Asbestos Expert Panel Report

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-a] production, activation of TNF-a 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., Getzeichter 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.

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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 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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