observer comment period (Section 4.2).

### 4.1 Panelists' Final Statements

After addressing all agenda items, each panelist was asked to make a final statement with his or her individual conclusions and recommendations. These summary statements were used to draft the executive summary of this report. A review of the summary statements, in the order in which they were presented, follows:

- *Dr. Case's summary statement.* Dr. Case said there is a strong weight of evidence that asbestos and SVFs shorter than 5 μm do not cause cancer in humans and no further research is needed on this matter. For lung fibrosis or asbestosis, on the other hand, he noted that the role of fibers shorter than 5 μm is not as clear and might require further study. Dr. Case suggested designing a laboratory animal study to characterize the extent to which fibers translocate into the pleura, and to determine whether translocation preferentially occurs for any fiber dimensions or types.

  To prevent health effects from occurring in the future, Dr. Case noted that scientists need a better understanding of exposure levels; he advocated characterizing the fiber length distribution in exposure samples at sites with residential exposures. For the Libby site, Dr. Case indicated that further research is needed to understand the unusual pleural pathology among residents. He suggested conducting systematic further study of available data, including more blinded reading of x-rays and examination of pleural histopathology data, if they exist. Dr. Case also recommended cooperating with communities believed to have elevated asbestos exposure (e.g., Libby) to establish protocols to obtain human lung specimens after death; these protocols must ensure that blinded analysis of samples occurs and matched controls are selected.

- *Dr. Lockey's summary statement.* Dr. Lockey first said he concurred with the conclusions of Dr. Case. He then identified several research opportunities for Lower Manhattan and Libby—two sites where contamination with short fibers has been observed in residential communities.

Regarding the WTC site, Dr. Lockey recommended that health agencies characterize exposure in residential settings using proper industrial hygiene measuring techniques, such that the samples collected reflect personal exposures while individuals perform their normal activities of daily living. He suggested that samples be analyzed for asbestos fiber content using conventional analytical methods (i.e., those that count fibers longer than 5 μm) and that particulate samples be collected to characterize the amount of material shorter than 5 μm. Dr. Lockey indicated that health agencies could then compare the measured level of fibers longer than 5 μm to occupational exposure limits with appropriate adjustment factors to account for the fact that potential sensitive sub-populations, such as children, are being potentially exposed. To evaluate particulate levels, Dr. Lockey recommended, health agencies should compare the measured levels of particulates to current recommended occupational and environmental exposure levels and to sampling results from similar non-WTC urban areas to determine if elevated particulate exposures are occurring. He added that the available human and animal data suggest that "asbestos particulate" (i.e., asbestos fibers shorter than 5 μm) does not present a hazard for cancer or, in the case of the relative short term exposure from WTC, pulmonary asbestosis.

Regarding the Libby site, Dr. Lockey identified several data gaps and research needs. First, he again suggested that future exposure assessment work involve collecting air samples that best reflect personal exposure levels during typical activities of daily living, including personal air sampling for populations—such as children—that have potentially high exposures because of environmental activities. Dr. Lockey recommended that health agencies refer to the existing literature to determine the implications of exposures to fibers longer than 5 μm. Dr. Lockey was not sure how to evaluate risks of pleural abnormalities associated with exposures to short, thin, durable tremolite fibers, because these fibers typically have not been quantified in previously published scientific articles. He did recommend, however, that ATSDR study chest x-ray results from the Libby population to quantify the number of residents with pleural plaques and diffuse pleural fibrosis. This distinction, he noted, is important because the medical literature reports that diffuse pleural fibrosis can impair pulmonary function and can be a very progressive disease, while pleural plaques have, in themselves, more limited clinical significance. Dr. Lockey also recommended that ATSDR investigate whether correlations exist between the pulmonary function tests (e.g., spirometric results) and the types of pleural abnormalities observed. Finally, Dr. Lockey supported a recommendation made previously to initiate a protocol to conduct lung tissue analysis among residents.

- *Dr. McConnell's summary statement.* Dr. McConnell first said he supported most of the conclusions and recommendations identified by Dr. Case and Dr. Lockey. His main finding for the meeting was a review of the trends among the laboratory animal studies. Dr. McConnell indicated that these animal studies consistently demonstrate that fiber pathogenicity increases with fiber length. However, he noted that short fibers, if administered in high enough doses, can also produce disease.

Regarding future research directions in animal studies, Dr. McConnell encouraged health and environmental agencies to specify exactly what questions must be answered in order to address health issues at sites of concern. Once agencies indicate the fiber type, dose, fiber length distribution, and health endpoint of concern (e.g., pleural changes), then toxicologists can design and conduct animal studies to address these specific issues.

- *Dr. Lippmann's summary statement.* Dr. Lippmann supported the other panelists' recommendations for characterizing personal exposures at sites where asbestos and SVF contamination is in residents' homes. Sampling of indoor environments during simulated extreme activity was also recommended. Dr. Lippmann suggested that sampling from these sites continue to use the conventional fiber counting methods (i.e., counting those longer than 5 μm), but recommended that environmental and health agencies archive the sampling filters for further analysis in the future, should the need for examining shorter fibers become necessary. He added that fiber sampling and analytical protocols should be standardized and adopted to ensure that samples collected from different sites for different purposes can be compared.

  Dr. Lippmann encouraged further research into site-specific issues, such as pleural disease in Libby, but he also recommended that future laboratory animal studies quantify fiber dose-response behavior as a function of fiber composition and fiber dimension. He indicated that short-term research needs should be identified and met with appropriate screening studies or intermediate studies.

- *Dr. Mossman's summary statement.* Dr. Mossman agreed with other panelists' suggestions and recommendations. She supported initiating further human studies at sites such as Libby, but she added that additional studies of laboratory animals are needed to quantify how dose-response varies with fiber dimension and durability. Dr. Mossman also indicated that *in vitro* studies can (a) provide insights, within a short time frame, into important questions about relative toxicity of various materials (e.g., fibers of different lengths, fibers with different mineral content), (b) further examine theories of mechanisms of toxicity, and (c) direct future research in laboratory animals. She recommended that such studies challenge target cells with well-characterized fiber samples to study how fiber length relates to cell proliferation, DNA damage, and cytotoxicity. Dr. Mossman emphasized that such short-term studies should use appropriate positive and negative controls and should select endpoints that can be later confirmed in animal studies.

- *Dr. Oberdörster's summary statement.* Dr. Oberdörster concluded that most of the available data suggest that fibers less than 5 μm in length behave like non-fibrous particles; however, he noted that a few recent publications (e.g., Brown et al. 2000) have raised some questions about this. To determine more conclusively whether short fibers truly behave like particles and to assess how fiber dimension relates to toxicity, Dr. Oberdörster recommended conducting a simple intertracheal instillation study in rats with different fiber length categories using lung lavage, pleural lavage, and histopathology to

characterize toxic endpoints. For each asbestos and SVF material tested, he suggested evaluating dose-response for different size-selected fiber samples, as well as for an analogous non-fibrous material; if needed, this could be followed by a more expensive inhalation study with different well-defined fiber size categories. Second, Dr. Oberdörster recommended that future public health evaluations consider susceptible populations for asbestos and SVF exposure.

- *Dr. Wallace's summary statement.* Dr. Wallace recommended that future research take advantage of the emerging capability of generating samples of well-classified fibers, particularly those in the range of small fiber lengths. He believed this new capability can support very meaningful *in vitro* studies, such as those described in Dr. Mossman's summary statement, which can then lead into nasal-inhalation studies in rats. Recalling the experience of conducting *in vitro* studies for crystalline silica, Dr. Wallace urged very thorough planning of future *in vitro* studies of short asbestos and SVFs to ensure that the assays selected model the surface conditioning of deposited materials which occurs *in vivo*, especially for short fiber studies, to avoid false positive results. Dr. Wallace recommended that priority be placed on investigating the correlation between *short* asbestos fibers in the lung and pulmonary interstitial fibrosis (see Section 3.2.2), given the toxicologic findings of *in vitro* activities of short glass fibers (Ye et al. 1999) and the inverse correlations between fiber length and lung fibrosis score in some studies of human lung tissue ( Churg et al. 1989, 1990; Nayebzadeh et al. 2001).

## 4.2 Observer Comments and Ensuing Discussions

Observers were given the opportunity to provide comments before the meeting adjourned. The panelists were not required to respond to the observer comments. However, some comments led to further discussion among the panelists, as documented here. The observer comments are summarized in the order they were presented:

### Comment 1: Winona Rossel, Local 829 of industrial theatrical stage employees

Ms. Rossel commented that the role of industrial hygiene for the residences in Lower Manhattan is to get rid of the WTC dust. She urged removal of the dust because scientists truly do not know the health implications of the complex mixture of chemicals in the dust. Ms. Rossel said officials should take precautions when addressing this site and remediate and clean homes, rather than continue to study the dust samples. As an example of her concern, Ms. Rossel said, a local high school that had already been abated had to be cleaned further recently, when carpets were found to contain WTC dusts. She also

recommended that a registry be formed to track health effects among the community members.

**Panelists' Discussions:** The panelists discussed the concerns expressed by community members after all three comments in this section were presented. Refer to the summary following "Comment 3" for the panelists' remarks.

**Comment 2: Katherine Ewes, resident of Lower Manhattan**

Ms. Ewes, a resident of Lower Manhattan, informed the panel that asbestos, pulverized glass, and iron have been detected in samples from ventilation systems in residential buildings. Ms. Ewes said it would be helpful if the panelists would suggest research on these materials, particularly interactions between asbestos and iron.

**Panelists' Discussions:** The panelists discussed the concerns expressed by community members after all three comments in this section were presented. Refer to the summary following "Comment 3" for the panelists' remarks.

**Comment 3: Kimberly Flynn, 911 Environmental Action**

Ms. Flynn indicated that she is a member of 911 Environmental Action, a coalition of residents and community groups in Lower Manhattan. Ms. Flynn indicated that her group's priority is to stop all continuing exposures to WTC dusts. Ms. Flynn noted that the people who were exposed to dusts on September 11 should definitely be followed up on for health effects, but she emphasized that exposures in residential areas must stop. Ms. Flynn challenged use of occupational exposure limits to evaluate exposures to WTC dusts, because residents in the area are potentially exposed to WTC dusts 24 hours per day and some populations (e.g., housekeepers) might be receiving unusually high exposures. Ms. Flynn said she was pleased that the panelists advocated air sampling to characterize "real world" residential exposure scenarios, like children playing on carpets.

Ms. Flynn acknowledged that there are many uncertainties regarding the health effects associated with WTC dust, such as possible synergistic effects, but she was disappointed with how some agencies have responded to public concerns. She was particularly frustrated that agencies have acknowledged the complexities and uncertainties of the WTC dust issue, without taking precautionary measures to cease exposure or provide risk communication messages to the public. Ms. Flynn asked the panelists, in all of their thinking and research design, to be as protective as possible.

**Panelists' Discussions:** The panelists acknowledged the public concern about WTC dusts, and offered several insights in response. One panelist encouraged residents to participate in research projects that have already been funded, such as one being conducted by faculty at New York University. Another panelist made two comments. First, this panelist noted

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that WTC dust has unique features (e.g., extreme alkalinity) that need to be considered in future site evaluations. Second, agreeing with the observers, he noted that eliminating exposures to WTC dusts is an important factor. Finally, a different panelist addressed a comment regarding exposures to short chrysotile fibers. He noted that the medical and scientific literature offer no evidence of exposure to short chrysotile fibers being of significant health concern, except in cases of prolonged exposures at extremely high doses; he added that the presence of long chrysotile fibers in residences would clearly be of greater concern. This panelist also acknowledged that other components of WTC dust (e.g., metals, polycyclic aromatic hydrocarbons) might be of health concern, but he indicated that the experts at this meeting were convened to discuss their knowledge of fiber toxicity.

During this discussion, a representative from ATSDR added that the agency has initiated a registry to track health effects that might be associated with the collapse of the World Trade Center buildings.

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