Report on the Expert Panel on Biomarkers of Asbestos Exposure and Disease

May 9-10, 2006

Prepared for:

Agency for Toxic Substances and Disease Registry
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NOTICE

This report was prepared by ERG, an ATSDR contractor, as a general record of discussion for the expert panel meeting on Biomarkers of Asbestos Exposure and Disease. This report captures the main points of the scheduled presentations, highlights discussions among the expert panelists, and documents the public comments provided at the meeting. This report does not contain a verbatim transcript of all the issues discussed, nor does it 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 asbestos. Except as specifically noted, no statements in this report represent analyses or positions of ATSDR or ERG.

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List of Abbreviations

ATEM	analytical transmission electron microscopy
ATSDR	Agency for Toxic Substances and Disease Registry
BAL	bronchoalveolar lavage
ILO	International Labour Organization
TAR	Tremolite Asbestos Registry

Executive Summary

The Agency for Toxic Substances and Disease Registry (ATSDR) is investigating a number of sites where asbestos is the primary contaminant of concern. To review the state of the scientific knowledge on asbestos biomarkers, ATSDR invited ten scientific experts in the fields of pulmonary medicine, lung pathology, asbestos exposure assessment, toxicology, epidemiology, and mineralogy to a meeting on May 9–10, 2006 in Atlanta, Georgia. Discussions at the meeting focused on the following techniques for earlier detection of asbestos exposure or disease.

- Fiber burden of lung tissue collected from humans at autopsy.
- Fiber burden of lung tissue collected from living humans.
- Fiber content of sputum samples collected from living humans.
- Fiber content of bronchoalveolar lavage (BAL) fluid of living humans.
- Fiber analysis techniques (tissue, BAL fluid, or sputum) in sentinel animals (household pets or other resident animal species).
- Counting asbestos bodies in human tissue, BAL fluid, or sputum.
- Blood mesothelin or osteopontin levels, or other blood tests.
- Clinical tests such as spirometry to look for functional changes.
- Clinical tests such as x-ray or CT scans to look for pathological changes (pleural plaques, pleural thickening, and pleural effusions).

The panelists agreed that the most promising techniques for determining recent environmental asbestos exposure were (1) analyzing lung tissue collected from young people at autopsy and (2) determining fiber content from BAL fluid of carefully selected subjects. They also commented that determining fiber content from sputum samples and blood tests such as mesothelin and osteopontin could prove to be useful in the future, but not without some additional research.

For a variety of reasons, the majority of the panelists did not recommend the following techniques: (1) collecting lung tissue from living humans, (2) using fiber analysis techniques in sentinel animals, (3) as a sole measure, counting asbestos bodies in human tissue, BAL fluid, and sputum, (4) assessing lung function with clinical tests such as spirometry, and (5) for recent exposures, evaluating for pleural or parenchymal changes in chest x-rays and CT scans. However, some techniques could have applicability in certain situations.

Perhaps most useful to ATSDR would be a combination of techniques using a tiered approach. For example, panelists recommended conducting air sampling to confirm that there are elevated asbestos levels in the environment. Environmental exposures to people could be established by fiber analysis using medical examiner autopsy cases of young people or BAL fluid from carefully selected healthy volunteers. Possibly, sputum samples could be collected for fiber analysis and results confirmed with BAL sampling. In communities with a long exposure duration and where exposure has already been confirmed by another technique, it might be worthwhile to perform chest x-rays or CT scans to determine the consequence of exposure. Depending on the community and their level of exposure, it might also be appropriate to evaluate newer biomarkers for disease (e.g., blood tests for mesothelin and osteopontin).

The panelists also recommended taking full advantage of any testing that is conducted. For example, blood could be drawn from the people volunteering for the BAL procedure. The blood could be banked until additional research has been conducted to allow a better interpretation of the results. Further, the lung tissue from autopsies and the BAL fluid from volunteers could be analyzed for biological responses, such as cytokine and growth factor expression.

The panelists also stressed the importance of establishing baseline or background levels and obtaining a good exposure history to accompany any technique used. Exposure assessment is essential to evaluating health hazards.

1.0 Introduction

The Agency for Toxic Substances and Disease Registry (ATSDR) invited ten expert panelists to a meeting to review and discuss the state of the scientific knowledge on biomarkers of asbestos exposure and disease—an issue that is related to the agency's ongoing work at many sites. The panelists included a cross-section of scientific experts in the fields of pulmonary medicine, lung pathology, asbestos exposure assessment, toxicology, epidemiology, and mineralogy. The expert panel review took place in a meeting open to the public on May 9–10, 2006 in Atlanta, Georgia. Discussions at the meeting focused on existing, new, and emerging techniques for earlier detection of asbestos exposure or disease and recommendations for future research. ATSDR will use input received during discussions to aid in developing scientifically defensible exposure assessments and recommendations for public health actions in situations where humans may be exposed to asbestos.

1.1 Background and Purpose

ATSDR conducts activities to evaluate possible public health implications of exposures associated with hazardous waste sites and other environmental releases. A crucial part of this evaluation is to understand the extent of human exposures and whether exposures have resulted or could result in the development of disease.

ATSDR is investigating a number of sites where asbestos is the primary constituent of concern. Detecting asbestos-related diseases or the potential for disease to develop from exposures within communities near sites can be particularly difficult because of the long latency period before disease appears, the relatively small number of people exposed, and because the nature of community exposures may differ from occupational exposures. Community members and other interested parties have asked ATSDR how best to use biomarker data to assess the health of exposed communities.

ATSDR is seeking to review the state of the scientific knowledge on asbestos biomarkers which could be used to provide an estimate of exposure and potentially predict whether disease will occur. ATSDR hopes to use the output of these expert discussions to focus further research on the most promising techniques and enhance the agency's ability to respond to communities.

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

Ten experts in pulmonary medicine, lung pathology, asbestos exposure assessment, toxicology, epidemiology, and mineralogy were selected. 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) to help ensure 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 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 various aspects of biomarkers of asbestos exposure and disease. A copy of the charge is included in Appendix C. Several weeks prior to the expert panel meeting, every panelist received a copy of the charge, logistical information for the meeting, and a preliminary bibliography of publications on biomarkers of asbestos exposure and disease.

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 pre-meeting comments were distributed to the expert panelists, and made available to the observers who registered in advance to attend the expert panel meeting. These initial comments are included in this report, compiled according to technique, as Appendix D. It should be noted that the pre-meeting comments are preliminary in nature. Some panelists' technical findings may have changed after the pre-meeting comments were submitted.

1.2.2 Activities at the Expert Panel Meeting

The ten panelists and 23 observers attended the expert panel meeting, which was held at ATSDR in Atlanta, Georgia on May 9–10, 2006. The meeting was open to the public, and the meeting dates and times were announced in a press release. Appendix E lists the observers who confirmed their attendance at the meeting registration desk. Because the expert panelists discussed all of the charge topics on the first day, ATSDR drafted additional questions for discussion on the second day. The revised agenda is provided in Appendix F. The remainder of this section describes the introductory presentations given at the meeting. Appendix G provides slides from the presentations.

Introductory Remarks from ATSDR

Tina Forrester, Director of the Division of Regional Operations, welcomed the observers and guests to the expert panel meeting on biomarkers of asbestos exposure and disease, and explained ATSDR's rationale behind convening the panel meeting. ATSDR is evaluating sites where asbestos is a concern. Dr. Forrester explained that exposure to naturally occurring asbestos is different than occupational exposures. The communities near these sites tend to have many questions about their exposure and potential health effects. She acknowledged that because of the latency between the onset of disease and the time of exposure, answering their questions is not an easy task. ATSDR is interested in knowing if there is a way to assess the community's exposure and potential health effects earlier. Dr. Forrester then introduced the ATSDR asbestos site team—Jill Dyken, John Wheeler, Vikas Kapil, and Susan Muza.

Tom Sinks, Deputy Director of the National Centers for Environmental Health/ATSDR, thanked the expert panelists for attending. He reiterated that asbestos has been a major contaminant of concern for ATSDR for the past 5 to 6 years. Dr. Sinks hopes that panel discussions will provide direction on this issue for ATSDR's upcoming health assessments and consultations.

Jill Dyken and John Wheeler presented *Expert Panel to Discuss the State of the Scientific Knowledge on Biomarkers of Asbestos Exposure and Disease*. Dr. Dyken described ATSDR's involvement with sites where asbestos is a concern. She highlighted ATSDR's work evaluating health-related impacts to the communities near the Libby Mine, a vermiculite mine in Montana where the ore is contaminated with asbestos minerals. She noted that many sites across the United States processed Libby Mine vermiculite and that the exposures are known to be high for the workers especially. Dr. Dyken showed a map of the occurrences of asbestos and the 100 fastest growing counties in the Unites States. ATSDR is currently wrestling with the complicated exposures from these locations where exposures are not well defined and different types of asbestos are present.

Dr. Wheeler discussed the asbestos concerns at Oak Ridge High School in El Dorado Hills, California; Swift Creek, Washington; and Ambler, Alaska.

- Oak Ridge High School's soccer field was built on a vein of asbestos material and some material has migrated into the school.
- A mountain avalanche brought asbestos material into Swift Creek, which is a major drainage feature in northwest Washington. People engage in recreational activities on the built-up sides of the creek, which contain chrysotile fibers.
- A quarry in Ambler, Alaska contains chrysotile fibers. Gravel from this quarry was used to maintain the road from the quarry to the airport.

Dr. Wheeler listed the main questions that communities tend to ask and noted that it is difficult to answer what might appear to be relatively simple questions.

- Can you test me to see if I have been exposed to asbestos?
- What level of exposure should I be concerned about?
- Is our community a safe place to live?
- Can ATSDR perform a health study to tell us if our health is compromised?

Dr. Wheeler said that ATSDR has made public health decisions about asbestos exposures on the basis of health effects (disease) and/or exposure data leading to a risk of disease. The risk assessment paradigm is the preferred method; however, linking exposures with an estimate of risk contains much uncertainty. Differences in analytical techniques and epidemiologic procedures are confounders that also lead to increased uncertainty. Further, it is impossible to relate risk assessment to an individual's exposure. Dr. Wheeler noted that in recent years ATSDR has looked at activity-based sampling (e.g., personal samplers) to measure exposure, however, there are still many uncertainties associated with this method as well.

Dr. Kapil presented *Asbestos Related Health Studies at ATSDR*. He said that most of the health studies ATSDR has completed are related to the Libby Mine. There are over 200 sites that may have received shipments of asbestos-contaminated vermiculite from the Libby Mine. Epidemiologic activities are being conducted at about 100 of the sites. ATSDR selected 28 of these sites (designated "Phase 1 sites") for detailed review. In 2000 and 2001, ATSDR conducted community medical screening (e.g., health history, chest x-ray, and spirometry) in Libby and enrolled eligible persons in the Tremolite Asbestos Registry (TAR). From this screening, ATSDR found the following:

- Most participants had multiple exposure pathways.
- Overall, prevalence of pleural abnormalities was 18 percent.
- There was a much higher prevalence of pleural abnormalities among workers and household contacts.

ATSDR is conducting similar medical screening of former vermiculite workers in Marysville, Ohio. Workers were originally screened in 1980. ATSDR repeated the chest x-rays and spirometry and compared the 1980 findings to the current findings. Preliminary results indicate that 26 percent show pleural abnormalities. This is the first clear evidence of asbestos-related disease in workers at sites outside of Libby.

Dr. Kapil completed his presentation by discussing ATSDR's future plans:

- Complete Marysville mortality review
- Consider screening of household contacts
- Screen community residents in Minneapolis
- Conduct screening at other vermiculite sites
- Continue screening and TAR in Montana

Introduction of Panelists and Review of Charge

Dr. Forrester introduced the panel facilitator, Fernando Holguin. Dr. Holguin then asked each panelist to introduce themselves and explain their main area of expertise. A biography of each panelist is provided in Appendix B. Leslie Stayner was unable to attend the panel meeting in person, however, joined in discussions via the telephone. After each panelist introduced themselves, Dr. Holguin reviewed the charge.

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 then asked to review and comment on the draft report, ensuring that its contents accurately reflected the tone and content of the discussions at the expert panel meeting. The draft report was then revised based on the panelists' comments.

1.3 Report Organization

The structure of this report follows the order of the charge questions discussed on the first day, followed by the additional questions discussed on the second day. Section 2 through Section 10 summarizes comments on the charge questions related to nine potential techniques for assessing asbestos exposure and/or disease in communities. Section 11 through Section 18 summarizes comments on eight additional questions presented to the experts during the meeting. Section 19 summarizes the observer comments. Section 20 summarizes additional discussions. Section 21 summarizes the final statements. Section 22 contains the references cited in the summary. [*In subsequent sections, the panelists' initials are used to attribute comments.*]

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)
- Biographies of the expert panelists (Appendix B)
- Charge to the expert panelists (Appendix C)
- Pre-meeting comments, compiled according to technique (Appendix D)
- List of registered observers of the expert panel meeting (Appendix E)
- Agenda for the expert panel meeting (Appendix F)
- Presentation slides from the expert panel meeting (Appendix G)

2.0 Comments on Fiber Burden of Lung Tissue Collected From Humans at Autopsy

Overall, the expert panelists thought that determining fiber burden of lung tissue collected from humans at autopsy has the limitation of reflecting both fiber accumulation and fiber clearance. They discussed at length some advantages to analyzing lung tissue collected from young people at autopsy to provide more accurate retained lung burden (see Section 2.4). Fibers accumulated from past exposures, especially to chrysotile, would be affected by clearance and would not be reflected in current tissue fiber burden. Also, it would be difficult to relate an individual's exposure to the entire community. The panelists also expressed concern over the decrease in autopsies being performed and the difficulty in obtaining an accurate exposure history.

2.1 Advantages

The panelists discussed the following advantages to determining fiber burden of lung tissue collected from humans at autopsy:

- Supplies useful information about fiber content in the lung at the time of sampling (RD).

- Reduces sampling error since relatively large amounts of lung tissue from multiple sites can be obtained (DW).

- Indicates that the disease process is beginning (potential for disease) (VC).

- Provides a useful indicator of asbestos exposure for individuals who have been exposed to amphibole forms of asbestos (LS).

2.2 Disadvantages

The panelists discussed the following disadvantages to determining fiber burden of lung tissue collected from humans at autopsy:

- Does not account for what may have been in the lung in the past and eliminated via clearance mechanisms (RD).

- The levels and types of asbestos in the lung may not reflect the population of fibers that reached the extrapulmonary sites where asbestos induced diseases occur (RD).

- It would be challenging to document the person's exposure history (e.g., Did that person smoke?) (DW, VC, MC).

- The number of autopsies being performed has decreased (MC, VC, VR, LS).

- Projecting the individual person's autopsy results to the entire community would be difficult (VC, MC).

- Lung fiber burden analyses are not an accurate measure of the lifetime exposure to chrysotile, because it tends to break down and is removed from the lung (i.e., has a low biopersistence) (VR, LS).

2.3 Other Considerations

The following are additional considerations discussed during the panel meeting:

- Choosing the right people and controls is essential. When evaluating community exposures it is imperative to have good exposure information for the people who are representing the entire community (DW). Smoking history and lung disease have to be considered in the study design because they have the potential to affect lung fiber burden (DW). Mobility of the community is also an important factor (MC, GH, MG).

- The low autopsy rate is a barrier that would have to be addressed for the autopsy technique to be a viable option. Perhaps ATSDR can create incentives to encourage the performance of autopsies (DW). Coordinate closely with the medical examiner's office to save lung tissue samples (VR).

- It might be useful to design a case control study to look at medical examiner autopsy cases of individuals with no known residential or occupational exposures to asbestos. This would allow one to compare lung tissue specimens from people who lived their entire lives near an environmental exposure site (e.g., El Dorado) to those with no known exposure (VR).

- Obtaining samples from autopsies provides an opportunity to quantitatively analyze the entire mineral content of the lung. Looking at the entire mineral content and identifying all fibers (including non-asbestos fibers) in the lung might prove to be useful (e.g., could provide a clue to the source of exposure) (DW, MG, JA, VR, RD, LS).

- Sometimes it is difficult to get permission to obtain and analyze autopsy samples (JA). Privacy concerns and legal issues need to be addressed (JA, GH).

- It is very important to clearly define the technique used to prepare and count the samples (e.g., What fibers are included in a count? Which areas of the lungs are sampled?) if one is to make meaningful comparisons between findings of different studies (RD).

- Cross contamination should be avoided. Make sure the person collecting the samples uses pre-filtered materials and solutions to prevent water source contamination (RD).

- It would be possible to perform a prospective study of a biased population (people who died of lung cancer) to obtain important information about asbestos exposure and mesothelioma. However, conclusions about a community's exposure to asbestos could not be drawn from this kind of study (MC).

2.4 Autopsies of Young People

The expert panelists discussed using fiber burden of lung tissue collected from young people at autopsy. They agreed that there is an advantage to studying autopsy results from young people because these results would be less likely to be confounded by past exposures other than those to the general community, such as occupational exposures or exposures from living in other communities. Thus, these results could potentially provide useful information about that person's recent community exposure. These results could form a basis for developing preventive recommendations for a community to reduce the exposure before the onset of disease. The panelists noted, however, that it would not be possible to determine a community's risk of disease based on the autopsy results. Below are some specific comments made by the panelists:

- If exposures are found to be occurring in the younger population, it would be indicative of recent exposures. Then, perhaps steps could be taken to reduce or prevent continuing exposures. However, it would be difficult to determine risk from evidence of exposure (JA).

- Determining the lung fiber burden from autopsies of children would be realistic and would provide valuable information about exposure in a community. It is too late to reduce exposures to the community if one waits to determine lung burdens from living people who already have mesothelioma (GH).

- Determining lung burdens from autopsies on young children (perhaps complimented with air sampling) would be a reasonable approach for establishing whether exposures to asbestos are occurring in the community. Background lung burden levels in non-exposed children would need to be determined (MC).

- Autopsying a teenager who was born and raised in a specific community would give a good indication that the teen's exposure came from living in that community (VC).

- An accurate exposure history should be easier to obtain from the parents of the young person being autopsied. Also, young people will not have the complications of occupational exposures to asbestos (VR).

- Unlike autopsying an older person, chrysotile fibers might actually be detected in a younger person's lung tissues (LS).

3.0 Comments on Fiber Burden of Lung Tissue Collected From Living Humans

Most expert panelists felt that even though collecting lung tissue from living humans is one of the most accurate methods for determining fiber burden, it is an unethical technique to use for determining exposure to asbestos fibers. Further, samples collected during procedures, such as lobectomies or pneumonectomies, would be highly biased toward an already sick population and would not be representative of a community's exposure.

3.1 Advantages

The panelists discussed the following advantages to determining fiber burden of lung tissue collected from living humans:

- Determining fiber burden of lung tissue can provide useful information about fiber content in the lung at the time of sampling (RD). Taking lung tissue samples from living individuals is the best way to assess asbestos presence (MC). The lung is the ultimate sampler of what an individual is exposed to in the ambient air (VR).

- A more accurate assessment of the patient's residential and occupational exposure history could be provided, and confounding factors could be identified (VR, DW).

- Fiber burden of lung tissue from living humans could be used to verify that asbestos exposure occurred in a community (MC).

- It is a useful indicator of asbestos exposure for individuals who have been exposed to amphibole forms of asbestos (LS).

3.2 Disadvantages

The panelists discussed the following disadvantages to determining fiber burden of lung tissue collected from living humans:

- There are ethical concerns with performing an invasive procedure on healthy individuals (LS).

- It is difficult to obtain these types of samples and they are limited to people who are already sick and undergoing major surgery (MC). The samples would be highly biased toward people with lung cancer and would, therefore, not be useful for estimating a community's exposure (LS).

- It will not account for what may have been in the lung in the past and eliminated via clearance mechanisms (RD).

- The levels and types of asbestos in the lung may also not reflect the population of fibers that reached the extrapulmonary sites where asbestos induced diseases occur (RD).

- Lung fiber burden analyses are not an accurate measure of the lifetime exposure to chrysotile, because it tends to break down and is removed from the lung (i.e., has a low biopersistence) (VR, LS).

3.3 Other Considerations

The following are additional considerations discussed during the panel meeting:

- Living tissue samples could be collected from individuals who are ill and who have had lung tissue removed for other purposes (e.g., lobectomy or pneumonectomy) (VR).

- Smoking history and lung disease have to be considered in the study design because they potentially affect lung fiber burden (DW).

- The sample around a tumor may not be representative of the total fiber burden in the lungs (VC).

- There are logistical concerns, such as whether sufficient procedures are being performed in a given community to have an appropriate number of tissue samples (DW, GH).

- Larger hospitals (surgery centers) retain tissue samples that could be used for fiber analysis. Certain regional hospitals are geographically well-defined (JA).

4.0 Comments on Fiber Content of Collected Sputum Samples

The main advantage to determining fiber content from sputum samples is that sputum is relatively easy to collect and is non-invasive. However, when analyzing for asbestos bodies, the technique is very insensitive and negative results cannot be used to rule out community exposure to asbestos. Analyzing for fiber content may prove more useful, but additional developmental work is needed to standardize and validate this approach.

4.1 Advantages

The panelists discussed the following advantages to determining fiber content of collected sputum samples:

- It is a non-invasive technique (VR, VC, MC).

- It is a very specific technique. If one finds asbestos in sputum samples, then it positively confirms exposure to asbestos (MC, VR).

- The technique is reasonably reliable in heavily exposed individuals (RD).

4.2 Disadvantages

The panelists discussed the following disadvantages to determining fiber content of collected sputum samples:

- When analyzing for asbestos bodies, it is a very insensitive technique for determining exposure to asbestos (MC, RD, VR, VC, RD, DW).

- The technique will not allow for a comparison between an environmentally exposed community and a control population (VR).

- The technique cannot be used as a screening tool because of the high level of false negatives (MC).

- Very little background information exists about analyzing sputum for uncoated asbestos fibers (DW).

4.3 Other Considerations

The following are additional considerations discussed during the panel meeting:

- Sputum samples could be useful for identifying occupational exposures (GH).

- There is high variability in results depending on the region of the lung from which the samples were obtained (VC, VR).

- Greenberg et al. (1976) and McLarty et al. (1980) reported consistency or lack thereof for finding ferruginous bodies in spontaneous versus induced sputum in Amosite exposed individuals (DW). Therefore, the method of collection and processing is important (i.e., sputum vs. saliva samples; whole saliva vs. plugs) (DW, RD, VR).

- Additional investigation is needed into whether a difference exists between induced and spontaneous sputum (JA, DW).

- Short fibers less than 8 to10 micrometers do not stimulate the formation of ferruginous bodies (RD, DW, LS). Chrysotile is less efficient in the stimulation of the formation of ferruginous bodies even when some longer fibers of chrysotile are present. However, chrysotile can occasionally be found as the core of some ferruginous bodies and in some rare exposures occur as the core material in a majority of ferruginous bodies (RD).

- Depending on the form of asbestos, different sample preparation and detection methods (e.g., light microscopy vs. electron microscopy) could improve the results (RD, JA, MG).

5.0 Comments on Fiber Content of Collected Bronchoalveolar Lavage (BAL) Fluid

Many of the expert panelists thought that determining fiber content from BAL fluid was the most "promising technique" for establishing whether a community is being exposed to asbestos. The procedure is relatively safe and less invasive than a biopsy. It also produces results that are well correlated with lung tissue burdens and disease. However, some of the panelists felt that the technique was still an invasive, non-necessary procedure that has some ethical ramifications. As with any technique, a strict protocol would need to be in place to limit the variability in recovery.

One panelist suggested that analysis of BAL fluid in living patients and fiber burden analysis of lung tissue in deceased medical examiner cases offer the most potent methodology for assessing the exposure of a community to environmental asbestos fibers (VR). Another suggested that BAL sampling could be used to confirm the results of sputum samples (DW).

5.1 Advantages

The panelists discussed the following advantages to determining fiber content of collected BAL fluid:

- One may only need a few volunteers (10–20) with a known residence to participate in order to establish that there is asbestos exposure occurring (GH). In addition, volunteers can be paid to participate in the study (GH, VR).

- There is a good relationship between BAL fluid fiber burden and disease (VC).

- Because BAL samples millions of alveoli at once (i.e., provides a good statistical sample), there is a good relation between BAL fluid fiber burden and lung tissue burden. This is true for both occupational (i.e., high) and environmental (i.e., low) exposures (VR, RD).

- The technique is easily reproducible and is relatively safe for the volunteer (GH).

- Healthy individuals and young adults with no known exposure to asbestos (control), as well as those with recent exposure (exposed), can be tested (GH).

- The technique can determine the presence and type of asbestos exposure from the asbestos fiber type present when analytical transmission electron microscopy (ATEM) is used to analyze digested material for uncoated fibers (RD).

5.2 Disadvantages

The panelists discussed the following disadvantages to determining fiber content of collected BAL fluid:

- There are some ethical concerns about paying people to volunteer for an unnecessary procedure, but published position statements have found that the use of BAL in carefully designed research studies is ethical (DW).

- It would be difficult to assign a risk level from the results of the BAL (VR).

- It is unknown whether the technique is sensitive enough to detect differences between an exposed community and a control population (VR).

- There is a lot of variability in recovery, depending on the individual (VR).

5.3 Other Considerations

The following are additional considerations discussed during the panel meeting:

- Asking for volunteers may introduce a bias (MC). A bias could also be introduced if a BAL was performed on a person already undergoing a bronchoscopy because the patient likely has some lung condition that precipitated the procedure (JA, LS).

- It might be useful to look at the cell activity (e.g., inflammatory cytokines) while collecting lung material to count fibers to determine a dose-response relationship and identify early stages of the disease process (VC, JA).

- Collection of BAL fluid would be useful to determine whether or not a population has been exposed, but there would be little point in providing that information to individuals because there would be no specific clinical follow-up possible (MC). It would be appropriate to aggregate data from an ethical research study, but not to provide an individual medical advice based on research findings in BAL fluid (DW). However, it would be hard to reject a request by the individual for his/her results (JA).

- The study should have a strict protocol with controls. The middle lobe of the right lung and the lingula of the left lung tend to produce the best BAL fluid results (GH).

- The issue of measuring asbestos fibers in exhaled breath condensate was raised. However, re-aerosolization of asbestos fibers in exhaled droplets of respiratory lining fluid is unlikely. The sticky mucus blanket inhibits re-aerosolization. Exhaled breath condensate was not felt to be a realistic option for assessing lung fiber burden (VR, DW).

- Determining the mineral content in the BAL fluid might lead to finding an indicator (MG).

6.0 Comments on Fiber Analysis Techniques (Tissue, BAL Fluid, or Sputum) in Sentinel Animals (Household Pets or Other Resident Animal Species)

The expert panelists were in agreement that techniques in sentinel animals can verify that exposure has occurred, but that the levels in the animals cannot be correlated to levels in people.

Because human exposures cannot be quantified from sentinel animals and there is large variability among animal exposures, none of the panelists recommended using this technique.

6.1 Advantages

The panelists discussed the following advantages to using fiber analysis techniques in sentinel animals:

- Animals can be used to show the potential for exposure in a community, perhaps as an initial screen (JA, VR, DW).

- Non-domestic animals can be used to find background levels of asbestos (MG).

6.2 Disadvantages

The panelists discussed the following disadvantages to using fiber analysis techniques in sentinel animals:

- One cannot quantify human exposure from the levels detected in animals (JA, DW). The levels found in animals may underestimate or overestimate actual levels in people (VC).

- There is large variability between species and within animals of the same species (e.g., large and small dogs) (GH, MG).

- Animals would have to be sacrificed (MC).

6.3 Other Considerations

The following are additional considerations discussed during the panel meeting:

- Additional research is needed to show whether there is a correlation between levels in animals and levels in people (JA), and which species correlate the best (DW). However, given that there are limited resources, some panelists do not think it is worthwhile to pursue research in this area (GH, VR).

- The types of animals that could be used include sheep from slaughterhouses, game animals killed during hunts, or pets that are euthanized for unrelated reasons (MG, JA).

- Different activities would cause different levels of exposure, in both animals and humans (MG).

7.0 Comments on Counting Asbestos Bodies in Human Tissue, BAL Fluid, or Sputum

Counting asbestos bodies in human tissue, BAL fluid, and sputum is easy and reproducible. However, not all fiber types and lengths form asbestos bodies. Therefore, the technique of counting ferruginous bodies in tissue sections is not sensitive, especially for short fibers and chrysotile. There are published indicators that the sensitivity increases when a digested sample

is evaluated by light microscopy for the presence of ferruginous bodies combined with the evaluation of the digested material via the use of ATEM for core identification of ferruginous bodies as well as characterization of the uncoated asbestos burden.

7.1 Advantages

The panelists discussed the following advantages to counting asbestos bodies in human tissue, BAL fluid, or sputum:

- Asbestos bodies are easy to identify with light microscopy (VR).
- The results are easy to reproduce (VR).
- Asbestos bodies correlate well with the concentration of amphibole fibers, which are the fibers that correlate best with mesothelioma (VR).
- Counting asbestos bodies in BAL fluid could be used as a screening technique to indicate exposure to amphibole fibers has occurred (VR).

7.2 Disadvantages

The panelists discussed the following disadvantages to counting asbestos bodies in human tissue, BAL fluid, or sputum:

- Chrysotile does not readily form asbestos bodies (VR, RD, LS).
- The presence of ferruginous bodies in any sample only represents a population of the longer fibers in that sample. These numbers tell us nothing about the actual numbers of uncoated fibers of any length or type (RD).
- Counting asbestos bodies may underestimate exposures to fibers that are greater than 5 microns in length and less than 20 microns in length (VR).

7.3 Other Considerations

The following are additional considerations discussed during the panel meeting:

- The study should combine analyses of asbestos bodies by light microscopy and fibers by electron microscopy (VR). Electron microscopy can also be used to find smaller ferruginous bodies and define the presence and types of uncoated asbestos fibers in a sample (RD).
- The presence of asbestos bodies is a marker of exposure, not of disease (VR).

8.0 Comments on Blood Mesothelin or Osteopontin Levels, or Other Blood Tests

While very promising, the panelists agreed that blood tests for mesothelin and osteopontin "are not ready for primetime." There are currently many unanswered questions about how the detected levels correlate with the development of mesothelioma, specifically there is an unacceptable level of false positives and false negatives. Further, this technique may not be useful for screening asbestos exposure in communities with low-level environmental exposures. Additional research should be conducted to improve the sensitivity and specificity of the technique.

8.1 Advantages

The panelists discussed the following advantage to testing for blood mesothelin or osteopontin levels:

- The current research is promising in that blood levels of patients with mesothelioma are much higher than those of individuals without this disease (VR, MC, DW, FH).

8.2 Disadvantages

The panelists discussed the following disadvantages to testing for blood mesothelin or osteopontin levels:

- There is an unacceptably high rate of false negatives and false positives, which could lead to needless worry or treatments (VR, GH).

- There are too many unanswered questions (VR, GH). For example, the role of these tests in detecting early disease is unknown. It is not known whether these tests can distinguish atypical mesothelial hyperplasia from early pre-invasive mesothelioma. The percentage of cases with atypical mesothelial hyperplasia that will go on to develop mesothelioma is also unknown (VR).

8.3 Other Considerations

There was some discussion about the ethical ramifications of testing blood mesothelin or osteopontin levels, given that the technique still requires substantial research and validation. Below are some specific comments made by the panelists:

- Serological tests are the best way to screen a community for disease (MC).

- Blood mesothelin tests are very promising. Additional research needs to be conducted to continue to develop and improve the specificity and sensitivity of the tests (MC, DW). The research study should be strictly designed (GH). Controlled animal experiments should be conducted before testing the methods in the human population (VR).

- Until there is a treatment to go along with early detection of mesothelioma, there are ethical concerns about using these blood tests in the general population (GH). The psychological burden and subsequent battery of tests might do more harm than good on a patient found to have increased mesothelin or osteopontin levels (GH). For serum osteopontin, the most accurate cutoff value had a specificity of 85.5%, yielding a false positive rate of 14.5 percent (Pass et al. 2005). For serum mesothelin-related protein, the published specificity of 95 percent suggested a false positive rate of 5 percent (Robinson 2005) (DW).

- It might be useful in a community with high exposures, but would not be a practical screening technique in low risk communities (MC, VR, GH).

- Blood mesothelin or osteopontin levels could be used as a biomarker of disease. Once people are identified, different therapies could be tested on individuals that are at higher risk to try to stop the progression of the disease (MC).

- Conducting blood tests on a large number of people is an expensive proposition (DW). Blood could be drawn while performing the BAL on the volunteer (VR). Once the blood is drawn, it could be banked until additional research has been conducted to allow a better interpretation of the results (DW).

9.0 Comments on Clinical Tests Such as Spirometry to Look for Functional Changes

None of the panelists recommended using clinical tests such as spirometry to look for functional changes. The techniques are insensitive and unspecific. Further, it is a measure of disease rather than exposure.

9.1 Advantages

The panelists did not discuss advantages to using spirometry to look for functional changes.

9.2 Disadvantages

The panelists discussed the following disadvantages to using spirometry to look for functional changes:

- Spirometry is not sensitive enough to measure low level exposures (VC).

- The findings are unspecific to asbestosis (GH).

- The results could be confounded by airway decline (FH).

- Very early changes with small decrease in lung function can be seen in large populations only (GH).

9.3 Other Considerations

The following are additional considerations discussed during the panel meeting:

- Spirometry is a test for disease, not exposure (GH).
- The "noise" sometimes exceeds the annual declines that one might expect to find (DW).

10.0 Comments on Using Clinical Tests Such as X-Ray or CT Scans to Look for Pathological Changes (Pleural Plaques, Pleural Thickening, and Pleural Effusions)

While chest x-rays and CT scans can detect pleural changes, most panelists did not recommend using this technique as a screening tool for exposure to asbestos because of the long latency for findings other than pleural effusion and because radiographic signs of pleural changes can result from factors other than asbestos exposure. Radiographic screening could be used after exposure is confirmed by another technique to determine the consequence of exposure. Bilateral calcified pleural plaques is the pattern best associated with asbestos exposure. However, there are issues with sensitivity and specificity in radiographic detection of pleural changes. For example, other conditions such as obesity can cause the radiographic appearance of pleural plaques. There was also some concern about the ethical ramifications from finding changes that could potentially require a lifetime of follow-up.

10.1 Advantages

The panelists discussed the following advantage to using x-ray or CT scans to look for pathological changes:

- The technique is practical and inexpensive (DW).
- The results are reproducible (DW).
- A high percentage of patients with mesothelioma develop pleural plaques. Therefore, if one screens a population with adequate latency and there are no abnormalities, it is unlikely that mesothelioma will develop (VR).

10.2 Disadvantages

The panelists discussed the following disadvantages to using x-ray or CT scans to look for pathological changes:

- There is the possibility of false positives (e.g., from obesity) even with the use of B readers (GH).
- There is a long latency time (about 20–30 years) for pleural plaques to develop (GH).

- Finding pleural plaques is not specific to asbestos exposure (GH). Pleural effusions can also be caused by exposure unrelated to asbestos (VR).

- Because CT scans are more sensitive, they can find small nodules in the lungs that would require (potentially costly) follow-up (GH).

10.3 Other Considerations

The following are additional considerations discussed during the panel meeting:

- Knowing the community's exposure and time from first exposure would help determine whether CT scanning is a viable option as a screening tool in the community (GH).

- CT scans are probably better used to confirm that the established exposure is causing health issues, rather than as a screening technique for exposure (MC).

- There is some debate about whether pleural plaques count as a disease. According to the medical dictionary, having pleural plaques qualify a person as having a disease, even if the person is asymptomatic (VR). However, most people live with pleural plaques and die from some unrelated cause (GH). The correlation between the presence of pleural plaques and lung cancer or mesothelioma risk depends on the population (VR, GH).

- To achieve higher reproducibility and improve on inter-reader variability in evaluating for parenchymal and pleural changes, chest radiographs should be evaluated by multiple readers using the International Labour Organization (ILO) classification system. Quality assurance/quality control and spike films should be used to maintain a central reading tendency. ILO also recommends blinding and readers should be given a mix of radiographs, including ones from a control group, so that the readers are not aware of the exposure status (DW, GH).

- There also needs to be strict criteria for the way that the CT films are taken and interpreted. It is important to document whether the pleural plaques are bilateral and calcified (DW).

- CT scans are more sensitive and more specific than chest x-rays, however, are also more expensive. If money was not a factor, taking CT scans is preferable to chest x-rays alone. Perhaps an integrated approach using both CT scans and chest x-rays would yield favorable results (DW).

11.0 Comments on Question 1: ATSDR evaluates asbestos exposures in communities using the health/risk assessment paradigm of obtaining a best estimate of exposure combined with corresponding risk levels to make health determinations. Given the state of biomarkers of exposure and disease, are there any methods ATSDR should be utilizing instead of (or in conjunction with) health assessment techniques?

The panelists suggested utilizing the following techniques, reiterating some of the points made when discussing the various asbestos measurement techniques (see Sections 2 through 10):

- Depending on the community and their level of exposure, it might be appropriate to conduct clinical tests to look for disease (DW). Blood tests for mesothelin and osteopontin could be useful in this regard (MC).

- It might be useful to determine fiber content of BAL fluid in exposed populations (DW, RD). Fiber content in BAL fluid may indicate that exposure levels measured in the environment correlate with evidence for increased risk (VR). While collecting BAL fluid, also analyze the cells for cytokine and growth factor expression, which may show a correlation (VC). Remember to answer the question of ethics (RD).

- If other methods have already identified that there is an elevated level of exposure, it may be worthwhile to determine the fiber burden in lung tissue collected from medical examiner autopsy cases (VR). Specifically focusing on autopsies in young people in the community might give some indication about recent community exposure (DW). If collecting tissue for fiber counts, it would also be worthwhile to look at the tissue for biological response (VC).

- There are many different innovative ways to sample the air (e.g., on a gravel road, drive one car behind the other) (MG).

12.0 Comments on Question 2: BAL appears to present the best correlations to lung fiber burdens and also presents a test that can be performed ethically and economically. What would need to be done to make this technique useful for estimating increased exposure? Increased risk?

The panelists suggested the following:

- Establish baseline/background levels, which can be difficult to obtain because it requires a good history (VR, VC).

- Perform a case control analysis for exposed and non-exposed people and compare the fiber content collected from the BAL fluid (VR). Testing a minimum of 15 controls and 15 exposed people with cytokine expression would enable a comparison (VC).

- If the community is exposed to a specific fiber, then the diagnosis of exposure might be simpler (RD). A control would be unnecessary, rather it would be important to determine

whether there is a significant difference between the exposed community and the non-exposed community (VR).

- Obtain a good history and control for age and smoking (VR, VC).

- Standardize the BAL technique and analysis. Look at both asbestos bodies and fibers (DW).

- The risk of complications from a BAL is low, even in older individuals. However, one should make sure that the benefit would outweigh the risk (DW). BAL should not be performed on people with impaired lung function (GH, DW). Have the procedures performed at medical centers that do BALs on a regular basis (VC).

- Consider the National Institutes of Health's guidelines for conducting research (JA).

13.0 Comments on Question 3: Please consider two exposures: a long-term, relatively continuous vs. a high-level "burst" or "bursts" of exposure at the beginning of the time period. Even if the overall number of fibers was the same, would you be able to tell the difference in any fiber burden test (autopsy, BAL, sputum)? Would the expected risk of disease be similar or different?

The panelists discussed the following:

- Research conducted on mineral dust indicates that there is no evidence that a spike versus a continuous exposure makes a difference. Concentration over time is important. Communities generally would not be exposed to a spike high enough to be an issue (VR).

- The dose is the best marker of risk of disease, regardless of whether exposure is low and continuous or in spikes. Total dose is the determining factor (VR, VC, DW). If the total dose is the same, there is no difference between a child being exposed to a burst and an adult being exposed continuously (VR, MC). Another panelist commented, however, that some research indicates that the exposure reaction is different for people with a one month a year exposure versus a continuous exposure (JA). The continuous exposure had a different distribution. Although, one probably would not be able to tell the difference in a community with short-term exposures (JA).

- Most circumstances do not lead to a long-term, low exposure dose. Most exposures are bursts (GH), though many people experience both types of exposure (VR).

- There is a relationship between lung fiber burden and disease (DW, VR). However, having a risk for developing a disease places the person in the risk group, it does not determine whether the person will actually get the disease (MC).

- There is an increased risk of disease when the fiber burden in the lungs exceeds the overload capacity (VR). However, the lungs have a clearance mechanism that, unless impaired, effectively keeps the fiber burden below an overload level (VR, RD, VC, JA).

- There is natural variation among people, and some people have poor alveolar clearance rates (VR). Because asthma is an upper respiratory disease, there is likely no affect on clearance rates (VC). Having asthma might actually be protective against exposure to asbestos (VR).

- Longer fibers are more pathogenic, but shorter fibers lead to inflammation, which could potentially lead to disease (VC).

14.0 Comments on Question 4: Would results of fiber burden analysis by autopsy, BAL, or sputum differ depending on the mineralogy of amphibole asbestos, similar to the differences between chrysotile and amphibole?

None of the panelists thought there would be a difference in clearance or disappearance between different amphibole asbestos fibers (VC, VR). If there were a difference, it would probably be insignificant (MG). Two panelists hypothesized that the size of the different amphibole fibers might make a difference (GH, RD).

15.0 Comments on Question 5: How do fiber dimensions change over time after deposition in the lung? Is there a correlation with exposure fiber dimensions on which risk models are based?

The panelists noted the following about fiber dimensions, as well as some observations related to fiber clearance, breathing style, and childhood exposures:

- Smaller fibers clear more readily than larger fibers (RD).

- Theoretically, longer fibers may inhibit macrophage movement by triggering a coating mechanism, which could be the reason that longer fibers are not cleared (VR, VC).

- Some studies have shown that longer fibers (great than five microns in length) reach the pleura; however, the majority of studies have shown that the fibers found in the pleura are shorter than this length (RD).

- Fiber dimensions do not change with time once in the lungs (VC). The average length of fibers increases in the lungs with time because the longer fibers are retained, while the shorter ones are cleared (VR).

- Chrysotile bundles may disassociate (JA).

- In the case of mouth-breathers, there is no evidence that thicker fibers would be deposited in the lungs. Those fibers would likely get deposited higher in the bronchial tree (VR).

- A child has more particle deposition (VC). However, they have the same latency as other people and there is no fundamental difference in obtaining and retaining asbestos fibers in small children (GH).

- All of these differences account for nothing biologically, as there are no differences in incidence of mesothelioma (MC).

16.0 Comments on Question 6: Would serum biomarkers be useful for populations/communities exposed to asbestos and other asbestiform fibers—particularly amphiboles (like in Libby, MT)?

The expert panelists agreed that serum biomarkers cannot currently be used to assess levels of exposure in a population, and that additional research is justified (VC, MC, DW, VR). If ATSDR decides to collect BAL samples, one panelist recommended taking advantage of the opportunity and collect blood samples simultaneously (VC). Another panelist suggested refraining from any particular action as a result of the serum level findings (VR).

17.0 Comments on Question 7: Would osteopontin be useful as a marker of exposure in exposed communities—as a research tool or to correlate with pleural disease absence/presence?

Two panelists (VR, MC) said that additional research is needed before osteopontin can be used as an indicator of disease. Currently, it can only be used as an indicator of exposure to asbestos. If blood tests for osteopontin are conducted, it is imperative to have a very clear informed consent that does not promise any definitive results to the volunteers.

18.0 Comments on Question 8: Please comment specifically on carbon monoxide (CO) diffusing capacity as a clinically useful means of evaluating restrictive disease.

The panelists made the following comments:

- Carbon monoxide diffusing capacity is a good, simple test that is non-invasive (DW).

- A number of studies correlate carbon monoxide diffusing capacity with early fibrosis (DW).

- Standardizing the instrumentation is crucial (DW).

- Emphysema and smoking are confounders. Adjustments need to be made for age, sex, height, weight, occupation, etc. (VR, VC).

- Because of the noise associated with the test, it is unlikely to be helpful in addressing restrictive disease in communities with low levels of exposure (VR).

19.0 Observer Comments

William Spain, Georgia Environmental Protection Division, thanked ATSDR for assembling the panel and allowing the public to attend. He said that the United States Geological Survey identified 52 sites in Georgia that are a concern due to "naturally occurring" asbestos. There are many complex questions that need to be addressed simultaneously to properly investigate these sites. He said it would be a missed opportunity if his agency and ATSDR failed to communicate in the early stages of the investigation. He also pointed out that many people find it difficult to understand scientific concepts. He suggested reporting concentrations in fibers per liter or fibers per cubic meter.

Aubrey Miller, EPA Region 8, commented that pleural changes are not a biomarker for disease, they are a disease that causes reduced pulmonary physiology and risk for malignancy. He said that Norman Whitehouse and David Schwartz showed a significant decrease in pulmonary function in people with pleural abnormalities (e.g., pleural plaques). Amphibole-exposed populations show progressive pleural abnormalities.

Arnold Den, EPA Region 9, asked the panel members to discuss biomarkers for noncancer diseases. One panelist (VR) responded that there are discrepancies that need to be addressed and there should be strict criteria for identifying plaques. Some patients with pleural plaques show no impairment. Rapid decrease is essentially unheard of in people with pleural plaques only. It is very uncommon to have pleural plaques and diffuse visceral fibrosis. A modest increase in lung cancer mortality is difficult to detect in epidemiologic studies. It is uncommon to see people die from asbestosis. Some cases that are diagnosed as asbestosis are actually severe emphysema. Another panelist (GH) said that he has seen pleural plaques develop thickening and that it is mainly a factor of dose and exposure. If a person has high exposure, he/she develops plaques and pleural thickening. There is also a good correlation between lung cancer and dose, however, asbestosis is mostly correlated with disease. The higher exposed, the faster the progression.

Mark Johnson, ATSDR Regional Operations, commented that there is an opportunity to characterize health impacts of early life exposure and onset of disease at the Grace facility. Waste rock was used as fill for homes. The state health department evaluated exposures and indicated that about 600 children were exposed through playing on piles of waste rock. One panelist (VR) responded that there is a similar circumstance at a Louisiana plant that used crocidolite to make cement pipes. The leftover tailings were used in driveways and playgrounds.

20.0 Additional Discussions

The panelists discussed the following additional topics during the panel meeting.

20.1 Ambient Air Monitoring

The panelists briefly talked about ambient air monitoring to confirm asbestos exposure. They highlighted the importance of understanding background levels. One panelist suggested a nation-wide air sampling program to determine background levels of asbestos (MG). Another said that air sampling would be useful for determining exposure, but acknowledged the limitations of environmental sampling and the difficulty of relating the levels found in the air to the potential

for disease (VC). A third panelist suggested using personal air samplers to obtain information about exposure (JA).

20.2 Libby Mine

At the panelists prompting, Dr. Kapil, ATSDR, provided some additional information about the Libby Mine site. He said that the community often asks whether spirometry can be helpful in assessing functional abnormalities, and often has questions about exposure to amphibole fibers. Aubrey Miller (EPA Region 8) said that the major problem is a lack of a baseline for comparison. ATSDR is following the population to study the disease progression. The total population is about 10,000 and about 25 cases of mesothelioma have been reported over the last 25 years. Most of those cases are former Libby Mine workers. A significant amount of pleural disease and abnormalities also have been reported. ATSDR conducted a mortality study in Libby and found that lung cancer mortality and mortality due to asbestosis is elevated. However, there were limitations to the study (specifically, people would have had to have died in that geographical region to be counted and many people moved away from Libby when the mine closed). Dr. Kapil commented that there has been some effort to cross-reference the former Libby Mine workers. He said that all diagnostic analyses have been conducted by the community physicians, not ATSDR, and that there have been anecdotal reports of rapid onset of disease in the community.

Dr. Wheeler, ATSDR, discussed the roughly 260 “Sons of Libby” sites. Of these, ATSDR identified 28 sites that received the most vermiculite from the Libby Mine or was identified by EPA as needing further action. ATSDR is investigating populations at these sites and trying to obtain air sampling data to estimate past exposures, however, there was little environmental sampling conducted in the past. In many cases the communities around these sites are fairly removed from the facilities, and air deposition into the communities is unknown but is expected to be low. However, the same kind of “take home problems” that are seen in Libby are occurring at these sites as well. ATSDR is trying to identifying the exposed populations, but it is an extremely difficult process.

Aubrey Miller stated that EPA regional offices also are involved with the clean up and evaluation of Sons of Libby neighborhoods. He said there is evidence of disease in the workers, as well as environmental exposure and contamination. He mentioned a case report of a person who played in a pile of waste material as a child and died of lung cancer and asbestosis at 42 years.

Dr. Kapil indicated that, in cooperation with the state health departments, ATSDR is conducting health statistic reviews using mortality data at nearly 100 sites. They have not seen an elevation of asbestos related cancer or disease in the sites evaluated so far. ATSDR is hoping to conduct health screenings at a few sites this year—one on community members, another on workers and household contacts, and a third on household contacts.

One panelist commented that workers at Marysville present a unique circumstance of defined exposure (DW). He stressed the importance of following this cohort and documenting its clinical outcome over time.

20.3 Alternate Terms for "Naturally Occurring Asbestos"

During his public comments, William Spain (Georgia Environmental Protection Division) suggested using an alternate term for "naturally occurring asbestos," such as "free range asbestos," "free range amphiboles," or "free range asbestos fibers." One panelist agreed that a different term was needed to avoid confusion and suggested using "non-commercial asbestiform" and "non-commercial non-asbestiform" or "environmental exposure" to relate to the noncommercial setting (MG). Another suggested "asbestos in situ" and commented that if the distinction between naturally occurring asbestos and commercial asbestos is made clear, the confusion surrounding the terms will disappear (VR).

20.4 Miscellaneous Comments

One panelist noted that if you want to tell the community whether it is at risk, try to document the exposures as much as possible (LS). However, even if exposure is confirmed, another panelist commented that it would not tell you whether the community has a significant contribution to lung burdens and overall risk of disease (VR). Even if there is a perfect technique to determine asbestos exposure, not everyone's risk of developing a disease is the same (MC).

21.0 Final Statements

At the end of the expert panel meeting, the panelists were asked to make final comments. Below is a summary of their statements.

Dr. Abraham wanted to go on record saying that based on the information about the occurrence of amphibole asbestos fibers and the sentinel animal tissue studies in El Dorado, the risk of exposure and possible long-term health effects exist though risks cannot be quantified. Therefore, if he had young children in his household and had a choice to live in an area that would cause asbestos exposure or elsewhere (all other things being equal), he would not choose to live in such an area.

Dr. Carbone stated that in communities with high levels of asbestos exposure something needs to be done to help prevent disease progression in these communities. There is an opportunity to develop preventative, therapeutic approaches—offer parallel clinical trials as the detection strategies are implemented. In addition, it is important to verify the validity of the new techniques, which would have a higher impact on the entire population, if validated. The community would be easier to work with if you could offer them something in return.

Dr. Castranova commented that if tissue samples are collected, there is a research opportunity to potentially identify a biomarker of an effect. Whether taking lung tissue samples from autopsy victims or BAL fluid from volunteers, he recommends also analyzing the tissue for cytokine expression.

Dr. Dodson pointed out that many of the discussions focused on verifying exposure in a community, but there was little discussion about prevention. Intervention should be offered to the people in communities with known or suspected asbestos exposures.

Dr. Gunter said that there may be a more complicated mineral reaction in the lung, which might explain some of the diseases. He stressed the importance of not inducing public fear and using terms that make sense. He commented on the importance of air sampling in helping to determine risk from exposure.

Dr. Hillerdal commented that El Dorado seems to have an increased risk of mesothelioma, but that the levels are not high enough for asbestosis to be a concern. He stressed the importance of telling the exposed community how to reduce their risk. Determining the fiber content in BAL fluid is a good technique to prove that people are exposed. However, screening for diseases in El Dorado is not going to give good results since the latency time is so small.

Dr. Roggli recommended a tiered approach to evaluating communities with potential environmental exposures. First, look for elevated levels in the environment. Then, further validate the exposures with medical examiner autopsy cases or BAL fluid from healthy volunteers. In communities with a long exposure duration, it might be worthwhile to perform chest x-rays or CT scans to look for an effect from the asbestos exposure. Spirometry might be useful in providing a baseline.

Dr. Weissman acknowledged the challenge of dealing with exposed individuals, who have concerns about their risk of developing a disease with a long latency. However, analyzing individuals' biological samples for evidence of exposure in the community could help the entire community by guiding approaches to primary and secondary prevention. To be useful, it is critical that studies be carefully and thoughtfully designed.

Dr. Forrester, ATSDR, concluded the meeting by thanking the panelists for attending and Dr. Holguin for serving as the panel facilitator. It was a great opportunity for ATSDR, who has the difficult job of evaluating community exposures to asbestos.

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Appendix A. List of Panelists

ATSDR
AGENCY FOR TOXIC SUBSTANCES AND DISEASE REGISTRY

Expert Panel on Biomarkers of Asbestos Exposure and Disease

ATSDR
Atlanta, Georgia
May 9-10, 2006

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Appendix B. Panelist Biographies

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Jerrold L. Abraham, MD is Professor of Pathology and Director of Environmental and Occupational Pathology at the State University of New York (SUNY) Upstate Medical University in Syracuse, NY. He received his BS in Biology from MIT in 1966 and MD degree from University of California, San Francisco in 1970. He is Board Certified in Anatomic Pathology. His interest in occupational lung disease and analysis of particulates in tissues began with his service in the U.S. Public Health Service at the NIOSH laboratory for Occupational Respiratory Disease in Morgantown, WV from 1972-1975. He was on the Pathology Faculty at UC San Diego 1975-1983, and has been at SUNY in Syracuse since that time. His research activities have involved asbestos as well as many other aspects of environmental and occupational disease, and identification of foreign materials in lungs, etc., using electron microscopy and other techniques. He has published over 110 peer-reviewed articles. He has been a member of committees such as the 1982 NIOSH/CAP (College of American Pathologists) asbestos committee and the American Thoracic Society (ATS) Tremolite Committee. Dr. Abraham presented a study of asbestos fiber content in lungs of animals from the El Dorado California area at the 2005 ATS meeting. [further examples of the types of work in his laboratory can be found at http://www.upstate.edu/pathenvi]

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Michele Carbone M.D., Ph.D., was born in Rome Italy in 1960. He became a US citizen in 2000. Dr. Carbone is currently Professor in the Department of Pathology Cancer Center and Director of the Thoracic Oncology Program at Loyola University Medical Center in Chicago, Illinois. Starting June 1, 2006 Dr. Carbone will move to the NCI-designated Cancer Center at the University of Hawaii, in Honolulu, where he will be the Associate Director for Basic Science, Director of Thoracic Oncology, and Clinical Professor of Pathology. Dr. Carbone received his MD in 1984 from the Medical School of Rome "La Sapienza" and a Ph.D. in Human Pathology in 1993 from a combined program with the Medical School of Rome "La Sapienza" and the National Institute of Health in Bethesda, Maryland. In 1999 he became board certified at the University of Chicago in Anatomic Pathology and is a licensed Physician and Surgeon in the State of Illinois since 1996. In 2006, Dr. Carbone and his team (Drs. B. Mossman, J.R. Testa, H.I. Pass, N. Cox, Y.I. Baris, S. Emri, U. Dogan, I. Steele) have been awarded by the National Cancer Institute (NCI) a PO1 titled "Pathogenesis of Mesothelioma" in the amount of 10 million dollars over 5 years. It is the first time that this very prestigious grant is awarded to study the pathogenesis of this malignancy. Moreover, Dr. Carbone is the principal investigator of two separate NCI RO1s to study mesothelioma and the contribution of SV40 and asbestos to the pathogenesis of this disease. He is also the principal investigator of a National grant from the American Cancer Society to study the role of genetics in the pathogenesis of mesothelioma. Dr. Carbone has published 127 peer reviewed publications, mostly in the field of mesothelioma pathogenesis, his most recent publication is Dogan et al., Cancer Res. May 2006. Dr. Carbone has been the recipient of the NIH Fogarty Fellow award for 8 consecutive years. In 2001, he was nominated Knight of the Republic of Italy for his scientific discoveries and his work in promoting scientific collaboration among US and Italy. Dr. Carbone has organized and chaired numerous National and International meetings on mesothelioma and he is a co-Editor with Drs. H.I. Pass and N. Vogelzang of the mesothelioma textbook, "Malignant Mesothelioma: advances in pathogenesis, diagnosis and translational therapies. Springer, 2005."

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Dr. Castranova received a B.S. in biology from Mount Saint Mary's College, Emmitsburgh, Maryland in 1970, graduating magna cum laude. He received a Ph.D. in physiology and biophysics in 1974 from West Virginia University, Morgantown, West Virginia before becoming an NIH fellow and research faculty member in the Department of Physiology at Yale University, New Haven, Connecticut. In 1977, Dr. Castranova received a research staff position at the National Institute for Occupational Safety and Health and an adjunct facility position at West Virginia University, Morgantown, West Virginia. He has served at these institutions since that time.

Dr. Castranova's research interests have concentrated in pulmonary toxicology and occupational health. He has been a co-editor of four books and has co-authored over 400 manuscripts and book chapters.

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Ronald F. Dodson Ph.D. received his B.A. in biology and general sciences (second major) as well as a M.A. in biology and chemistry from East Texas State University. His doctorate was from the Life Sciences Division of Texas A&M University with an emphasis in Biological Electron Microscopy. Dr. Dodson conducted postdoctoral studies in the Department of Anatomy at the University of Texas Health Center at San Antonio. Dr. Dodson was then appointed to the faculty of Baylor College of Medicine where he served for seven years before he was recruited to the University of Texas Health Center at Tyler and charged with beginning a formal research program.

Dr. Dodson held titles at the University of Texas Health Center at Tyler including: Chief of the Department of Cell Biology and Experimental Pathology, Chairman of the Department of Cell Biology and Environmental Sciences, Associate Director for Research, Director of the Occupational/Environmental Training Division, Co-Director of TIOSH, and Vice President for Research. Dr. Dodson also was appointed as Professor of Biology (with tenure) at the University of Texas at Tyler in 1984. The primary area of his research conducted from his time of arrival at UTHCT and continuing to the present involves determination of dust levels in tissue, body fluids and environmental samples by light and electron microscopy. His laboratories have developed some of the techniques available for preparation of these samples for analysis by Analytical Transmission Electron Microscopy. Dr. Dodson has published over one hundred articles on dust related issues and given numerous presentations on the same topic. He has authored or co-authored chapters in books as well as co-edited a recent book on the subject of asbestos exposure and public health. He has served on numerous academic committees at the Health Center that were charged for compliance with local, state and federal regulations as well as comparable committees in the University of Texas System. Dr. Dodson is a Fellow in the American College of Chest Physicians and the American Heart Association. Dr. Dodson also was a member Asbestos Advisory Committee of the Texas Department of Health that wrote the state regulations governing Asbestos in Public Buildings for the State of Texas. Dr. Dodson holds a license as an Inspector/Manager Planner and Supervisor/Contractor (restricted) through the TDH (EPA model accreditation compliant).

Dr. Dodson retired from academia at the end of August 2005 and at present serves as President of Dodson Environmental Consulting, Inc. and as a Senior Consultant for ERI Consulting, Inc.

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Dr. Roggli received a BA degree in biochemistry and environmental engineering from Rice University in 1973, and an MD degree from Baylor College of Medicine in 1976. He entered a residency training program in pathology with Baylor Affiliated Hospitals in 1976 and completed that training in 1980. He is board certified in Anatomical and Clinical Pathology by the American Board of Pathology. Dr. Roggli joined the staff of Duke University and Durham VA Medical Centers in 1980, and is currently Professor of Pathology at Duke University Medical Center.

Dr. Roggli has been interested in the diagnosis and causation of asbestos-related diseases since 1976. He has published more than 150 articles in peer-reviewed journals, approximately half of which have something to do with asbestos or asbestos-related diseases. He has also contributed to 27 chapters in textbooks and edited four textbooks. Dr. Roggli is the primary editor and author of the first and second editions of Pathology of Asbestos-Associated Diseases (latest edition published in 2004), and was a participant in the 1997 Helsinki conference on diagnosis and attribution of asbestos-related diseases. He has performed tissue asbestos analyses in more than 1000 cases and has written extensively on this subject. He has also received grant support from the VA Merit Review Program for studying the fate of asbestos in laboratory rats and has consulted with federal agencies regarding the effects of asbestos on the respiratory system. Dr. Roggli serves on the editorial boards of Modern Pathology and Archives of Pathology and Laboratory Medicine.

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Appendix C. Charge to Panel Members

ATSDR
AGENCY FOR TOXIC SUBSTANCES AND DISEASE REGISTRY

Charge to Panel Members

The purpose of the panel is to discuss and summarize the best current science for each question posed to the panel. Consensus or specific advice on each of the following questions is not requested. If you are unable to address a question for a particular technique, please reply "no comment."

Please consider the following list of potential techniques for assessing asbestos exposure and/or disease in communities in addressing the questions posed below:

A Fiber burden of lung tissue collected from humans at autopsy
B Fiber burden of lung tissue collected from living humans
C Fiber content of sputum samples collected from living humans
D Fiber content of bronchoalveolar lavage (BAL) fluid of living humans
E Fiber analysis techniques (tissue, BAL fluid, or sputum) in sentinel animals (household pets or other resident animal species)
F Counting asbestos bodies in human tissue, BAL fluid, or sputum
G Blood mesothelin or osteopontin levels, or other blood tests
H Clinical tests such as spirometry to look for functional changes
I Clinical tests such as x-ray or CT scans to look for pathological changes (pleural plaques, pleural thickening, and pleural effusions)

Biomarkers of Asbestos Exposure

1. For each of the techniques (A-I), please consider the following questions. If you are unable to comment on a particular technique, please reply "no comment."

    - What are the advantages and disadvantages of this technique as a method for assessing community-level exposures to asbestos? Is the technique more suited to measuring exposure on an individual level?
    - Does this technique result in a high confidence in predicting asbestos exposures above a "background" level? Are results reproducible?
    - What results would be considered an elevated exposure level? If this is not known, what research should be conducted in order to determine test results that would be considered elevated?

2. Please rank the above techniques (A-I) in terms of cost, practicability, invasiveness, and confidence in results as a means to describe relative implementability in assessing exposures in a medium-to-large community.

Correlations Between Biomarkers of Exposure and Asbestos-related Disease

3. What is the correlation between each of the above techniques (A-I) and asbestos-related adverse health effects (e.g., can pleural changes, such as pleural plaques, pleural thickening, or pleural effusions, be used to assess the risk of disease?). Please rank confidence as high, medium, or low and address both cancer (lung cancer and mesothelioma) and noncancer (asbestosis, pleural disease) effects.

Other Potential Techniques

4. Are there any other techniques for assessing asbestos exposure which were not included in the above list? If so, please address questions posed in questions 1, 2, and 3 above.

The following citations are listed for panelist consideration to help stimulate thought and discussion related to the charge questions. ATSDR selected these papers to represent the breadth of the issues to be discussed by the panel. Their selection does not indicate ATSDR's position on any particular issue. ATSDR recognizes that these only represent a subset of research articles on the topic of asbestos biomarkers. Expert panelists are encouraged to cite other relevant literature when responding to charge questions.

Dodson RF, R Graef, S Shepherd, et al. 2005. Asbestos burden in cases of mesothelioma from individuals from various regions of the United States. Ultrastructural Pathology; 29:415-23.

Dodson RF. 2006. Chapter 3: Analysis and relevance of asbestos burden in tissue. In: Asbestos: Risk Assessment, Epidemiology, and Health Effects. Dodson RF, Hammar SP, eds. Boca Raton: Taylor & Francis Group.

Dumortier P, F Rey, JR Viallat, et al. 2002. Chrysotile and tremolite asbestos fibres in the lungs and parietal pleura of Corsican goats. Occup Environ Med; 59:643-46.

Luce D, M Billon-Galland, I Bugel, et al. 2004. Assessment of environmental and domestic exposure to tremolite in New Caledonia. Archives of Environmental Health. 59(2):91-100.

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Robinson BWS, J Creaney, R Lake, et al. 2005. Soluble mesothelin-related protein--a blood test for mesothelioma. Lung Cancer; 49(S1):S109-11.

Roggli VL and LL Sanders. 2000. Asbestos content of lung tissue and carcinoma of the lung: a clinicopathologic correlation and mineral fiber analysis of 234 cases. Ann Occup Hyg; 44(2):109-17.

Sartorelli P, G Scancarello, R Riccardo, et al. 2001. Asbestos exposure assessment by mineralogical analysis of bronchoalveolar lavage fluid. JOEM; 43(10).

Appendix D. Pre-meeting Comments Organized by Technique

Pre-meeting Comments Organized by Technique

A. Fiber burden of lung tissue collected from humans at autopsy

Abraham

1. This technique can assess community-level exposure, and is well suited to such sampling, but ONLY if there is unusual cooperation from the population and medical examiners/coroners. Collection of autopsy material can and has been used for such studies, but it is nearly useless unless one can also collect individual lifetime residential and occupational/avocational data for each individual person whose lungs are a part of such a study.

    - Fiber burden of lungs does NOT measure "exposure" but measures retained fibers in the lung. This MAY correlate well with exposure but is not the same and would need validation of any correlation claimed.
    - If a truly representative cross section of a community's population is collected, then an autopsy series can be quite revealing, perhaps more so than on an individual level.
    - This technique does allow determination if the lung burden of fibers is above or below the pre-determined values for 'background' levels of specific types and dimensions of fibers, assuming standardized methodology for comparison.
    - Results are reasonably reproducible, given sufficient sampling selection and methodologic consistency. [the use of the term "predicting" throughout this discussion seems ill advised and this participant does not recommend its use.]
    - Results indicative of elevated lung burden (not 'exposure') depend on the background values determined by each laboratory's methodology, so it is not possible to state any single number or range in response to this question.

Carbone (Did not follow a similar format, see General Comments Section at end)

Castranova

Assessment of community or individual exposure
Good indicator of individual exposure.
Would require strong history to eliminate occupational exposure or exposure at another site. Problem is that data are obtained years after the environmental problem arises.

Must have a strong history to relate to exposure at a particular site.

Predictive / reproducible –
Yes. Must maintain standard counting rules.

Dodson

Advantages
1. Multiple sites from tissue can be sampled and evaluated for asbestos content including not only lung but also extrapulmonary sites where several asbestos related diseases occur.
2. A determination of both the levels of ferruginous bodies and/or uncoated fibers can be obtained for comparative purposes.

3. Increased number of sites for sampling will provide better information regarding of tissue burden since there will be greater capability to overcome issues of random sampling errors from smaller numbers of samples.
4. Tissue burdens of uncoated fibers and ferruginous bodies per gram of wet and/or dry tissue have been published for individuals with certain types of exposures and/or asbestos related diseases. Thus there are references for comparative purposes in occupational/paraoccupational and control groups. The limitations placed on the comparisons of data would be based on what length/diameter of fibers was and were not counted in a given study and if a comparable type of instrument was used in the analysis. (See references below)

Disadvantages

1. There will be appreciable cost and time involvement in any analysis if the methodology is selected for obtaining best level of information (ATEM) regarding uncoated fiber burden in tissue.
2. Limited numbers of Analytical Transmission Electron Microscopy laboratories are presently working in tissue burden analysis but there are numerous private laboratories across the country that are doing National Voluntary Laboratory Accreditation Program (NVLAP) level analysis of fibers collected from air samples and could thus adapt their model for tissue analysis. NVLAP certified labs are required to perform to reproducible and measurable standards.
3. Data from tissue analysis studies are often presented with count schemes that are confusing when attempts are made to compare findings with other studies. A clear definition is needed as to what fibers are included in a count scheme (based lengths but equally important diameters) if one is to make meaningful comparisons between findings of different studies.
4. Tissue burden of asbestos content of lung reflects what is in the lung at the time of sampling and not what may have been in the lung and eliminated via clearance mechanisms. The levels and types of asbestos in the lung may not reflect the population of fibers that reached the extrapulmonary sites where asbestos induced diseases occur.

Relevant literature-Asbestos fibers in tissue samples

Tissue preparation:

Dement (1990) appropriately summarized the status of tissue preparation in the following: “The use of indirect sample transfer for transmission electron microscopy (TEM) of asbestos fibers has been shown to break up the airborne fibers into smaller units. Depending upon the treatment, the observed concentration of fibers and their sized distribution change drastically. There is no biological justification for such a violent treatment, and the measured entity is not a biological justifiable measured quantity. Therefore, the use of indirect sampling should be discouraged, and the more gentle direct transfer method should be used”.

Dodson (2006) has discussed the various methods of tissue preparation for the determination as to the presence of asbestos bodies as well as uncoated asbestos fibers from tissue, lavage, or sputa samples as well as the advantages and disadvantages of each.

Instrument selection for analysis of uncoated asbestos fibers:

Langer et al. (1971) accurately defined the role of light microscopy in the detection of uncoated asbestos fibers from human samples. “The optical microscope delivers a select, biased population. First, we can only study what the microscope sees-and it only sees larger fibers, those thicker than 0.5μ in diameter”.

A recent response to comments regarding a paper published by Atkinson et al. (2006) further defined the limits of resolution (in the case of fibers-based on diameters) that is attainable for the light microscope.

Ashcroft and Heppleston (1973), as well as Pooley and Ranson (1986) have indicated that a small percentage of the fibers obtained from tissue and detected in the Analytical Transmission Electron Microscope would have been visible in an optical microscope.

Rood and Streeter (1984) have shown the difference in numbers of fibers detected in an analysis of human tissue by Scanning Electron Microscopy as compared with the number of fibers detected in an analysis by Analytical Transmission Electron Microscope.

Murai and colleagues (1994) reported that even if Analytical Transmission Electron Microscopy is used for analysis of lung tissue, an underestimation of the total fiber burden in a tissue sample could occur if the analysis is carried out at low magnification. "Short fibers less than 2µm-both chrysotile and amphiboles, as well as long, thin fibers less than 0.06 µm–would be missed at 2000x (TEM)".

Dodson et al. (1993) presented findings from a case in which tissue burden was analyzed by Analytical Transmission Electron Microscopy at a lower magnification (5,000x) count that included only fibers greater than 5µm as compared with data from a higher magnification count scheme (15,000x-20, 000x) that included analysis of fibers greater than 0.5µm in length. One chrysotile fiber was found in the low magnification scan while shorter chrysotile and amphibole fibers were found in the higher magnification scan. The total fiber burden determined by the data from the higher magnification scan was 1.7 million fibers per gram dry tissue. The lower magnification scan would have left the impression that the tissue was consistent in tissue burden with asbestos levels found in lung tissue from general populations.

It is suggested that a useful reference for reviewing the advantages and disadvantages of counting and/or analyzing fibers in the different types of available instruments (light microscope, scanning electron microscope, and analytical transmission electron microscope) is offered in the Health Effects Institute (HEI) report on Asbestos in Public and Commercial Buildings (Upton, 1991).

The Asbestos Hazard Emergency Response Act (AHERA) (Title II of the Toxic Substance Control Act 15, U.S.C. Sections 2641-2654 defines ATEM as the "state of the art" instrument and required the use of ATEM for final clearance in many abatements projects in schools. The laboratories involved in this program are required to be accreditation and evaluated for assurance that analysis by ATEM is done in accordance with a reproducible protocol using the same magnifications for analysis and with the inclusion of the same dimensions of structures in a count scheme (>0.5µm in length). The data is therefore mandated to be reproducible between laboratories and the laboratories are required to conform to certain quality assurance standards. Therefore a federal law has defined the ATEM as an instrument of choice for analysis of asbestos fibers and while the data in this regulation is concerning air samples, the logical applications should reasonably be applicable to analysis of fibers collected on filters from water or tissue samples.

Importance of including of short fibers in count scheme of tissue obtained from autopsy:

The majority of fibers in lung tissue from occupationally and nonoccupationally exposed individuals are less than five micrometers in length, do not form ferruginous bodies and not

detectable via light microscopy analysis (Langer et al. 1971) (Churg and Warnock, 1980), (Dodson 1980) (Dodson et al. 2004) (Dodson et al. 1997) (Dodson et al 1999) (Dodson 2006).

A feature of the asbestos found in lung tissue from individuals in the general population is that it is not only shorter than 5µm in length but also often consists of non-commercial amphiboles and/or chrysotile (Churg and Warnock 1980) (Dodson et al. 1999).

Sebastien et al. (1980) evaluated lung tissue and pleural tissue from exposed individuals. The findings were that short chrysotile (<5 µm) were the predominate type of fiber found in the pleural tissue and concluded that the characteristics of the tissue burden in the lung may not reflect the actual population of fibers that reach the extrapulmonary sites.

Suzuki and associates (Suzuki and Yuen 2001) (Suzuki and Yuen 2002) (Suzuki et al. 2005) have found that short chrysotile (<5µm) fibers are also relocated to the pleural tissue and were also found in tissue taken from mesotheliomas.

Dodson et al. (1990) using Analytical Transmission Electron Microscopy determined the ferruginous body and uncoated asbestos fiber content of lung tissue, lymph nodes, and pleural plaques obtained from former shipyard workers. The majority of the uncoated fibers in the nodes and plaques were <5µm in length with chrysotile being the predominate asbestos type found in the plaques. The lung tissue from one individual did not have detectable levels of chrysotile fibers (below limit of detection in the model) however the sample from the lymph node contained 5,500,000 chrysotile fibers per gram of dry tissue and the tissue from the pleural plaque contained 21,000,000 chrysotile asbestos fibers per gram of dry tissue. The length of chrysotile fibers in the pleural tissue was strikingly similar to the dimensions reported for chrysotile in those sites by Sebastien et al. (1980) and Suzuki and colleagues (2001, 2002, 2005).

Dodson et al. (2003) provided a review of the issue of fiber length and potential for induction of disease in man. The subsequent concerns for exposure to all lengths of asbestos following the World Trade Centers disasters in New York City emphasizes the importance that the public has placed on being provided the most thorough assessment of an asbestos exposure. This reasonably should always include data using the state of the art applications. In this section the issues of defining tissue burden from human tissue have been discussed with that objective in mind.

Gunter (Did not follow a similar format, see General Comments Section at end)

Hillerdal

Theoretically possible, but in practice difficulties because of:
1/ Availability of autopsies and tissue

2/ Difficulties with other exposure: has the person in question lived anywhere else? Has he/she had exposure to asbestos occupationally or in some other way? How can you get this information (info from relatives often not reliable)

3/ A minimal number of persons necessary

Roggli

This method is the most potent technique for measuring a lifetime of exposure to asbestos fibers. The lung is the ultimate sampler of what an individual is exposed to in the ambient air. Numerous studies

have shown an excellent correlation between lung asbestos fiber content and various asbestos-related diseases as well as various occupational and non-occupational exposures to asbestos.[1] Amphibole fibers in particular accumulate progressively in the lungs so that autopsy lung fiber burdens are a good measure of cumulative lifetime exposure. In the setting of a community or environmental exposures, the best information will be obtained from analysis of lung tissue from medical examiner (ME) cases, with careful correlation with the patient's residential history and occupational exposure history. A case control format can then be used to compare lung burdens of individuals living near the point source versus those who did not, with proper controlling for any occupational exposures that may be confounders. This method would work especially well for environmental exposures to tremolite, because these amphibole fibers have a long half-life in the lung, they are readily detected by any of the available electron microscopic techniques, exposure to these fibers occupationally is limited to very low level contamination of chrysotile (or talc), and the background levels for these fibers have been fairly well established.

Disadvantages of this method include limited access to the necessary tissue samples. In addition, exposure histories of the individual are complex, and there are many possible sources of asbestos exposure in the work, home and neighborhood environments. Also, lung fiber burden analyses are not an accurate measure of the lifetime exposure to chrysotile, which tends to break down with subsequent removal from the tissues at a much greater rate than the amphiboles. It may be difficult to get accurate exposure and residential information in deceased (ME) cases. Finally, the methodology is expensive and available in only a few specialized centers.

Stayner

1. Advantages/Disadvantages for Assessing Community or Individual Exposures

   Measuring lung tissue burdens of asbestos fibers in humans is a useful indicator of asbestos exposure for individuals who have been exposed to amphibole forms of asbestos (e.g., amosite or crocidolite). The primary advantage of this method over conventional exposure assessment methods is that it may provide an estimate of exposure that is integrated over a lifetime. This method is far less useful for the assessment of exposure to chrysotile asbestos because of its low biopersistence in the lung. Experimental studies in rodents have clearly demonstrated that chrysotile is cleared from the lungs much faster than amphiboles (Wagner et al 1974). Based on studies of lung clearance times in baboons (half life 90 days) it has been estimated that only a very small fraction ($1/(8 \times 10^{22})$) of chrysotile exposures from 20 years ago would be present in the lungs of exposed workers (Stayner, Dankovic and Lemen 1996). Thus measurement of lung burdens of chrysotile would have very little relevance for predicting lung cancer risk, since lung cancer and mesothelioma have a very long latency period (i.e., 20-30 years) and thus exposures from many years ago may be etiologically relevant.

   Another major limitation of this method is that it is well recognized to vary by laboratory method, and by variations in concentrations from one site of the lung to another (Roggli 1990).

   It is difficult to conceive of how this method could be used for developing unbiased estimates of community exposures to asbestos, unless autopsies were done on the entire populations or on a random sample of the population. Current autopsy rates in the U.S. are relatively low (<6%) [Burton et al. 2004]. These could hardly be reviewed as a representative sample of the population since autopsies are more commonly performed for certain diseases.

2. Does this technique result in a high confidence in predicting asbestos exposures above a "background" level? Are results reproducible?

Defining what a background level for asbestos lung burdens is very difficult. This background level would obviously vary by region of the country, and would be heavily influenced by exposures from the workplace. Background levels of asbestos lung burdens have been reported to vary over 3 orders of magnitude in studies of control (non-diseased) populations (reviewed by Roggli 1990). Some of this variability may be explained by differences in measurement techniques, but it also might reflect differences in the populations studied.

3. What results would be considered an elevated exposure?

   I suppose an easy answer to this question is anything above background. However, as mentioned above I don't think that defining background is straightforward. Also I suspect the real intent here is to define elevated exposures as those that are associated with a significant risk of disease At this time, one would have to presume that any level of exposure (including background) is associated with some risk of disease.

4. Correlations Between Biomarkers of Exposure and Asbestos-related Disease

   Lung burden of amphibole asbestos fibers have been shown to be strong predictors of mesothelioma (e.g. see McDonald et al. 1989, and Rogers et al. 1991), and asbestosis (e.g. Green et al. 1997) risk in several studies (e.g. see McDonald et al. 1989, and Rogers et al. 1991). The observed relationship between lung burdens of chrysotile and these diseases has been weaker but this might be explained by the relatively low biopersistence of chrysotile as discussed above. A consistent relationship has not been observed between lung burdens of either chrysotile or amphiboles in relation to lung cancer risk (e.g. Churg, Wright and Vedal 1993).

Weissman

- What are the advantages and disadvantages of this technique as a method for assessing community-level exposures to asbestos? Is the technique more suited to measuring exposure on an individual level?

  One of the most important advantages to autopsy specimens is the ability to obtain relatively large amounts of lung tissue from multiple sites, thereby reducing sampling error. There is also a substantial body of literature documenting methods and results of tissue fiber counts. Assessing uncoated fibers by electron microscopy allows detection of short fibers and fibers of small width. There are a number of challenges. Autopsy rates have markedly declined in recent times; recruiting adequate numbers of participants from a community can be challenging. There is a need to recruit appropriate controls, taking into consideration issues such as urban vs. rural residence and occupational exposures. Obtaining appropriate exposure histories of deceased individuals can be a challenge, as can obtaining appropriate smoking histories. Use of autopsy specimens obviously creates selection bias with regard to the age distribution of deceased individuals vs. the population in general. Finally, as is the case for all types of asbestos fiber sampling, greater clearance of chrysotile fibers than amphibole fibers can result in underestimation of chrysotile exposure. If these challenges are overcome, autopsy studies performed in appropriately sized samples of deceased individuals would appear to offer a usable approach to assessment of fiber burden in a community.

- Does this technique result in a high confidence in predicting asbestos exposures above a "background" level? Are results reproducible?

There is a body of literature answering both questions in the affirmative. A European Respiratory Society Task Force report (De Vuyst et al. Guidelines for mineral fibre analyses in biological samples: report of the ERS working group. Eur Respir J 1998; 11:1416-1426) provides data on background fiber counts and reproducibility of results. It emphasizes the need for standardized approaches to sample preparation, sample analysis, and presentation of data. It notes that interlaboratory reproducibility for complex analyses such as fiber counts by electron microscopy is less then for less technically demanding assays such as asbestos body counts by light microscopy.

- What results would be considered an elevated exposure level? If this is not known, what research should be conducted in order to determine test results that would be considered elevated?

  The ERS report noted above suggests values above 1 – 2x10-6 fibers/g dry lung for total amphibole fibers and 0.1 x 10-6 fibers/g dry lung for amphibole fibers longer than 5 microns. The "Helsinki Criteria" (Scand J Work Environ Health 1997; 23:311-316) suggest similar values.

B. Fiber burden of lung tissue collected from living humans

Abraham

1. The responses to this are mostly the same as for item "A" above. It IS possible to use tissues archived in pathology laboratories from persons having lung tissue removed for medical indications, but it would not generally be considered ethically acceptable to do invasive biopsies strictly for a survey of lung fiber burdens in a community!

Carbone (Did not follow a similar format, see General Comments Section at end)

Castranova

Assessment of community or individual exposure
Invasive. Not realistic for a community-based study. Therefore, will use a few individuals to represent the community. Requires a strong history to eliminate occupational exposure or exposure at another site.

Problem of how representative limited tissue samples are of the total lung fiber burden.

Predictive / reproducible –
Variation due to sampling sites.

Dodson

Advantage in determining fiber burden of lung tissue collected from living humans

1. In some instances the analysis of fiber burden from tissue derived from living humans may assist the clinician in evaluating the cause of the underlying disease.
2. Screening by light microscopy of tissue sections, while relatively insensitive would permit identification of ferruginous bodies if present in section and in proper orientation in the plane of section. This screen would be supplemental to any pathological screening of tissue and be relatively inexpensive and involve limited amount of additional time for analysis.

Disadvantage in determining fiber burden of lung tissue collected from living humans

1. Tissue samples would most likely be small and limited as to sites thus creating concern for increased risk of random sampling errors
2. Ultimate invasive procedure
3. Analysis including electron microscopy procedure would be costly and time consuming

Techniques, instrumentation, and comparative value of findings will be discussed in Section A-Fiber Burden of lung tissue collected from humans at autopsy.

Gunter (Did not follow a similar format, see General Comments Section at end)

Hillerdal

Difficulties of availability; only in those where operations are needed, for example resection for lung cancer which means selection; most likely only occasionally available but likely to have confounding factors.

Used to my knowledge only at the individual level.

Roggli

All the advantages listed above for analysis of lung tissue fiber burdens are equally applicable to this category. In addition, a more accurate assessment of the patient's residential and occupational exposure history should be obtainable.

Disadvantages include the difficulty of obtaining tissue samples for analysis from living patients. There is no clinical indication for doing an invasive procedure to obtain tissue in healthy individuals. Less invasive procedures such as transbronchial biopsies yield too small an amount of tissue.[2] Therefore, samples would necessarily come from individuals who are ill and who have had lung tissue removed for another purpose (e.g., lobectomy or pneumonectomy for lung cancer). Individuals with lung cancer often have chronic obstructive pulmonary disease and a heavy smoking history, which may affect their retention of pulmonary fibers, so controls would have to be carefully selected.

Stayner

All of the comments above would also apply to this method. However, clearly an additional concern would be the risks associated with taking lung tissue from living human beings. I would expect that this might have serious ethical concerns particularly given the limitations in interpreting the findings from these analyses for either individuals or communities that are discussed above. (See A)

Weissman

- What are the advantages and disadvantages of this technique as a method for assessing community-level exposures to asbestos? Is the technique more suited to measuring exposure on an individual level?

The advantage of this technique is the extensive body of literature on fiber burden in lung tissue, as noted for item "A." The disadvantage is that only those undergoing lung resections (usually for cancer) can be adequately sampled. Less invasive approaches, such as transbronchial lung biopsy, do not provide adequately sized samples for analysis. The requirement for a sampled individual to have a condition requiring lung resection obviously introduces selection bias. In addition, the condition requiring resection might, in itself, somehow affect fiber counts through mechanisms such as -

impairment of fiber clearance or displacement of normal lung tissue by tumor. The approach could be used for individuals or populations.

- Does this technique result in a high confidence in predicting asbestos exposures above a "background" level? Are results reproducible?

  See comments for autopsy material. The main difference from autopsy would be the use of smaller tissue samples, which could introduce sampling error.

- What results would be considered an elevated exposure level? If this is not known, what research should be conducted in order to determine test results that would be considered elevated?

  See comments for autopsy material.

C. Fiber content of sputum samples collected from living humans

Abraham

1. This sampling method certainly could be done in a community, probably best using INDUCED SPUTUM (IS), which has been demonstrated to be able to sample for environmental exposures by Fireman and colleagues in Israel. [see additional refs] This is a relatively non invasive technique. The caveat is that it is quite variable in quantity and quality of the resultant sputum for analysis, and subject to overlay from other conditions such as infection going on in the individual at the time of sampling.
   - Also, it would be quite difficult to quantify the burden of fibers on any sound denominator basis (although some might disagree with this caveat).

   Additional references:

   Abraham JL, Case BW, Burnett BR and Trent T. Lung-Retained Fiber in Pets Confirms Environmental Exposure to Naturally-Occurring Asbestos in Western El Dorado County, California. Proceedings of the American Thoracic Society 2005; 2:A818. [available in further detail at http://www.upstate.edu/pathenvi/studies/case6.htm]

   Fireman EM, Lerman Y, Ganor E, Lerman Y, Ganor E, Greif J, Fireman-Shoresh S, Lioy PJ, Banauch GI, Weiden M, Kelly KJ, Prezant DJ Induced sputum assessment in New York City firefighters exposed to World Trade Center dust. Environ Health Perspect 2004;112:1564–9.

   Schoning, P, Abraham, JL, Burnett, BR. Silicate and Metal Dust in lungs of Greyhounds. Am J Vet Res 57:1006-1009, 1996.

Carbone (Did not follow a similar format, see General Comments Section at end)

Castranova

Assessment of community or individual exposure
I'm not convinced induced sputum consistently samples the bifurcations of the respiratory bronchioles where fiber deposition occurs.

The strong point is that it is non-invasive and relatively simple, allowing wide sampling.

A strong history is required to extrapolate an individual level to an environmental site.

Predictive / reproducible –
Variable yield. Question of respiratory vs. conduction zone sampling.

Dodson

Advantages-non invasive
Disadvantages-very limited published data primarily focusing on presence of ferruginous bodies-see reviewed articles topic "F"

Relevant literature:

Bignon et al. (1974) reviewed a series of samples including parenchymal tissue, sputum and gastric juices. The emphasis of study was on presence of ferruginous bodies with the reference to fibers in sputum. Conclusion regarding uncoated fibers in sputum samples: wide range in ratio of coated to uncoated fibers. No fiber types or numbers provided in data.

Dodson et al.(1989) reviewed randomly selected samples of sputa for the presence of ferruginous bodies (data provided in section "F") and uncoated asbestos fibers in samples from twelve former workers in an amosite manufacturing facility and twelve individuals with no known occupational exposure to asbestos. The insensitivity of sputum samples for the detection of ferruginous bodies will be discussed in section "F" and was consistent with the findings by light microscopy of samples from the heavily exposed group in that no asbestos bodies were detected. However even given the inherent limitations for fiber identification and resolution in the Scanning Electron Microscopy, (see discussion section "A") there were uncoated amosite fibers found in ten of the twelve sputum samples from the occupationally exposed group. Only one sputum sample was found to contain a single asbestos fiber from the "control" group.

Recommendation: If one is to screen sputa samples for the presence of uncoated fibers that screen should be done with a preparative process that does not risk loosing or damaging the fibers, done on multiple samples, included short fibers in the count scheme and analysis carried out by Analytical Transmission Electron Microscopy (see section "B").

Gunter (Did not follow a similar format, see General Comments Section at end)

Hillerdal

A considerable exposure usually necessary for findings in sputum; certain technical difficulties; to my knowledge not tried in large studies for this purpose

Roggli

There is somewhat limited data correlating the finding of asbestos in sputum samples with lung fiber burdens, which as noted above are the most accurate measure of an individual's lifetime exposure.[3] Nonetheless, this method has the advantage of being entirely non-invasive, easy to collect, and relatively easy to analyze.

Disadvantages of this method include the observation that sputum asbestos content is primarily elevated in patients with heavy occupational exposures. For example, in the Tyler Asbestos Workers' Program, involving a cohort with heavy occupational exposure to amosite asbestos, only one third of these workers had asbestos bodies detected in their sputum samples.[3] In addition, there is relatively little data on the normal background range of asbestos in sputum samples, so control groups would have to be carefully selected. Even then, with the expected low levels of exposure from environmental sources, *it is likely that sputum samples would not show a significant difference between those living near a point source of exposure versus those living further away.*

Stayner

1. Advantages/Disadvantages for Assessing Community or Individual Exposures

   The primary advantage of this method is that it is non-invasive and safe. It appears that this method when combined with electron microscopy is far more sensitive then methods based upon counting asbestos bodies using light microscopy [Dodson 2006]. Counting fibers with TEM also appears to be able to detect chrysotile fibers, more reliably than counting asbestos bodies [Sartorelli et al, 2001]. However, it would seem that this method would be subject to the same limitations for assessing chrysotile as discussed above for lung burden studies. That is the relatively short half-life of chrysotile in the human lung would suggest that this method may be insensitive for detecting chrysotile exposures from 20-30 years ago.

2. Does this technique result in a high confidence in predicting asbestos exposures above a "background" level? Are results reproducible?
   No opinion

3. What results would be considered an elevated exposure?
   No opinion

4. Correlations Between Biomarkers of Exposure and Asbestos-related Disease
   No opinion

Weissman

- What are the advantages and disadvantages of this technique as a method for assessing community-level exposures to asbestos? Is the technique more suited to measuring exposure on an individual level?
  The advantage of evaluating sputum samples is that sputum can be obtained in a noninvasive and safe manner, making it suitable for screening large numbers of subjects. There are several disadvantages. If spontaneous sputum samples are used, a large proportion of subjects are unable to produce sputum. If induced sputum samples are used, greater time and effort are involved. In either case, it is important to have some method to determine whether the sputum sample represents contents of the deep lung, or suffers from salivary contamination. As noted below, there is relatively little data documenting the usefulness of fiber counts in sputum samples. The approach is probably more suited to populations than individuals.

- Does this technique result in a high confidence in predicting asbestos exposures above a "background" level? Are results reproducible?
  Much of the work evaluating sputum sampling as a way to assess asbestos exposure analyzes for asbestos bodies rather than fibers. As compared to other methods, there is little data documenting

"normal" fiber levels. In the case of asbestos bodies, analysis of sputum has been found to be insensitive but specific for lung asbestos burden. There is little data addressing reproducibility of the technique.

- What results would be considered an elevated exposure level? If this is not known, what research should be conducted in order to determine test results that would be considered elevated? Further research using defined populations would be appropriate.

D. Fiber content of bronchoalveolar lavage (BAL) fluid of living humans

Abraham

1. This is definitely an invasive technique, although approved for some research studies. This panel member questions whether most IRBs would approve of its use for purposes of community environmental exposure monitoring!

Carbone (Did not follow a similar format, see General Comments Section at end)

Castranova

Assessment of community or individual exposure
Evidence suggest that values are related to exposure, duration of exposure, and progression of disease. May yield a good individual exposure. However, a strong history is required to relate exposure to a particular environmental site.

Somewhat invasive. Not practical for a wide community study. Therefore, a few individuals would represent the community. Requires a good history.

Predictive / reproducible –
Some variability is expected.

Dodson

Advantage in Evaluation of Bronchoalveolar Lavage Samples-Provides material rich in pulmonary macrophages as well as surface material (including dust) from the lower airways

Disadvantage in Evaluation of Bronchoalveolar Lavage Samples- The lavage technique is one that involves an invasive procedure and therefore carries some degree of risk for the patient during collection of the sample.

Relevant Literature-Asbestos Fibers in Bronchoalveolar Lavage Samples See Section F for specific papers. See Section A for applicable preparative techniques, instrumentation requirements and/or limitations

Gunter (Did not follow a similar format, see General Comments Section at end)

Hillerdal

Better than sputum; more likely to find fibers; however, not a very nice experience and certain costs involved; to my knowledge not tried in large studies for this purpose

Roggli

There are very good data correlating the finding of asbestos bodies in BALF with asbestos body content of lung parenchyma.[3] Data are considerably scarcer correlating asbestos fiber content in BALF with asbestos fiber content of lung. This technique has the advantage of being less invasive than lung biopsies, although it is more invasive than obtaining sputum samples and is not without potential complications. BALF is a more sensitive indicator of asbestos exposure than sputum sample analysis and can be performed on healthy individuals. *Analysis of BALF in living patients and fiber burden analysis of lung tissue in deceased (ME) cases in combination probably offer the most potent methodology for assessing the exposure of a community to environmental or neighborhood asbestos fibers.*

This method requires an individual highly trained in the technique of bronchoscopy, and is a somewhat invasive procedure. The technique is a surrogate for lung fiber burden analysis but the correlation is less than perfect. It is not known whether this technique is sensitive enough to detect differences between those living near a point source of exposure versus those living further away (i.e., what is the statistical power of a null finding?).

Stayner

1. Advantages/Disadvantages for Assessing Community or Individual Exposures

   The primary advantage of BAL is its high sensitivity relative to the sputum method discussed above [Teschler et al. 1996]. Its primary disadvantage is that it is a somewhat invasive procedure, which might present some minimal risk and discomfort to the individual.

2. Does this technique result in a high confidence in predicting asbestos exposures above a "background" level? Are results reproducible?
   No opinion

3. What results would be considered an elevated exposure?
   No opinion.

4. Correlations Between Biomarkers of Exposure and Asbestos-related Disease
   No opinion

Weissman

- What are the advantages and disadvantages of this technique as a method for assessing community-level exposures to asbestos? Is the technique more suited to measuring exposure on an individual level?

  Segmental BAL sampling has important advantages. It is not as invasive as biopsy. It samples a large area of lung. There is a fair amount of data on using BAL to assess asbestos exposures,

although much more data exists analyzing for asbestos bodies by light microscopy than for fibers by electron microscopy. There are also some important disadvantages. Although not as invasive as surgical biopsy, it is still invasive, relatively expensive, and not easily performed in large numbers of volunteers. It does require local anesthesia and, in some people, sedation. Post-lavage fever, and rarely pneumonia, can occur. There is a need for BAL to be performed in a standardized fashion. Percent returns can vary depending on the segment lavaged.

- Does this technique result in a high confidence in predicting asbestos exposures above a "background" level? Are results reproducible?

  Although data are limited, assessment of fibers in BAL by electron microscopy appears to have the ability to discriminate asbestos-exposed from control individuals. In one study (Sartorelli et al. Asbestos exposure assessment by mineralogical analysis of bronchoalveolar lavage fluid. J Occup Environ Med 2001; 43:872-881) it was stated, "in 99% of the cases ($p < 0.0001$), the confidence intervals of fiber concentration were 1054 to 1812 ff/mL and 102 to 186 ff/mL, respectively, in the exposed population and in the control subjects." There is little published data on reproducibility.

- What results would be considered an elevated exposure level? If this is not known, what research should be conducted in order to determine test results that would be considered elevated?

  As already noted, most BAL analysis has focused on asbestos bodies, not fiber counts. Ranges of fibers in one study are as noted above. Further research using defined populations to develop normal ranges for BAL fiber counts would be appropriate.

E. Fiber analysis techniques (tissue, BAL fluid, or sputum) in sentinel animals (household pets or other resident animal species)

Abraham

1. This approach has been demonstrated to yield valuable evidence that exposures are occurring in a community environment.

   - The limitations of extrapolation to human disease risk remain to be investigated.

   - In at least the situation reported by Dumortier et al, there IS demonstrated human disease in the community and the animal (goat) lung fiber burden studies serve to allow much more analysis of the fiber burden without any invasive procedures in humans.

   - Data also exists to show how at least in one species (greyhounds) there is a quantitative relationship between dust in the lungs with age of the dog, and that the dust in the lung reflects the major source of dust to which the animals were exposed in their 'working' (i.e., racing on a dirt track) lives [Schoning et al 1996].

   - Data on a small sample of animals from El Dorado County confirms the exposure to asbestos in the animals, and at least the potential exposure in humans, and indicates that a carefully designed sampling of a larger number of animals would be worth further investigation [Abraham et al, 2005]

   - The difficulty in obtaining lung tissues from animals would be different for domestic farm animals, household pets, and feral/wild animals. IF animals analogous to the goats studied by

Dumortier et al were available that would be the easiest group to study. Pets cannot be expected to be sacrificed by owners for such studies, and varying species or breeds of animals make comparisons more difficult.

Carbone (Did not follow a similar format, see General Comments Section at end)

Castranova

Assessment of community or individual exposure
Likely to have low participation for BAL or sputum on pets. If exposure is near a school, a household pet is not likely to have the same exposure. The same is true for resident animal species.

Tissue fibers are better than BAL or sputum.

Predictive / reproducible –
BAL and sputum should have variability with sputum being much worse.

Tissue burden requires standard counting rules. Variability due to variability in exposure related to the pet (outdoor or indoor pet).

Dodson

Advantage in Evaluation of Fiber Analysis Techniques (Tissue, BAL fluid, or Sputum) in Sentinel Animals (Household pets or other residual animal species):

1. Samples from an "environmental exposure" similar to that in which humans live.

Disadvantage in Evaluation of Fiber Analysis Techniques (Tissue, BAL fluid, or Sputum) in Sentinel Animals (Household pets or other Residual animal species):

1. Different Anatomy of respiratory system and posture than humans
2. Differences in clearance rates between species
3. Some animal species apparently do not form ferruginous bodies
4. Contact would probably be with DVM in area or a PI would have to obtain protocol approval for study through accredited animal committee for such evaluation unless material was provided as discarded from DVM or involved agency would hold protocol.
5. There are limited numbers of studies where the asbestos burden (ferruginous bodies and/or uncoated asbestos fibers) have been evaluated in lung tissue from Sentinel animals or in lavage material from same.
6. I am not aware of any studies assessing sputa collected from such animals. This limited basis of "control" data would make data primarily observational rather than comparative in nature.

Relevant Literature-Fiber Analysis (tissue, BAL fluid, or sputum) in Sentinel animals (household pets or other resident animal species)
See Section A for applicable preparative techniques, instrumentation requirements and/or limitations
See Sections D, F for specific papers on data from human material including some cases of environmental exposure

Gunter (Did not follow a similar format, see General Comments Section at end)

Hillerdal

Has been tried in small scale (goats in Biancavilla area, moles in Turkey, Baboons in South Africa, etc) but requires tissue (how do you collect sputum samples from a goat or cat?) and thus the animal has to be slaughtered which owner of pets may have certain opinions about; also difficulties in evaluating exposure. If some wild animal is living in some numbers in such a way that they are likely to have exposure similar to humans, this method should be tried.

Roggli

Tissue should be readily available from household pets, and lung tissue analyses should be relatively easy to perform on deceased pets. The exposure environment should be similar to that of the owners/residents of the community.

Disadvantages are numerous. Very little if any data are available on normal ranges of lung fiber burdens for animals/pets. Even less information is available concerning the correlation between fiber burden levels in pets and those in humans. For example, it has been my experience that the lungs of dogs are quite dirty compared to humans, presumably related to a lifetime of sniffing the ground (as dogs are wont to do). The lifespan of pets is considerably shorter than that of humans; hence, fewer total number of years to accumulate a lung fiber burden. In the absence of background information regarding, for example, the tremolite content of dog lungs, it is unknown whether the signal to noise ratio would be too unfavorable to detect useful results. Even if a difference is detected between exposed and unexposed pets, how do you extrapolate that information to risk for humans?

Stayner

1. Advantages/Disadvantages for Assessing Community or Individual Exposures

   Fiber analysis in sentinel animals is obviously not a method for assessing individual exposures (of humans), but may be useful for evaluating community exposures. The same limitations of these methods described above for humans would of course also apply to analyses using sentinel animals. One would also have to be concerned as to whether the behaviors resulting in exposures are similar for the sentinel animals as humans.

2. Does this technique result in a high confidence in predicting asbestos exposures above a "background" level? Are results reproducible?
   Same issues as above with the individual methods.

3. What results would be considered an elevated exposure?
   No opinion

4. Correlations Between Biomarkers of Exposure and Asbestos-related Disease
   No opinion

Weissman

- What are the advantages and disadvantages of this technique as a method for assessing community-level exposures to asbestos? Is the technique more suited to measuring exposure on an individual level?

The advantage is the ready availability of material for analysis. The disadvantage is lack of data correlating fiber levels in lungs of various animal species with fiber levels in lungs of similarly exposed humans. Clearly, the technique would be more suited to evaluating community exposures than individual exposures.

- Does this technique result in a high confidence in predicting asbestos exposures above a "background" level? Are results reproducible?

  There is only limited data available for this approach. Published reports exist suggesting utility for analysis of samples from sheep in Sicily and goats in Corsica to evaluate environmental exposures to naturally occurring asbestos.

- What results would be considered an elevated exposure level? If this is not known, what research should be conducted in order to determine test results that would be considered elevated?

  Research is needed using defined populations of animals to answer these questions.

F. Counting asbestos bodies in human tissue, BAL fluid, or sputum

Abraham

1. This one category should be split into three (tissue, BAL, sputum), as each has differing significance, and practicality, invasiveness etc. Fundamentally, asbestos bodies are a relatively simple thing to count, but do not truly represent asbestos fibers of all types equally, nor do asbestos bodies represent uncoated fibers by the same ratio of coated to uncoated fibers from one individual to another.
   - There is a problem quantifying asbestos bodies in BAL or sputum, as noted elsewhere in these commentaries (denominator and sampling problems/limitations).

Carbone (Did not follow a similar format, see General Comments Section at end)

Castranova

Assessment of community or individual exposure
I see no advantage to counting asbestos bodies over counting fibers. The main issue is lower numbers.

Predictive / reproducible –
Variability would be expected to be greatest in sputum and least in tissue samples.

Dodson

Asbestos Bodies in Tissue Samples:

Advantages-Large structures detectable by light microscopy
Disadvantages-Defined for each category of sample

General issues of concern-
1. Represent a population of the longer fibers since ferruginous bodies only form on asbestos fibers longer than eight to ten micrometers.

2. Some individuals (like some species of animals) do not readily form ferruginous bodies.
3. Determination of the numbers of ferruginous bodies in a sample does not permit (via use of a ratio) an assumption of the numbers of uncoated fibers in the sample.
4. The numbers of ferruginous bodies in a sample does not provide any information as to the levels of short fibers or chrysotile fibers in most samples (chrysotile does not readily form ferruginous bodies).

Advantages in Determining the Levels of Asbestos Bodies from Tissue-

1. Asbestos bodies can be seen by light microscopy and therefore evaluation carried out with a less expensive, less technically complex instrument and at less cost than analysis by electron microscopy
2. Ferruginous bodies can be considered as formed on asbestos cores if the section evaluated on a slide contains a body orientated in a proper plane (see references on subject).
3. There are considerable reports relating to the relevance of finding ferruginous bodies in tissue sections and/or the significance of the numbers found in samples isolated from tissue.

Disadvantage in Determining the Levels of Asbestos Bodies from Tissue-

1. Ferruginous coatings can form on nonasbestos fibers and nonfibrous entities thus making it difficult to make a distinction of potential asbestos bodies in a tissue sections
2. Ultimate identification of core material is dependent on Analytical Transmission Electron Microscopy
3. See section at top on General Issues associated with interpreting the meaning of levels of asbestos bodies as related to uncoated asbestos fiber burden in tissue.

Relevant literature-Asbestos Bodies in Tissue Samples:

The Report of the Pneumoconiosis Committee of the College of American Pathologists and the National Institute for Occupational Safety and Health (Craighead et al., 1982) indicated that the finding of several ferruginous bodies in the presence of fibrosis would meet the pathological definition of asbestosis.

Churg and Warnock (1979) evaluated the cores of ferruginous bodies from individuals considered from the general population. Their findings indicated that asbestos bodies were formed predominately on amphiboles. The same authors (Churg and Warnock, 1980) defined environmental exposures as 100 or less ferruginous bodies per gram of wet tissue with one point of reference in their work being a range of from 2 to 84 ferruginous bodies per gram of wet tissue (mean: 33). The latter number is more like the levels in general populations reported by Breeden and Buss (1976), and Roggli et al. (1986). These are also similar to the levels reported from our own studies of tissue from the general population (0-20 ferruginous bodies per gram of wet tissue)(Dodson et al.1999)(Dodson et al.2001a)(Dodson et al.1984). It is not uncommon for the level of ferruginous bodies in members of the general population to be below our limit of detection. One study of thirty-three individual considered as meeting the criteria defined for inclusion as members of the general population from East Texas were found to have levels below our limit of detection in twenty-six individuals (Dodson, 1999).

Couch and Churg (1984) pointed out that tissue sections offer a rather insensitive source for finding ferruginous bodies due to random sampling issues. They concluded, “the demonstration of a single asbestos body on casual inspection of several lung sections implies asbestos exposure many times above background”.

Churg (1989) has offered a useful guide for the defining if a ferruginous body seen in a tissue section is actually an asbestos body. He concluded that a structure had a high likelihood of being an asbestos body when found in a tissue section if it was "a beaded structure formed on a clear, elongated, transparent, usually straight core". By using such a definition a trained analyst can distinguish the vast majority of non-asbestos ferruginous bodies.

Ferruginous bodies form most efficiently in lung tissue however they have been observed in other tissues and work from our laboratory found asbestos bodies formed (at a less efficient rate than in lung tissue) in both the spleen and liver (Dodson et al. 2001b).

A more sensitive method for analyzing tissue for the presence of ferruginous bodies involves destructive elimination of the tissue components and collection of the asbestos bodies and/or uncoated asbestos fibers on a filter (Dodson, 2006).

There are several procedures for isolating ferruginous bodies and uncoated asbestos fibers from tissue, however as noted by Dement (1990) it is imperative that the process avoids disruption or loss of either asbestos bodies or uncoated asbestos fibers. He further suggested that the use of indirect methods (which he indicated have been shown to break up airborne fibers into smaller units) should be avoided during tissue preparation. The process advocated is a more direct method of particulate collection.

Dodson et al. (1996) evaluated the potential for the presence of ferruginous bodies to indicate a definable ratio for the presence of uncoated asbestos bodies. The ratio of uncoated asbestos fibers to asbestos bodies was highly variable.

Asbestos bodies in occupationally exposed individuals are usually found to have amphibole cores. The reasoning for this is that much of the chrysotile inhaled in the lung is of insufficient length to stimulate the formation of ferruginous bodies. If chrysotile is inhaled as a sufficiently long fiber it can stimulate the formation of ferruginous bodies. Holden and Churg (1986) found that 64% of the cores in a study of lung tissue from miners and millers were formed on chrysotile although the majority of the uncoated fiber burden was amphiboles. Levin et al. (1995) found that 72% of the ferruginous bodies isolated from the lung tissue of a clutch refrabricator were formed on chrysotile.

The more common finding regarding the ratio of amphibole to chrysotile cores in ferruginous bodies is represented in an analysis of ferruginous bodies in a group of occupationally exposed individuals with mesothelioma (Dodson et al.1997). Of the 841 ferruginous bodies isolated from the tissue of the 55 individuals only one was formed on a chrysotile core.

As previously mentioned some individuals (as with some animal species) do not seem to be efficient for coating inhaled fibers even when a suitable population of fibers of the appropriate length (Dodson 1984)(Dodson 1985) is in the lung. As an example tissue from two former amosite workers were evaluated following a digestion procedure for the presence of asbestos bodies and uncoated asbestos fibers. No ferruginous bodies were found (within the limits of detection in the model) however the lung tissues were found to have 1.2 and 2.1million amosite fibers/gram of tissue.

Recommendations: Level of ferruginous bodies above that found in general populations indicate either an occupational or paraoccupational exposure had occurred in the past. Appreciably more information and greater sensitivity can be obtained regarding tissue burden of ferruginous bodies if the tissue is digested and cleared filters are assessed by light microscopy rather than attempting

to evaluate tissue sections for ferruginous bodies. The limits on information gained at this level of assessment must be appreciated with recognition that ferruginous bodies represent only the population of longer coated fibers that remain in the tissue at the time of sampling. The level of ferruginous bodies in a sample of tissue tells little regarding the tissue burden of uncoated asbestos fibers in the sample and particularly chrysotile since this form is usually not found as cores of ferruginous bodies.

Asbestos Bodies in Sputum Samples:

Advantages-Large structures detectable by light microscopy
Disadvantages-Defined for each category
General issues of concern-

1. Represent a population of the longer fibers since ferruginous bodies only form on asbestos fibers longer than eight to ten micrometers.
2. Some individuals (like some species of animals) do not readily form ferruginous bodies.
3. Determination of the numbers of ferruginous bodies in a sample does not permit (via use of a ratio) the establishment of uncoated fibers in the sample.
4. The numbers of ferruginous bodies in a sample doe not provide any information as to the levels of short fibers or chrysotile fibers in most samples (chrysotile does not readily form ferruginous bodies).

Relevant literature-Asbestos Bodies in Sputum Samples:

Gupta and Frost (1981) assessed the presence of ferruginous bodies in midday sputum induced and early morning spontaneous sputum samples collected for three following mornings in 5226 individuals. Ferruginous bodies were reported as observed in 15 (0.3%) of the 5226 persons with only six of the 15 having given a history of asbestos exposure.

Bignon et al. (1974) reviewed a series of samples including parenchymal tissue, sputum and gastric juices. The emphasis of study was on presence of ferruginous bodies with the reference to fibers in sputum. Conclusion regarding uncoated fibers in sputum samples: wide range in ratio of coated to uncoated fibers. No data was presented as to fiber types. The evaluation of the samples from 125 patients with various asbestos exposures pointed out a “significant association between the presence of ferruginous bodies in sputum and the degree of asbestos occupational exposure”. In a subset group a comparison was made of the occurrence of ferruginous bodies found in sputum with the concentration of ferruginous bodies in lung parenchyma. They reported an absence of ferruginous bodies in sputum samples when the concentration of parenchymal samples was fewer than 1000 ferruginous bodies per cm^3.

McDonald et al. (1992) reviewed sputum samples from vermiculite miners and concluded that the asbestos body counts in sputum reflected the intensity and duration of past exposure. Additionally they reported on sputa samples from “nearly 600 volunteers from 11 cohorts of workers exposed to asbestos and other mineral fibers”. They concluded that little reliance could be put on the results from a single sputum sample (particularly if negative) from a given individual.

Sebastien and associates (1984) found that sputum samples from inhabitants of the villages of Karain and Tuskoy in central Turkey (areas with a high frequency of mesothelioma) were positive for ferruginous bodies while 94% of the samples collected from neighboring villages were free of ferruginous bodies.

Wheeler and colleagues (1988) reviewed sputum and bronchial washings for the presence of ferruginous bodies from eleven individuals in Houston, Texas. Their conclusions were: 1. Asbestos bodies in sputum and bronchial washings are a specific marker for asbestos exposure; 2. the iron stain is more sensitive and efficient in the detection of asbestos bodies in sputa and bronchial washings than is the Papanicolaou stain; 3. bronchial washings may be more sensitive for the detection of asbestos bodies than sputa; and 4. multiple levels and iron staining of cell blocks increases the yield of asbestos bodies.

Several studies for the significance of ferruginous bodies in sputum samples were carried out on samples obtained from a heavily exposed cohort of former amosite workers at a facility in Tyler, Texas. This type of asbestos that can be inhaled in a longer form and stimulates the formation of ferruginous bodies.

Greenberg et al. (1976) reported on findings including ferruginous bodies from 1,184 sputum samples collected from 456 former workers in the amosite manufacturing facility. The conclusion reflects the insensitivity of sputum analysis for the presence of ferruginous bodies in that only one-third of the former asbestos workers were found to have ferruginous bodies in their multiple samples.
It was noted that ferruginous bodies were most numerous in aerosol-induced sputa specimens and could be readily identified by the routine Papanicolaou stain.

Farley and colleagues (1977) reviewed specimens collected for cytopathological examinations at six month intervals from 628 former workers. There were also 138 samples from control patients evaluated. The conclusion was that the presence of ferruginous bodies in sputa is "evidence of probable significant occupational exposure to asbestos dust. Their absence does not indicate the lack of exposure."

McLarty and associates (1980) reviewed more than 10,000 sputum specimens collected from both aerosol-induced and three day pooled spontaneous specimens over a five year period. These had been collected from the former amosite workers (N-858) and from 188 controls. The conclusions from the screen of the samples from the former amosite workers were that aerosol-induced specimen from non-smokers was more likely to be a satisfactory specimen and to yield more ferruginous bodies than is a spontaneous specimen.

Dodson et al. (1989) reviewed randomly selected samples of sputa prepared by a digestion procedure. The material was reviewed for the presence of ferruginous bodies (light microscopy) and uncoated asbestos fibers (Electron Microscopy) (discussed in section "C"). Samples were from twelve former workers in an amosite manufacturing facility and twelve individuals with no known occupational exposure to asbestos. The variability of finding ferruginous bodies even in samples from heavily exposed individuals was discussed above, as was the relevance of the finding of a ferruginous body in a sputum sample. The findings in this study further emphasized these facts in that no ferruginous bodies were found in the samples from the twelve former amosite workers or the twelve individuals from the general population. Although ten of the samples from the exposed individuals were found to have uncoated amosite fibers when the digests were evaluated by electron microscopy.

Recommendation: If one is to screen sputa samples for the presence of ferruginous bodies it should be recognized that there is great variability of finding such structures in random samples from individuals known to have been exposed to asbestos fibers of a type recognized as readily stimulating the formation of asbestos bodies.

Asbestos Bodies in Bronchoalveolar Lavage Samples

Advantages-Large structures detectable by light microscopy
Disadvantages-Defined for each category of sample General issues of concern-

1. Represent a population of the longer fibers since ferruginous bodies only form on asbestos fibers longer than eight to ten micrometers.
2. Some individuals (like some species of animals) do not readily form ferruginous bodies.
3. Determination of the numbers of ferruginous bodies in a sample does not permit (via use of a ratio) an approximation of numbers of uncoated fibers in the sample.
4. The numbers of ferruginous bodies in a sample does not provide any information as to the levels of short fibers or chrysotile fibers in most samples (chrysotile does not readily form ferruginous bodies).

Advantage in Evaluation of Bronchoalveolar Lavage Samples-Provides material rich in pulmonary macrophages as well as surface material (including dust) from lower airways

Disadvantage in Evaluation of Bronchoalveolar Lavage Samples-The lavage technique is one that involves an invasive procedure and therefore carries some degree of risk for the patient during collection of the sample.

Relevant literature-Asbestos Bodies in Bronchoalveolar Lavage Samples:

Xaubet and colleagues (1986) evaluated respiratory clinical, radiographic, and functional findings with bronchoalveolar lavage (BAL) of cellular changes in 52 asbestos workers (27 with and 25 without asbestosis). Asbestos bodies in BAL were quantified in 34 of 52 asbestos workers (21 with and 13 without asbestos and in the control group). Ferruginous bodies were present in 83% of the asbestos workers but were absent in the control group.

BAL material was evaluated in samples from 108 exposed workers and 57 patients who underwent diagnostic fiberoptic bronchoscopy for various clinical purposes by Sartorelli et al. (2001). Samples were analyzed by phase-contrast light microscopy for the presence of ferruginous bodies and by transmission electron microscopy for determination of the presence and types of uncoated asbestos fibers. 82.2% of the exposed population tested positive for asbestos bodies. The results of the study were interpreted to indicate, “fiber concentration in BALF can be considered as a reliable biomarker of past asbestos exposure, even many years after the end of exposure”.

De Vuyst et al. (1982) assessed the presence of asbestos bodies in lavage material in a group of 62 patients with suspected asbestos related disease, 2 patients with known exposure to asbestos but without related disease, and 40 controls. AB bodies were found in the lavage material from all patients with obvious exposure (28 of 28) most patients with suspected exposure (26 of 28) as well as in 5 of 8 patients without known exposure but with suspicion of asbestos related disease (mesothelioma or pleural plaques). Only 5 of the 40 samples from control subjects were positive but to a low degree: AB counts of less than 1AB/ml of fluid. The conclusions of the study were: “the findings of AB in BAL fluid correlates with the occupational risk and can disclose unknown exposure better than a questionnaire, but a positive lavage is not proof of disease”.

The same group (DeVuyst et al. 1983) used assessment of BAL material by ATEM to aid in the diagnosis of “imported” pleural asbestosis. In this case report a Turkish woman had immigrated to Belgium and had no history of occupational exposure to asbestos. However the investigators

found a type of asbestos in the lavage material recognized as naturally occurring as an environmental dust in the site of her original home.

An additional study by De Vuyst and associates (1987a) assessed the presence of asbestos bodies in lavage material from 563 subjects. The presence of asbestos bodies was found to reflect occupational exposure to asbestos and the bodies were rarely found in unexposed control subjects at concentrations of >1/ml of fluid. The conclusions of this study were the presence of asbestos bodies in BAL fluid appears to be a marker of exposure and not of disease. "AB are more likely to be detected in patients presenting with asbestos-related diseases but in whom exposure is not confirmed by the occupational history (65 of 78 cases)".

Two interesting studies involving light and Analytical Transmission Electron Microscopy evaluation of lavage material was reported by DeVuyst and colleagues. In one study (De Vuyst et al. 1987b) evaluation of lavage material from workers exposed to French, American or Australian talc. There were differences in the uncoated asbestos fiber types, asbestos body numbers and other mineral content based on the source of the talc to which the workers were exposed.

De Vuyst et al. (1988) assessed asbestos body content in bronchoalveolar lavage fluids compared with digested lung tissue from one hundred consecutive subjects submitted to a thoracotomy procedure mostly for lung cancer. "Absence of AB's or low AB counts (<1 AB/ml) in BAL corresponded in about 70% of cases to concentrations of less than 1,000 AB/gm and 100% of cases to concentrations less than 10,000 AB/gm. Above 10 AB/ms GAL, all lung tissues contained more than 10,000 AB/gm. Since lung tissue is not readily available in patients undergoing assessment of their asbestos exposure, BAL fluid analysis seems to be a useful too to evaluate lung AB concentrations (when conditions of patient permit)".

A study by Corhay et al. (1990) compared the findings of ferruginous bodies in BAL collected from 65 steel workers with findings from lavage material collected from 54 white-collar workers. Analysis of core material of ferruginous bodies collected from lavage material from steel workers indicated the core materials were mainly amphiboles. "The BALF from steel workers who denied any contact with asbestos revealed an increased AB burden vs. controls. This demonstrates that steel workers may be subject to an occult exposure to amphiboles in the steel plant environment".

Tuomi et al. (1992) evaluated the alveolar content of fibers and asbestos bodies in bronchoalveolar lavage from 21 asbestos sprayers (exposed mainly to crocidolite) by light, Scanning Electron Microscopy (SEM), and Transmission Electron Microscopy (TEM) Asbestos body counts as determined by light microscopy exceeded 1/ml in 95% of the cases. The total fiber count by TEM exceeded 1000 fibers/ml in 70% of the cases. The conclusion reached was the counting of asbestos bodies alone might underestimate the total load.

BAL material from 30 utility workers and 30 normal volunteers was evaluated for the presence of AB's in a study by Vathesatogkit et al. (2004). ABs were found frequently in the BAL vs. none in sample from the controls. The conclusions from the study were "the presence of AB in BAL cells is associated with a higher prevalence of parenchymal abnormalities, respiratory symptoms, and reduced pulmonary functions".

Dodson and colleagues (1991) compared the findings of AB and uncoated asbestos fibers (determined light and analytical transmission electron microscopy) from lavage samples obtained from twelve former asbestos workers and eleven individuals considered as being from the general

population. No ferruginous bodies were found in the samples from the general population however ferruginous bodies were found in lavage material from ten of the twelve individuals from the exposed group. The lavage from only one of the members of the control group (a blue collar individual) was found to be positive for uncoated asbestos (one fiber) whereas all of the exposed group were found to have uncoated fibers of asbestos in their lavage samples. The sensitivity of analysis for the presence of asbestos in lavage material is enhanced when the digested material is screened by Analytical Transmission Electron Microscopy for the presence of uncoated asbestos fibers.

An additional study by Dodson and associates (1993) analyzed the ferruginous bodies found in bronchoalveolar lavage from foundry workers. The analysis of the cores of the ferruginous bodies by light and Analytical Transmission Electron Microscopy confirmed the core material from various forms of ferruginous bodies including some formed on elongated non-asbestos structures that were difficult to distinguish in tissue sections from asbestos bodies.

Roggli and colleagues (1994) evaluated the bronchoalveolar lavage fluid by light microscopy and Scanning Electron Microscopy obtained from 9 patients with asbestosis, 17 asbestos exposed but without asbestosis, 15 with idiopathic pulmonary fibrosis and 9 nonexposed volunteers. They concluded that "the findings of >1 AB per 10^6 cells or 1AB/ml. BALF by light microscopy and of asbestos bodies or commercial amphiboles by SEM are indicative of considerable exposure to asbestos in the majority of cases".

Recommendation: If one is to screen lavage samples by light microscopy for the presence of ferruginous bodies it should be recognized that the presence of a ferruginous body indicates a level of past exposure to asbestos that is different than that observed in the samples from most of the general populations. It should also be remembered that the finding of a ferruginous body indicates that an exposure to longer fibers of asbestos had occurred in the past but does not mean there is an asbestos related disease present. A more definitive assessment of lavage material can be achieved when the data regarding the numbers of ferruginous bodies is combined with data obtained by analytical transmission electron microcopy defines the presence and types of uncoated asbestos fibers in a sample.

Gunter (Did not follow a similar format, see General Comments Section at end)

Hillerdal

see above C and D

Roggli

Trained observers readily identify asbestos bodies, and no special instrumentation is required beyond a light microscope. Reproducibility between laboratories is much better for asbestos bodies than for fibers detected by electron microscopy.[4] There are more data available regarding background ranges for asbestos bodies than for fibers detected by EM. Asbestos bodies correlate well with the concentration of amphibole fibers 5 µm or greater in length, which are the fibers that correlate best with asbestos-related disease. *The greatest amount of information is obtained when analysis of asbestos bodies by light microscopy is combined with analysis of fibers by electron microscopy.*

Asbestos bodies are a poor indicator of previous exposure to chrysotile, and some individuals do not seem to produce asbestos bodies very readily. Asbestos bodies are a highly specific but poorly sensitive marker of asbestos exposure in sputum samples.[3] Although most asbestos bodies can be

distinguished from non-asbestos ferruginous bodies by light microscopy, ferruginous bodies forming on erionite or refractory ceramic fiber cores are not distinguishable from asbestos bodies at the light microscopic level.[2]

Stayner

1. Advantages/Disadvantages for Assessing Community or Individual Exposures

   The primary advantage of this method is that it is totally non-invasive and safe. The method also appears to be highly specific, which is to say that individuals who have asbestos bodies are very likely to have been highly exposed to asbestos [e.g., Teschler et al. 1996]. The primary disadvantage of this method is its lack of sensitivity for detecting asbestos exposures. The sensitivity is improved if BAL is used rather than sputum [Paris et al 2002]. Still even using BAL the sensitivity of this method for detecting exposure appears to be lower than using TEM to count fibers in tissues [Sartorelli et al. 2001]. Thus obtaining a negative finding should not be taken as strong evidence for a lack of exposure even to high levels of asbestos.

2. Does this technique result in a high confidence in predicting asbestos exposures above a "background" level? Are results reproducible?

   There appears to be a high degree of laboratory variability of these tests suggesting a lack of reproducibility [ATS 2004].

3. What results would be considered an elevated exposure?

   No opinion

4. Correlations Between Biomarkers of Exposure and Asbestos-related Disease

   The presence of asbestos bodies in sputum has been associated with increased risk of interstitial pulmonary disease and pleural fibrosis and to spirometric findings of restrictive lung disease [McLarty et al. 1980]. Among individuals with asbestos to exposure, the presence of asbestos bodies in BAL has been associated with a higher prevalence of parenchymal abnormalities, respiratory symptoms, and reduced pulmonary function [Vathesatogkit et al. 2004].

Weissman

- What are the advantages and disadvantages of this technique as a method for assessing community-level exposures to asbestos? Is the technique more suited to measuring exposure on an individual level?

  Counting asbestos bodies by light microscopy is a well-established method to assess burden of asbestos exposure. Well-established normal levels exist for human tissue and BAL fluid; while it has been established that identification of asbestos bodies in sputum is specific, but not sensitive, for increased lung asbestos burden. A major disadvantage of this approach is that asbestos bodies in general form on amphibole fibers greater than 8 microns in length. This is a particular problem in assessing community exposures to cleavage fragments, many of which will shorter and thus not form asbestos bodies. Quantifying asbestos bodies in tissue or BAL fluid are useful both for assessing individual lung burden and possible for assessing community levels of exposure. Due to the lack of sensitivity but noninvasive nature of sputum sampling, it is probably more applicable to assessing population exposures than individual exposures.

- Does this technique result in a high confidence in predicting asbestos exposures above a "background" level? Are results reproducible?

  Assessment of asbestos bodies in various tissues and samples has been well documented as correlated with lung burden. Because the methods for detecting asbestos bodies by light microscopy are "low tech" and simple to perform, there is greater reproducibility than for more complex analyses such as those using electron microscopy (as noted in the previously-cited ERS Working Group report).

- What results would be considered an elevated exposure level? If this is not known, what research should be conducted in order to determine test results that would be considered elevated?

  Lung tissue: > 1000 AB per gram dry lung tissue; or 1-2 AB per tissue section.
  BAL > 1 AB per ml lavage fluid (associated with high probability of > 1000 AB per gram dry lung tissue).
  Sputum: any AB found.

G. Blood mesothelin or osteopontin levels, or other blood tests

Abraham

1. This novel technique is not yet well enough tested and quantified and reproduced to be used without additional research for actual community assessment. It does NOT measure exposure at all, but seems from initial reports to be related to REACTION to exposure that MAY occur in some but not necessarily all exposed persons.

Carbone (Did not follow a similar format, see General Comments Section at end)

Castranova

Assessment of community or individual exposure
Measures mesothelioma or tumors not exposure. Not elevated in non-diseased, exposed individuals.

Predictive / reproducible –
Not relevant in exposure assessment of non-diseased subjects.

Dodson

Advantage in using mesothelin or osteopontin levels, or other blood tests
1. Permits collection of materials at given site and shipped to site with expertise in analytical capability for conducting evaluation.
2. Methodology should permit analysis to be conducted at multiple labs if protocol has acceptable level of inherent reproducibility

Disadvantages in using mesothelin or osteopontin levels, or other blood tests
1. Very little if acceptable level of reproducibility inherent in model
   Need to have established control data for comparison with findings from exposed groups

Gunter (Did not follow a similar format, see General Comments Section at end)

Hillerdal

Positive only in cases of mesothelioma; False positives exist; do not show EXPOSURE but DISEASE; large ethical questions (what do you do for instance when the person has increased mesothelin levels but no other (radiological etc) signs of disease?

Roggli

In the molecular age of medicine, markers such as these hold the potential promise of identifying individuals at risk for the development of mesothelioma. The tests are non-invasive, and blood levels of patients with mesothelioma are much higher than those of individuals without this disease. Unfortunately, these are not ready for 'prime time' for a number of reasons.

Published reviews of these substances indicate that they are not sensitive or specific enough to use as a screening technique. Thus the false positive and false negative rates would be unacceptably high. In a population with relatively low-level exposure to asbestos (e.g., environmental/neighborhood exposures), the expected rates of mesothelioma (far less than 1%) would be so low that false positive results become a real problem, with the potential for doing more harm than good through needless worry or over-concern (or unnecessary treatment). Furthermore, the role of these tests in detecting early disease is unknown. Patients with established disease (the ones most likely to show a positive result) are for the most part currently untreatable. We do not know whether these tests can distinguish atypical mesothelial hyperplasia from early pre-invasive mesothelioma. We also do not know what percentage of cases with atypical mesothelial hyperplasia will go on to develop mesothelioma.

Stayner

Neither of these tests appears to be useful indicators of exposure to asbestos, but rather potential early markers of disease for mesothelioma. In the study by Pass et al. [2005], osteopontin levels were found to be similar among individuals who had a history of exposure to asbestos, and individuals who were never exposed. Osteopontin was found to be substantially higher among individuals with mesothelioma when compared with either individuals with a history of asbestos exposure or non-exposed subjects. Similarly, the paper by Robinson et al. [2005] demonstrates that mesothelin is a sensitive and specific test for mesothelioma. It does not demonstrate that mesothelin is a useful marker of exposure. Thus these 2 proteins appear to be potentially useful for the early diagnosis of mesothelioma, but not for exposure assessment.

Weissman

- What are the advantages and disadvantages of this technique as a method for assessing community-level exposures to asbestos? Is the technique more suited to measuring exposure on an individual level?

  An advantage is that collection of venous blood by venipuncture is noninvasive and can be performed on large numbers of individuals. A disadvantage is that currently available blood tests do not have established utility for assessing asbestos exposure.

- Does this technique result in a high confidence in predicting asbestos exposures above a "background" level? Are results reproducible?

Serum osteopontin levels were recently documented to be more elevated in those with longer asbestos exposures than shorter ones, but there was much overlap between populations (N Engl J Med 2005:353:1564-1573). Reproducibility of the test is unclear. Serum soluble mesothelin-related protein was reported to be associated with development of mesothelioma; there is no data about relation of levels to asbestos exposure levels (Lung Cancer 2005; 49S1:S109-S111). Reproducibility of the test is unclear.

Mean serum Clara cell protein (CC16) concentration has been reported as increased in asbestos exposure, but utility is also unclear.

- What results would be considered an elevated exposure level? If this is not known, what research should be conducted in order to determine test results that would be considered elevated?

  The answers to these questions are currently unclear. It is unclear if results of these tests would correlate more that weakly with lung asbestos fiber burdens.

H. Clinical tests such as spirometry to look for functional changes

Abraham

Spirometry is far too non-specific to be used for such purposes.

Carbone (Did not follow a similar format, see General Comments Section at end)

Castranova

Assessment of community or individual exposure
Not sensitive enough to detect exposure in the absence of disease

Predictive / reproducible –
Lacks sensitivity.

Dodson

Advantage in using Clinical Tests such as Spirometry to Look for Functional Changes:
1. Well established clinical procedure with control data. Important in assessing patients for respiratory changes including those with pneumoconiosis.
2. Essentially non-invasive

Disadvantage in using Clinical Tests such as Spirometry to Look for Functional Changes:
None

Gunter (Did not follow a similar format, see General Comments Section at end)

Hillerdal

The problem is again that this is a measurement of disease; significant changes occur only when there is a lung fibrosis (asbestosis) of at least some degree; very early changes with small decrease in lung

function can be seen in large populations only and also is unspecific, must be correlated mainly to smoking but also some other factors.

Roggli

These tests are readily available, non-invasive, easy to perform, and normal ranges are well established. Large numbers of individuals could be screened relatively cheaply and easily. Since this procedure is performed on living individuals, the findings could be correlated with historical information obtained from the patient regarding occupation, smoking history, and residential history.

Functional changes from asbestos exposure occur with relatively high levels of exposure occupationally, and are unlikely to be detectable in populations exposed to environmental sources of asbestos fibers. Considerable confounding can be expected from cigarette smoking and other lung disease not related to asbestos in the population. The signal to noise ratio for this technique is likely to be far too high for useful information to be obtained.

Stayner

1. Advantages/Disadvantages for Assessing Community or Individual Exposures

   Spirometry or pulmonary function testing is generally viewed as a method for assessing respiratory disease (e.g. obstructive and restrictive diseases) and not as a method for measuring exposure. Individuals with asbestosis and other asbestos related diseases may show signs of restrictive and possibly obstructive lung disease based on pulmonary function testing [e.g. see Ohar et al. 2004]. However, these tests are not at all specific for asbestos as cigarette smoking and exposure to other occupational hazards (e.g. silica) may also result in changes in pulmonary function. Therefore it does not appear that pulmonary function testing would be a useful method for assessing exposures to asbestos for either individuals or communities.

Weissman

- What are the advantages and disadvantages of this technique as a method for assessing community-level exposures to asbestos? Is the technique more suited to measuring exposure on an individual level?

  Evaluation of lung function using tests such as spirometry and single breath diffusion capacity (DLCO) is noninvasive and relatively inexpensive. Unfortunately, although measures of pulmonary function show correlations exposure, they are both insensitive and nonspecific.

- Does this technique result in a high confidence in predicting asbestos exposures above a "background" level? Are results reproducible?

  As noted, results of physiological tests are, in isolation, not useful for predicting asbestos exposure level in a population. The results are reproducible when tests are performed in compliance with established, internationally accepted guidelines (such as those of the ATS and ERS).

- What results would be considered an elevated exposure level? If this is not known, what research should be conducted in order to determine test results that would be considered elevated?

  Not applicable – abnormal tests of physiology are not tightly linked to exposure levels.

I. Clinical tests such as x-ray or CT scans to look for pathological changes (pleural plaques, pleural thickening, and pleural effusions)

Abraham

1. This is widely used epidemiologically and well founded for screening for observable effects of asbestos exposures. It will show REACTION or OUTCOME from exposure and not actual exposure, of course.
   - These techniques are reproducible and probably have high confidence in demonstrating PAST exposure in a population. However, great caution must be exercised in accepting negative findings of such surveys as indication of lack of exposure, owing mostly to LATENCY issues. For example, in a community (e.g., El Dorado County areas) with more recent and ongoing alleged exposures, radiologic markers such as pleural plaques, etc may not be evident for decades in a large enough number of persons to detect any effect of such exposures.

Carbone (Did not follow a similar format, see General Comments Section at end)

Castranova

Assessment of community or individual exposure
Pleural changes are an indicator of fiber exposure and occur prior to identification of disease.

Must have a strong history to relate to exposure at an environmental site.

Predictive / reproducible –
Some subjectivity in reading.

Dodson

Advantage in using Clinical Tests such as X-ray or CT scans to look for pathological changes (pleural plaques, pleural thickening, and pleural effusions):
1. Well established clinical procedures with control data and data from patients with pneumoconiosis
2. Essentially non-invasive.

Disadvantage in using Clinical Tests as listed in I:
Costs associated with procedures and availability of sites in proximity to areas of exposures.

Gunter (Did not follow a similar format, see General Comments Section at end)

Hillerdal

Problem: long latency time (about 20-30 years) for pleural plaques, early ones prone to overdiagnosis;

Pleural effusions: unspecific, can be due to other causes
Pleural thickening: fairly unspecific, can be due to other causes, necessitates fairly high exposure and have rarely been seen in environmental exposure.

If a fairly large number of people (probably around 80-100) who:
1. are at least 40 years old;

2. have lived all their life (or at least 40 years) in the exposed area and the exposure is not due to some recent changes;
3. have no other known exposure to asbestos
are available, the presence of plaques is an excellent marker of exposure.

Roggli

Chest x-rays as a screening technique are relatively inexpensive and can be applied to a large population. CT scans are considerably more expensive and their utility as a screening technique is questionable at present. Both techniques are non-invasive but are associated with a finite radiation dose and therefore a finite risk of radiation-induced malignancy.

There is a wide range of prevalences of pleural plaques that has been reported in the general population, and the chest x-ray as a screening tool is somewhat insensitive to the detection of plaques.[5] Without knowledge of the expected rate of plaques in the control population, it is difficult to determine the statistical power necessary to find a difference in plaque detection between exposed and non-exposed groups. There is considerable interobserver variability in the interpretation of plain films (x-rays) for the presence of plaques and pleural thickening. [6] There are too many different causes of pleural effusion for this to be a useful marker of exposure. The signal to noise ratio for these techniques is likely to be too high for useful information to be obtained.

Stayner

1. Advantages/Disadvantages for Assessing Community or Individual Exposures

Pleural plaques are regarded by most scientists as a useful marker of past exposure to asbestos. They may be measured using non-invasive radiographic techniques. A possible concern is the exposure to radiation that these methods entail, although the risk from these exposures is likely to be minimal. Pleural thickenings or effusions are less specific to asbestos exposure then pleural plaques. Pleural thickenings are commonly seen in patients with prior fungal or tuberculosis infections [Cugell and Kamp 2004].

2. Does this technique result in a high confidence in predicting asbestos exposures above a "background" level? Are results reproducible?

CT scans appear to have a greater sensitivity for detecting pleural plaques than X-rays. However, pleural plaques may be detected at autopsy that were not detected by either X-ray or CT scans [see review by Cugell and Kamp 2004].

3. What results would be considered an elevated exposure?
No opinion

4. Correlations Between Biomarkers of Exposure and Asbestos-related Disease

Whether or not pleural plaques are predictors of mesothelioma or lung cancer risk remains controversial. Diffuse pleural thickening has clearly been shown to be associated with severe restrictive pulmonary disease [see recent review by Cugell and Kamp 2004].

Weissman

- What are the advantages and disadvantages of this technique as a method for assessing community-level exposures to asbestos? Is the technique more suited to measuring exposure on an individual level?

  The advantage of chest imaging studies such as chest radiograph or chest CT scan is that the procedures are noninvasive. Chest radiographs are more easily performed in large populations, are cheaper, and cause less exposure to radiation than chest CT scans. Chest CT scans, despite their greater expense, detect pleural changes with greater sensitivity and specificity and parenchymal changes with greater sensitivity and probably greater specificity. A disadvantage of chest imaging in assessing community asbestos exposure is that, with the exception of asbestos pleural effusions, abnormalities occur with long latency, often 20 years or more. These tests are applicable to both individuals and populations.

- Does this technique result in a high confidence in predicting asbestos exposures above a "background" level? Are results reproducible?

  Pleural plaques, particularly multiple lesions, are almost invariably associated with asbestos exposure. Pleural effusion, diffuse pleural thickening, rounded atelectasis, and interstitial changes all have extensive differential diagnoses and may be caused by conditions other than asbestos exposure. To achieve high reproducibility, chest radiographs can be evaluated by multiple readers using the ILO classification system. There can be great inter-reader variability, so epidemiologic studies should use at least two, and preferably more readers. Although a standardized scheme has been proposed for evaluating high-resolution chest CT scans, it has not been generally accepted. Still, a body of literature documents the greater sensitivity and specificity of HRCT.

- What results would be considered an elevated exposure level? If this is not known, what research should be conducted in order to determine test results that would be considered elevated?

  Although radiological abnormality can be expressed as a continuous variable, in general practice it is most often expressed as a categorical variable – positive or negative.

RANKING OF TECHNIQUES BY EXPERTS

Please consider the following list of potential techniques for assessing asbestos exposure and/or disease in communities in addressing the questions posed below:

A Fiber burden of lung tissue collected from humans at autopsy
B Fiber burden of lung tissue collected from living humans
C Fiber content of sputum samples collected from living humans
D Fiber content of bronchoalveolar lavage (BAL) fluid of living humans
E Fiber analysis techniques (tissue, BAL fluid, or sputum) in sentinel animals (household pets or other resident animal species)
F Counting asbestos bodies in human tissue, BAL fluid, or sputum
G Blood mesothelin or osteopontin levels, or other blood tests
H Clinical tests such as spirometry to look for functional changes
I Clinical tests such as x-ray or CT scans to look for pathological changes (pleural plaques, pleural thickening, and pleural effusions)

Abraham

COST: G<H<I<F<C<A<E<D<B
PRACTICABILITY: H>G>I>F>C>E>D>B>A
INVASIVENESS: B>D>E>C>G>A>I>H>E
CONFIDENCE IN RESULTS IN ASSESSING COMMUNITY EXPOSURES:
B>A>E>D>C>F>I>G>H

Carbone (Did not follow a similar format, see General Comments Section at end)

Castranova

Cost, practicability, invasiveness, and confidence –
Good – I, A
Medium – D, E, F
Low – B, C
Not applicable – G, H

What would be an elevated level?
For all potential techniques, the database for background levels is small. Further research to build such a database for background and for exposure response is required.

Dodson

No Comment

Gunter

I am somewhat hesitate [sic] to rank these methods based on my limited knowledge of them, but it would seem to me that lung tissues samples would be the most reliable, but one of the most invasive, followed by light and electron microscopic analysis of BAL. I have often thought of using wild animals (e.g., deer and elk) to help determine background dust levels in remote areas. Also, along

those same lines, I have thought that it might be worthwhile to remove the entire dust load from the lungs instead of just portions. However, while the Corsican goat lung fiber content seemed to correlated to geological settings, the values differ significantly from background levels for humans. Problems with using such animals might relate to breathing zones and would need to be corrected for such things as body weights.

I think there is an obvious correlation between cost, invasiveness, and reliability of A-I (the more expensive ones, are the most invasive, and most reliable), with the exception of the serum testing. As an outsider to this field it would seem to me that serum testing would be the most worthwhile area to purse for a screening. (See section 4 for thoughts on other "outside-the-box" screening methods.)

Hillerdal

If the persons in I are available, this is by far the best method. Any person fulfilling these criteria should have an X-ray (or preferably CT scan) and a spirometry.

In other cases: Probably sputum samples (for Asbestos bodies and Fibers) come first.

Roggli

Does this technique result in a high confidence in predicting asbestos exposures above a "background" level? Are results reproducible?

A. *Fiber burden of lung tissue collected from humans at autopsy*
This technique has the highest confidence of predicting asbestos exposures above a "background" level for the individual patient. The results are fairly reproducible.[1]

B. *Fiber burden of lung tissue collected from living humans*
Same as **A**.

C. *Fiber content of sputum samples collected from living humans*
This technique is insensitive for predicting asbestos exposures above "background" level for the individual patient, although it is highly specific. Reproducibility is less well defined than that for fiber burden of lung tissue.

D. *Fiber content of bronchoalveolar lavage fluid (BALF) of living humans*
This technique is more sensitive than analysis of sputum for predicting asbestos exposures above "background" level for the individual patient, but less so than lung fiber burden analysis. The results are fairly reproducible.

E. *Fiber analysis techniques in sentinel animals (e.g., household pets)*
The predictive value of this method for human exposures above "background" is largely unknown. The reproducibility should be similar to that of human lung fiber burden studies but little data are available.

F. *Counting asbestos bodies in human tissue, BALF, or sputum*
The predictive value of this method for human exposures above "background" level for the individual patient is greatest for lung tissue, least for sputum. The results are fairly reproducible and interlaboratory agreement is good.[1]

G. *Blood mesothelin or osteopontin levels, or other blood tests*
The predictive value of this method for human exposures above "background" level for the individual patient is unknown but is likely to be poor. Reproducibility of the test results is good.

H. *Clinical tests such as spirometry to look for functional changes*
The predictive value of this method for human exposures above "background" level for the individual patient is likely to be poor, since spirometry is insensitive to low levels of exposure above background. Reproducibility of this methodology is good, as it has become well standardized.

I. *Clinical tests such as x-ray or CT scans to look for pathological changes (pleural plaques, pleural thickening, and pleural effusions)*
The predictive value of chest x-ray for human exposures above "background" level for the individual patient is likely to be poor, since plain films are insensitive for the detection of plaques and many individuals with exposures above "background" level do not have plaques. Pleural effusion alone is too non-specific to be a useful predictive marker of asbestos exposure. Reproducibility of chest film interpretation is poor. CT scans are more sensitive but suffer from the same problem that many individuals with exposures above "background" level do not have plaques. Reproducibility of CT scan interpretation is less well defined.

What results would be considered an elevated exposure level?

A. *Fiber burden of lung tissue collected from humans at autopsy*
This will vary from laboratory to laboratory, depending upon the methodology employed.[1] For our laboratory using the SEM and counting fibers 5 µm or greater in length, the upper limit of normal for total fibers is 13,000 per gram of wet lung, and the median is approximately 3100 fibers/gm. For non-commercial amphibole fibers (e.g., tremolite), our upper limit of normal is 2500 fibers per gram of wet lung. For commercial amphiboles, our upper range is below the detection limit, which is approximately 500 fibers/gm. For chrysotile, our upper limit of normal is 1000 fibers per gram.[1]

B. *Fiber burden of lung tissue collected from living humans*
Same as for **A**.

C. *Fiber content of sputum samples collected from living humans*
There are no normal ranges for our lab, and little information is published on this subject.

D. *Fiber content of bronchoalveolar lavage fluid (BALF) of living humans*
Our control results for BALF are fewer than 500 fibers per million cells and fewer than 300 fibers per ml BALF. The detection of asbestos bodies by SEM or of commercial amphibole fibers is indicative of an occupational exposure.

E. *Fiber analysis techniques in sentinel animals (e.g., household pets)*
Unknown. For this technique to be useful, a careful 'case-control' study would have to be performed comparing animals with and without exposure to the source in question.

F. *Counting asbestos bodies in human tissue, BALF, or sputum*
Our normal range for human lung tissue samples is 0-20 asbestos bodies per gram of wet lung tissue, with a median value of 2-3 AB/gm.[1] For BALF, our normal range is fewer than 3 asbestos bodies per million cells recovered or fewer than 1 asbestos body per ml BALF. For sputum, the normal value is none detected.

G. *Blood mesothelin or osteopontin levels, or other blood tests*
For osteopontin, the established cutoff value for subjects with and without mesothelioma was 48.3 ng/ml. There was no significant difference for those with and without asbestos exposure.[7] I can't tell from the Robinson manuscript what the cutoff value is for mesothelin or whether there is a significant difference for those with and without asbestos exposure.[8]

H. *Clinical tests such as spirometry to look for functional changes*
Normal ranges for spirometry are typically greater than 80% of predicted value. There is no known correlation with exposure level, except that patients with very high exposures tend to have restrictive defects on spirometry.

I. *Clinical tests such as x-ray or CT scans to look for pathological changes (pleural plaques, pleural thickening, and pleural effusions)*
Detection of pleural plaques, pleural thickening, or pleural effusion would be considered an abnormal result. False negatives as well as false positives can occur. Unilateral plaques, pleural thickening, and pleural effusions can have causes other than asbestos exposure. Patients with exposure above background may have none of these findings.

Ranking of Tests (Best to Worst):

Cost	**Practicability**	**Invasiveness**	**Confidence in Results**
H	H	H	A=B
F	G	C	F=D
G	I	G	C
I	F	I	E
A=B=C=E	C	E	I
D	A=B=E	F=B=D	H
	D	A	G

Stayner

Table 1: Subjective ratings of methods for asbestos biomarkers of exposures

Method	**Cost**	**Practicality**	**Invasiveness**	**Confidence**
A. Fiber burden human lungs autopsy	No Opinion	High	Low	High for amphiboles, Low for Chrysotile
B. Fiber burden from living humans	No Opinion	Low	High	Medium for amphiboles, Low for Chrysotile
C. Fiber content sputum	No Opinion	High	Non	Medium for amphiboles, Low for Chrysotile

D. Fiber content BAL	No Opinion	Medium	Medium	Medium for amphiboles, Low for Chrysotile
E. Fiber analysis animals	No Opinion	Medium	Not applicable	Medium for amphiboles, Low for Chrysotile
F. Counting asbestos bodies in human tissues	No Opinion	High	Non (sputum) to Low (BAL)	High for high exposures to amphiboles
G. Mesothelin or Osteopontin	No Opinion	High	Low	Low
H. Clinical tests - spirometry	No Opinion	High	Low	Low
I. Clinical tests X rays CT scans	No Opinion	High	Low	Low

Weissman

A Fiber burden of lung tissue collected from humans at autopsy
Cost: high
Practicability: medium (using small subset of population)
Invasiveness: low
Confidence in results: high

B Fiber burden of lung tissue collected from living humans
Cost: high
Practicability: low to medium (using small subset of population)
Invasiveness: high (if extra samples are taken beyond those clinically needed)
Confidence in results: high

C Fiber content of sputum samples collected from living humans
Cost: medium
Practicability: medium
Invasiveness: low
Confidence in results: low to medium (depending on study design, especially controls)

D Fiber content of bronchoalveolar lavage (BAL) fluid of living humans
Cost: high
Practicability: low to medium (using small subset of population)
Invasiveness: medium to high
Confidence in results: medium (depending on study design, especially controls)

E Fiber analysis techniques (tissue, BAL fluid, or sputum) in sentinel animals (household pets or other resident animal species)
Cost: medium
Practicability: medium
Invasiveness: low
Confidence in results: unknown, ranging low to medium (depending on study design, especially controls)

F Counting asbestos bodies in human tissue, BAL fluid, or sputum
NOTE: ineffective for exposures to short fibers, such as cleavage fragments. Ratings are for exposures to asbestiform amphibole fibers.
Cost: Tissue, BAL – high; sputum – medium
Practicability: Tissue, BAL – low to medium; sputum – medium
Invasiveness: Tissue – autopsy low, surgical high; BAL – medium to high; sputum – low
Confidence in results: tissue, BAL – high; sputum – low to medium

G Blood mesothelin or osteopontin levels, or other blood tests
Cost: medium
Practicability: can be done, so high; but usefulness of tests is unknown
Invasiveness: low
Confidence in results: low, because tests are not standardized and meaning of results is unclear

H Clinical tests such as spirometry to look for functional changes
Cost: low to medium
Practicability: medium to high
Invasiveness: low
Confidence in results: Low if used in isolation to assess for asbestos exposure. High if used purely to assess for functional impairment without regard to causation.

I Clinical tests such as x-ray or CT scans to look for pathological changes (pleural plaques, pleural thickening, and pleural effusions)
Cost: medium (radiograph) to high (CT)
Practicability: high (radiograph), low to medium (CT)

Invasiveness: low

Confidence in results: Only multiple plaques are reasonably specific for asbestos exposure. In general, high confidence in results but low confidence that they reflect causation by asbestos.

CORRELATIONS BETWEEN BIOMARKERS OF EXPOSURE AND ASBESTOS-RELATED DISEASE

Abraham

General comment: It is not clear to this panel member that the results of finding evidence of past exposures by these biomarkers can really be used to assess the RISK of disease? This may be an impossible task at present. The only current way to assess RISK of future disease is to correlate KNOWN or measured EXPOSURES with epidemiologic studies of RISK based on identical measurement methods. [a commentary on some 'risks' of changing measurement criteria is contained on the website http://www.upstate.edu/pathenvi/studies/case8.htm]

A Fiber burden of lung tissue collected from humans at autopsy: good correlation with asbestosis. Not great correlation for individual cases for mesothelioma or lung cancer

B Fiber burden of lung tissue collected from living humans: good correlation with asbestosis. Not great correlation for individual cases for mesothelioma or lung cancer

C Fiber content of sputum samples collected from living humans: needs more research to have more reliable quantification to allow correlations to be adequately assessed

D Fiber content of bronchoalveolar lavage (BAL) fluid of living humans: needs more research to have more reliable quantification to allow correlations to be adequately assessed

E Fiber analysis techniques (tissue, BAL fluid, or sputum) in sentinel animals (household pets or other resident animal species): not enough data to allow reliable translation from animal lung burden or other data to human population risk

F Counting asbestos bodies in human tissue, BAL fluid, or sputum: needs more research to have more reliable quantification to allow correlations to be adequately assessed [Sartorelli et al 2001 a good example of important work in this direction]

G Blood mesothelin or osteopontin levels, or other blood tests: needs more research to have more reliable quantification to allow correlations to be adequately assessed

H Clinical tests such as spirometry to look for functional changes: no value for the purposes of this panel's charges

I Clinical tests such as x-ray or CT scans to look for pathological changes (pleural plaques, pleural thickening, and pleural effusions): well established correlations between radiologic pleural changes and risks of further asbestos-related disease, but more research needed as noted above, with respect to populations with more recent and ongoing exposures to asbestos.

Carbone (Did not follow a similar format, see General Comments Section at end)

Castranova

A. Cancer in an individual
High – G, I
Medium – B, C, D, F (little dose – response data available to predict disease)
Low – A (too late), H (not sensitive), E (not an individual)

B. Non-Cancer in an individual
High – I
Medium – B, C, D, F (little dose – response data available to predict disease)
Low – A (too late), H (low sensitivity), E (not an individual), G (not for non-cancer).

Dodson (See comments above for Technique A-I)

Gunter

It seemed the Dodson et al. (2005) paper attempted to address this very question. In that paper, and several of the others distributed, it seemed that more statistical analysis of the data might show, or not show, some of the correlations between diseases and biomarkers. It would seem worthwhile to assemble as much of these sorts of data sets (e.g., Dodson et al. 2005) and conduct thorough statistical studies to try and tease these correlations from the already collected data.

I noticed that "dose" was left out of the list. However, in several of the papers it was pointed out that dose was one of the best predictors. Possibly dose should be added back to the list, and attempts made to find predictors of dose, such as local rocks types for environmental exposures. The California Geologic Survey and the USGS have already started to pursue this direction by producing geologic maps showing rock types that might contain asbestos minerals.

Hillerdal

Any findings of fibers and/or asbestos bodies in sputum or tissue indicates an exposure and thus an increased risk for asbestos-related disease. The risk is relative to number and type of fibers found.

Pleural plaque (if fulfilling certain minimal radiological criteria) has a good specificity for asbestos exposure.

Roggli

Fiber burden of lung tissue collected from humans at autopsy

The results of this technique correlate well with risk of asbestos-related disease for a population. The findings would establish whether the population has been exposed to levels significantly different from background. The results for an individual are less predictive of an adverse health effect. Lower levels above background are predictive of pleural plaques and an increased risk of mesothelioma. Higher levels above background are predictive of asbestosis and lung cancer (unlikely to be increased from environmental exposures). Confidence is high for cancer and non-cancer effects.

Fiber burden of lung tissue collected from living humans

Same as **A**. Resected lung specimens are often for individuals who already have lung cancer. Findings would indicate whether the cancer in the individual case is likely related to asbestos exposure.

Fiber content of sputum samples collected from living humans

Sputum analysis for asbestos correlates with individuals at increased risk for asbestosis and lung cancer. This analysis would not likely separate the risk of mesothelioma and benign asbestos-related pleural disease from those at no increased risk. I have low confidence in this method.

Fiber content of bronchoalveolar lavage fluid (BALF) of living humans

BALF analysis correlates with lung fiber burden analysis and thus has a good predictive value for risk of disease (although not quite as good as lung fiber burden studies). This is the best technique

for evaluation of exposure of living otherwise healthy individuals. I have high confidence in this method.

Fiber analysis techniques in sentinel animals (e.g., household pets)

There is no demonstrated correlation between this methodology and risk of human disease. I have low confidence in this approach.

Counting asbestos bodies in human tissue, BALF, or sputum

This technique is reproducible and easy to implement on available specimens. It correlates somewhat (but far from perfectly) with lung fiber burdens and therefore has some predictive value regarding risk of disease. I have medium confidence in this technique.

Blood mesothelin or osteopontin levels, or other blood tests

As discussed above, these techniques are not yet ready for 'prime-time' screening. I have no confidence in the disease predictive value of these techniques based on currently available data.

Clinical tests such as spirometry to look for functional changes

Spirometry is easy to implement in population surveys and may identify a population with greater respiratory disease as compared to a control group. Chronic obstructive pulmonary disease is a major confounder. Biologically significant levels of exposure may not show detectable respiratory effects on a population. I have medium to low confidence in this approach.

Clinical tests such as x-ray or CT scans to look for pathological changes (pleural plaques, pleural thickening, and pleural effusions)

Radiographic studies are easy to implement in population surveys and may identify a population with increased prevalence of plaques or pleural disease. CT scanning is too expensive for screening. A population with increased prevalence of plaques is at increased risk for mesothelioma but not for lung cancer. I have medium confidence in this approach.

Stayner

Incorporated in above comments for Techniques A-I

Weissman

A Fiber burden of lung tissue collected from humans at autopsy
Cancer: high (quantified in Helsinki Criteria)
Noncancer: high

B Fiber burden of lung tissue collected from living humans
Cancer: high (quantified in Helsinki Criteria)
Noncancer high

C Fiber content of sputum samples collected from living humans
Cancer: unknown
Noncancer: unknown

D Fiber content of bronchoalveolar lavage (BAL) fluid of living humans
Cancer: unknown
Noncancer: unknown

E Fiber analysis techniques (tissue, BAL fluid, or sputum) in sentinel animals (household pets or other resident animal species)
Cancer: unknown
Noncancer: unknown

F Counting asbestos bodies in human tissue, BAL fluid, or sputum
For Tissue, BAL:
Cancer: high (Helsinki Criteria)
Noncancer: high

For Sputum – not as well established as for tissue, BAL

G Blood mesothelin or osteopontin levels, or other blood tests
Mesothelin, Osteopontin: Cancer: unclear - promising for mesothelioma, but remain to be confirmed. Noncancer: low

H Clinical tests such as spirometry to look for functional changes
Cancer: low
Noncancer: low (insensitive, nonspecific)

I Clinical tests such as x-ray or CT scans to look for pathological changes (pleural plaques, pleural thickening, and pleural effusions)
Cancer: relation to asbestosis confirmed (high). Relation to plaques accepted by ATS, but controversial, lower risk than asbestosis (medium). Relation to other radiological findings unclear, especially since they can have causes other than asbestos exposure (low).
Noncancer: Asbestos interstitial disease related to plaques (medium)

OTHER POTENTIAL TECHNIQUES

Abraham

YES!! Actually measuring exposures would be additional to all those listed! None of those measure exposures. BUT, current measures of exposures, such as done by EPA simulations in El Dorado, do NOT measure past or cumulative exposures. So there is no single technique at present, in this panelist's opinion, that can collect ALL the data needed to assess past and current exposures and evaluate risk. A combination of several measurements is probably needed, PLUS research to fill in gaps between measurements and more accurate risk assessment.

Carbone (Did not follow a similar format, see General Comments Section at end)

Castranova

Not that I'm aware.

Dodson

No Comment

Gunter

As I read though the materials it occurred to me that in many ways the interaction of minerals in the lung is not that much different from the interaction of minerals in the natural environment. Several years ago, thinking along those same lines, we received funding from NIH to study the possible conversions of minerals in the human lung. While most medical researchers realize that certain minerals dissolve in the lung more readily than others (e.g., chrysotile dissolving at greater rates than tremolite), to our knowledge no one had considered that one mineral might convert to another (e.g., chrysotile to talc, and these new minerals might form pleural plaques). Similarly, as these types of reactions are occurring, certain elements might be incorporated in minerals while others might be released into lung fluids. Thus, I wondered if anyone has ever studied the compositions of the liquid portion of sputum or BAL? Likewise, minerals have different isotopic ratios of major elements. If these minerals dissolved, there is a possibility the isotropic signature of the lung fluids might change.

Currently we are using theoretical thermodynamic and kinetic modeling to determine the fate of minerals in the lung. With these methods we can model reactions of minerals and hopefully gain ideas of what minerals are stable, how the unstable minerals alter, and the changes in the composition of the lung fluid.

As a last thought, has there ever been attempts to measure the concentration of different gases exhaled as a function of lung diseases? It would seem that as lung function decreases that the $O_2 - CO_2$ exchange decrease, so higher concentrations of CO_2 on exhalation might indicate this. Also, there might be other elements occurring on exhalation in diseased lungs – just an idea.

Hillerdal

No Comment.

Roggli

The other obvious approach to determining population exposure and risk is measurement of air sample levels. The advantages are that this methodology is well standardized and can be compared with EPA action levels and OSHA permissible exposure levels. Berman and Crump have proposed risk estimates for lung cancer and mesothelioma based upon average exposure levels and total exposure duration.[9] It is not likely that exposure levels at any particular contaminated site will be uniform, so the question is where to measure. Furthermore, there may be day-to-day variation in exposure levels due to prevailing winds, rainfall, thermal inversion, etc. However, a well-designed program for air monitoring may provide information regarding the likely exposure levels of a community. The procedure is noninvasive and cost effective. I have high confidence in this approach as complementary to the fiber analysis methodology discussed above.

With respect to short asbestos fibers (those < 5 μm in length), *this issue has already been addressed and decided upon at a previous ATSDR meeting.* There is no reason to reopen that discussion at this meeting, and I hope we will not divert precious time doing so.

Stayner

No Comment

Weissman

It has been proposed that combinations of abnormal findings may have better performance characteristics for diagnosis of asbestosis than single tests such as those described above. Individual variables that can be considered include exposure history, physical findings such as rales, lung function tests (especially DLCO), and chest imaging studies.

GENERAL COMMENTS

Carbone

The issue that has not been sufficiently considered in the papers and comments that I have seen, is that the risk of exposure is not the same for all exposed individuals. In other words, for some individuals a given amount of asbestos or erionite load may be sufficient to cause cancer or other diseases, and for others is not. An obvious example is that among crocidolite miners in South Africa the incidence of mesothelioma was about 5%. Therefore, in addition to looking for more precise methods to quantify exposure, we need to look for biomarkers that allow us to identify those factors that render certain individuals more susceptible to asbestos. In the pathogenesis of mesothelioma we have determined that genetics (Dogan U. et al., Cancer Research May 215 2006 in press) make certain families much more susceptible to erionite carcinogenesis than others. Moreover, following up on our initial observation of co-carcinogenesis in vitro among SV40 and asbestos in causing malignant transformation of mesothelial cells (Bocchetta et al., Proc Natl Aca sci USA 2000), we have determined the mechanisms responsible for co-carcinogenesis and demonstrated that crocidolite and asbestos are synergistic in causing mesothelioma in hamsters.

Moreover, animals exposed to amounts of crocidolite that are insufficient to cause mesothelioma, develop mesothelioma in the presence of SV40 infection. These data indicate that we must look at asbestos carcinogenesis not as an "all or none" phenomenon, but rather as to the outcome of a number of interactions among mineral fibers and other factors that determine who among exposed individuals will develop malignancy. Therefore, in studying asbestos carcinogenesis and especially in trying to identify those at risk for malignancy, it is important to study the biomarkers that render certain individuals more susceptible than others. Concerning possible biomarkers to identify patients at risk of malignancy, in studies conducted in Cappadocia among the mesothelioma villages of Tuzkoy, Karain and Sarihidir, our initial data support the reliability of serum markers for mesothelin to identify mesothelioma patients, and apparently and more importantly to predict among this high risk population those who are in the process of developing mesothelioma. If these preliminary data hold true the serological assessment of mesothelin and possibly osteopontin (under investigation) will lead to novel preventive and therapeutic strategies. Finally, we have recently elucidated an important mechanism of asbestos carcinogenesis which is mediated through the release of TNF-alpha and the activation of the NFkB pathway (Yang H. et al, Proc Natl Aca Sci USA, in press). Because of the availability of drugs that specifically interfere with this pathway, this finding should lead to novel preventive/therapeutic strategies. For example our results appear to support the use of anti-inflammatory drugs (COX-2 inhibitors) to try to reduce the risk of mesothelioma among asbestos exposed individuals. These drugs are presently under investigation to try to colon, lung and other carcinomas. Moreover, specific drugs that inhibit TNF-alpha and NFkB are also available. One of these drugs, Onconase, specifically targets NFkB and coincidentally has been used in mesothelioma where it has had some beneficial effects in a subset of patients. In summary, these drugs may be most effective in the early stages of asbestos carcinogenesis and for prevention.

In conclusion, I believe that the assessment of asbestos exposure through light microscopy and/or TEM, is a first step in identifying patients at risk. The next step is to identify the biomarkers that make some among the many exposed at higher risk for malignancy and this in turn should lead to novel preventive and therapeutic approaches.

Gunter

First it should be clear, based on looking at the "occupations" of the panelists that I'm "the odd person out." I am the only person on the panel without a background in the medical sciences; my

specialty is mineralogy. For years I have thought that mineralogists could aid in discussions such as we will be having. Over the past few years I have gotten involved with several issues related to inhalation of minerals dusts, and put efforts into better characterizing mineral samples and working with health-based researchers. So at the outset I thank ATSDR for asking me to serve on this panel.

When I was asked for my qualifications in the biomarker areas, I truthfully listed them as very low, but I indicated that I thought a mineralogist would be helpful in these deliberations. I hope to be able to address any mineralogical based questions that might arise during our meeting. Along with teaching and research in mineralogy, I also have taught the introductory geology courses. Thus, I hope, some of my background in geology might also prove useful. For instance, in geology we face many of the same type of sampling issues that occur in studying the lung. We often look for simple, cost effective methods to gain indirect evidence, because the direct methods would be prohibitively expensive.

I have read over all of the provided material and most of my comments will be based on the information in them. To the ones of you who have spent a considerable portion of your careers working in these areas, I hope my comments are not too simple-minded. As already stated, my main goal in this panel will be to provide mineralogical input and (hopefully) answer any questions that might arise in the areas of mineralogy and geology, especially how minerals might react in the lung.

Biomarkers of asbestos exposure

Based on the readings, it appears that often even though individuals have been exposed to high levels of asbestos (i.e., in an occupational setting), there is no reliable method to predict if a disease will occur, until the onset of that disease. While some of the methods worked for groups, they did not work on an individual level. Based on the comments in the "kick off" phone call that I unfortunately missed, it seemed one of ATSDR's biggest concerns is dealing with people who have had lower exposures (e.g., those living in El Dorado Hills)

Stayner

As a non-physician Epidemiologist, I must confess that I do not consider myself an expert in many of the clinical issues that we were asked to address for this meeting. In order to address these questions I had to in many cases review the literature, and in some cases rely on review articles because of time constraints. Thus some of the view that I have expressed below may be subject to change after hearing discussions of these issues at the meeting or with additional reading of the literature.

I have been actively involved in studying a retrospective cohort of textile workers exposed to chrysotile asbestos [Stayner et al. 1997]. We are currently conducting a re-analysis of this cohort with several years of additional follow-up. This new analysis will utilize new information on fiber size distributions obtained from re-analysis of exposure data using Transmission Electron Microscopy (TEM). Given my interest in chrysotile asbestos one of the overarching concerns that I have for many of the biologic methods reviewed here is their potential insensitivity for detecting past exposures to chrysotile asbestos. Chrysotile is not nearly as biopersistent in the lung as amphiboles, and this is clearly a concern for studies based of fiber lung burdens. It seems likely that this is also a serious concern for analyses based on either sputum or bronchial lavage.

I would also like to raise the question as to whether these biologic measurements should be regarded as superior to conventional industrial hygiene exposure assessment techniques. I recognize that it many cases it may no longer be possible to use these conventional measurement methods since the

asbestos exposure has been remediated. However, I wish to emphasize that when possible, I believe that these conventional methods are still the preferred method and the gold standard by which all of the other methods should be judged.

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Appendix E. Observer List

ATSDR
AGENCY FOR TOXIC SUBSTANCES AND DISEASE REGISTRY

Expert Panel on Biomarkers of Asbestos Exposure and Disease

ATSDR
Atlanta, Georgia
May 9-10, 2006

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Appendix F. Agenda

ATSDR
AGENCY FOR TOXIC SUBSTANCES AND DISEASE REGISTRY

Expert Panel on Biomarkers of Asbestos Exposure and Disease

ATSDR
Atlanta, Georgia
May 9-10, 2006

Agenda

Tuesday, May 9, 2006

Registration/Check In

Welcome, Goals of Meeting, and Introductions
ATSDR

Background on Research Needs
ATSDR

- Health Studies
- Health Assessment
- Community Needs

Introduction of Panelists and Review of Charge
Meeting Facilitator: Dr. Fernando Holguin, CDC and Emory University

Break

Public/Observer Comment Period
Meeting Facilitator: Dr. Fernando Holguin, CDC and Emory University

Panel Discussion
A. Fiber burden of lung tissue collected from humans at autopsy
B. Fiber burden of lung tissue collected from living humans
C. Fiber content of collected sputum samples
D. Fiber content of collected bronchoalveolar lavage (BAL) fluid

Lunch

Continued Panel Discussion

E. Fiber analysis techniques (tissue, BAL fluid, or sputum) in sentinel animals (household pets or other resident animal species)
F. Counting asbestos bodies in human tissue, BAL fluid, or sputum
G. Blood mesothelin or osteopontin levels, or other blood tests

Break

Continued Panel Discussion

H. Clinical tests such as spirometry to look for functional changes
I. Clinical tests such as x-ray or CT scans to look for pathological changes (pleural plaques, pleural thickening, and pleural effusions)

Day One - Wrap Up
Meeting Facilitator: Dr. Fernando Holguin, CDC and Emory University

Adjourn

Wednesday, May 10, 2006

Review of Day One and Goals for Day Two
ATSDR

Public/Observer Comment Period
Meeting Facilitator: Dr. Fernando Holguin, CDC and Emory University

Continued Panel Discussion
ATSDR's overarching questions

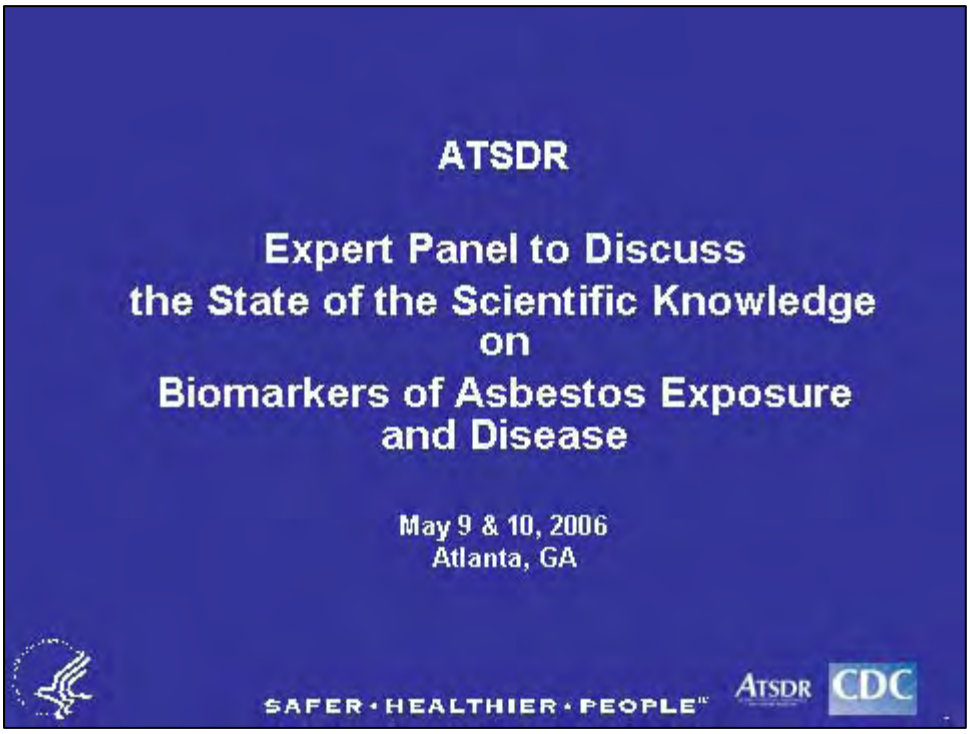
Lunch

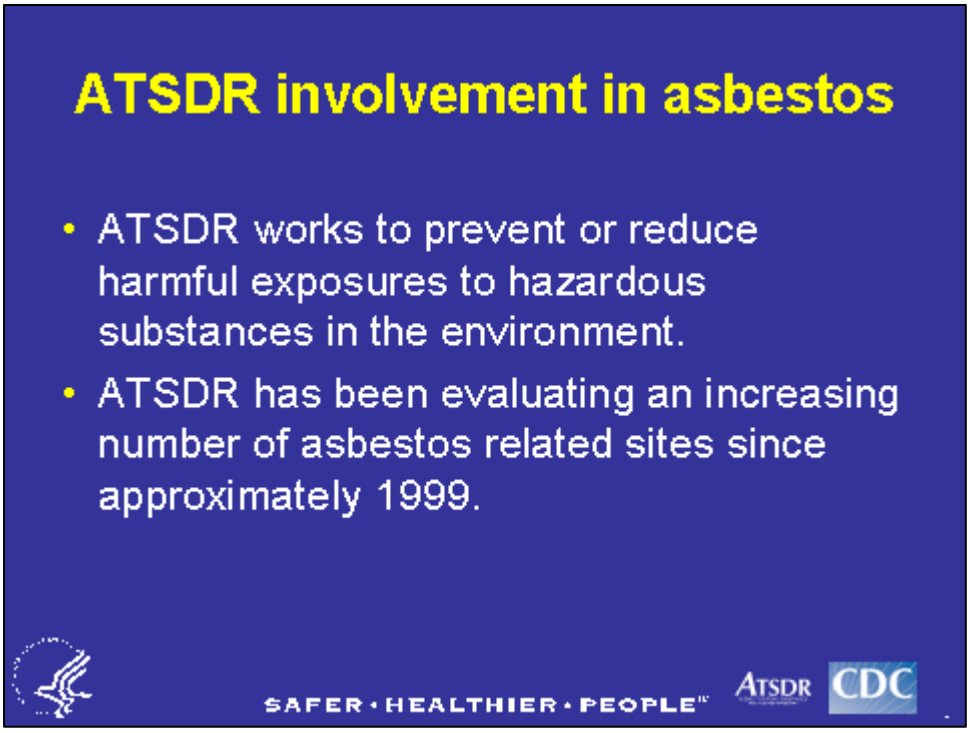
Final Conclusions and Key Recommendations
Dr. Holguin, Panel, and ATSDR

Wrap-up
ATSDR

Adjourn

Appendix G. Presentation Slides


ATSDR
Expert Panel to Discuss
the State of the Scientific Knowledge
on
Biomarkers of Asbestos Exposure
and Disease
May 9 & 10, 2006
Atlanta, GA
SAFER · HEALTHIER · PEOPLE™
ATSDR
CDC


ATSDR involvement in asbestos
• ATSDR works to prevent or reduce harmful exposures to hazardous substances in the environment.
• ATSDR has been evaluating an increasing number of asbestos related sites since approximately 1999.
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ATSDR
CDC


The Libby Mine


Sites that Received Vermiculite from the Libby Mine
AK
WA
OR
CA
ID
NV
MT
WY
UT
AZ
CO
NM
ND
SD
NE
KS
OK
TX
MN
IA
MO
AR
LA
WI
IL
MS
MI
IN
KY
TN
AL
OH
WV
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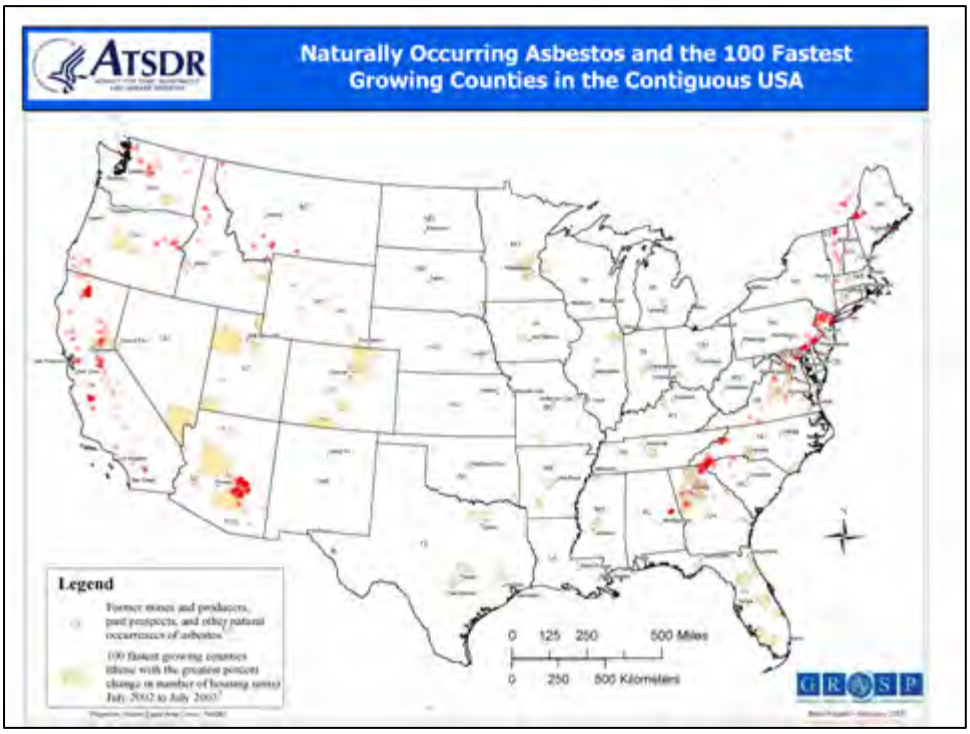
FL
SC
NC
VA
PA
NY
ME
National Asbestos Exposure Review
Phase 1 Sites
SAFER · HEALTHIER · PEOPLE™
ATSDR
CDC


ATSDR
Naturally Occurring Asbestos and the 100 Fastest Growing Counties in the Contiguous USA
Legend
0 125 250 500 Miles
0 250 500 Kilometers
GRASP


Oak Ridge, HS - El Dorado Hills, CA
HARVARD WAY
Oak Ridge High School
Silva Valley
H
G
SAFER · HEALTHIER · PEOPLE™
ATSDR
CDC

Swift Creek, WA

SAFER · HEALTHIER · PEOPLE™ ATSDR CDC

Ambler, AK

SAFER · HEALTHIER · PEOPLE™ ATSDR CDC

Community concerns

- Can you test me to see if I have been exposed to asbestos?
- What level of exposure should I be concerned about?
- Is our community a safe place to live?
- Can ATSDR perform a health study to tell us if our health is compromised?
  - (need proper endpoint to measure)

SAFER · HEALTHIER · PEOPLE™ ATSDR CDC

ATSDR Has Made Public Health Decisions about Asbestos Exposures on the basis of:

- Health Effects (Disease), and / or
- Exposure Data → Risk of Disease

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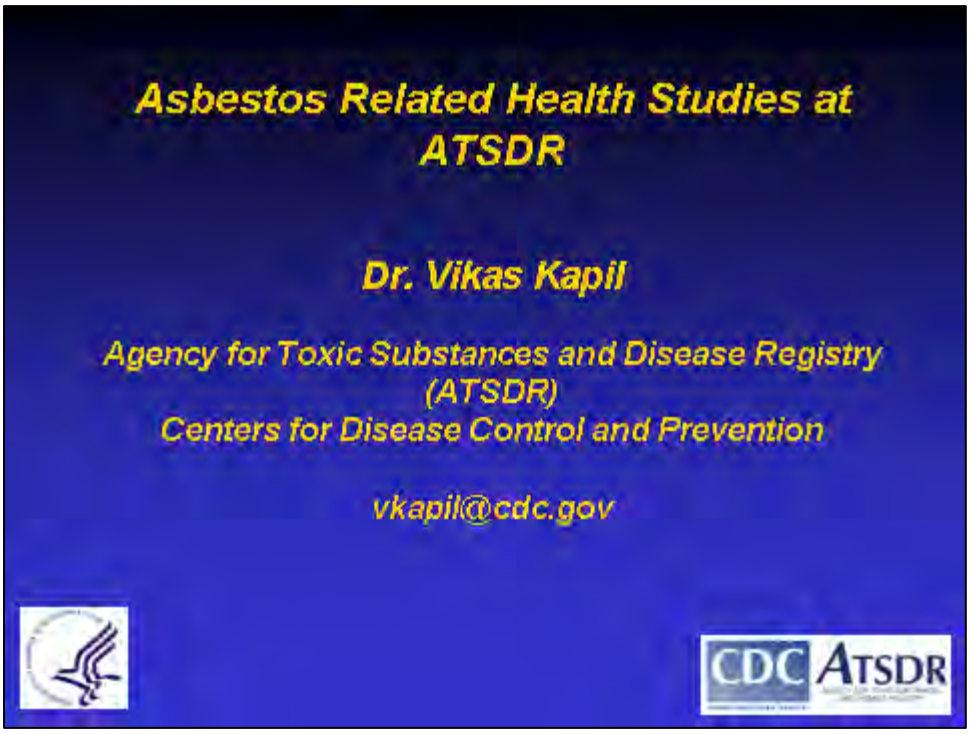
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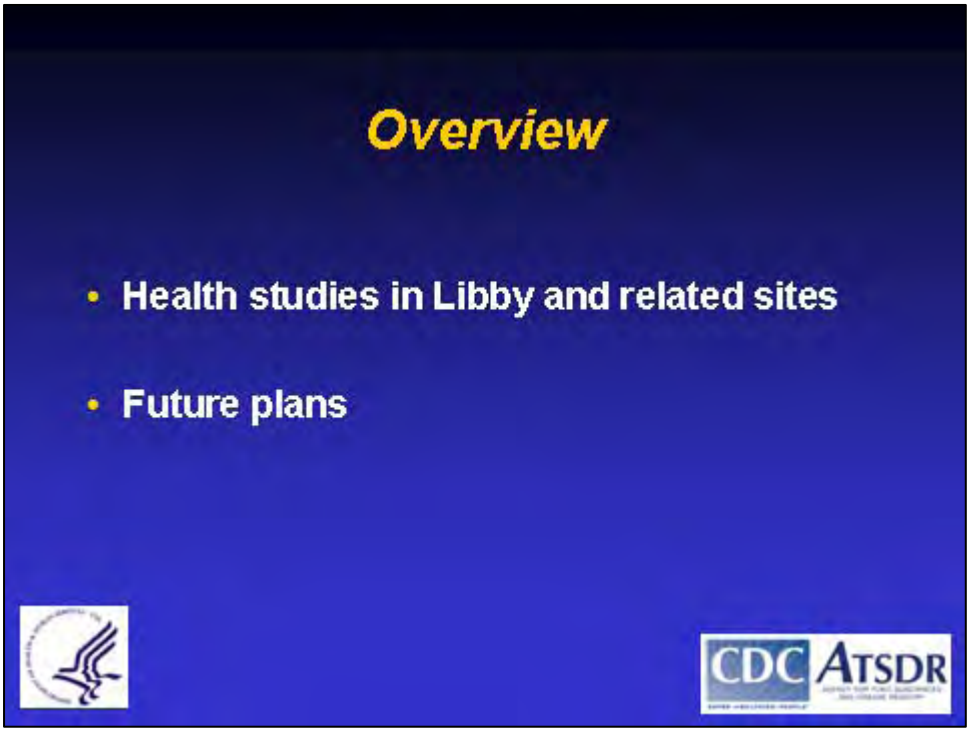
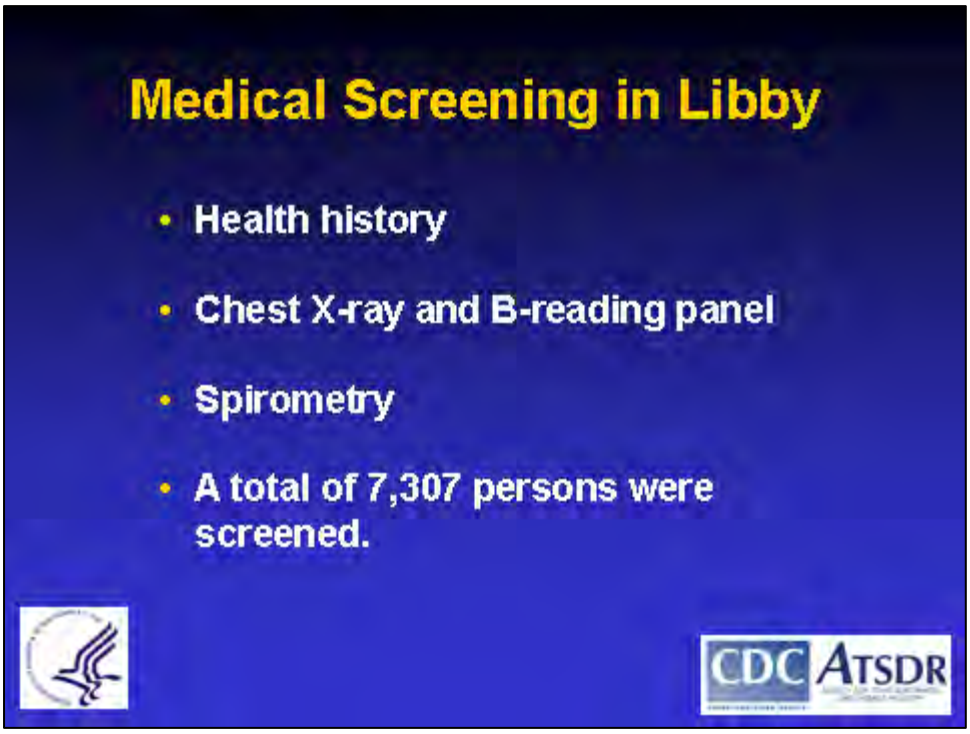
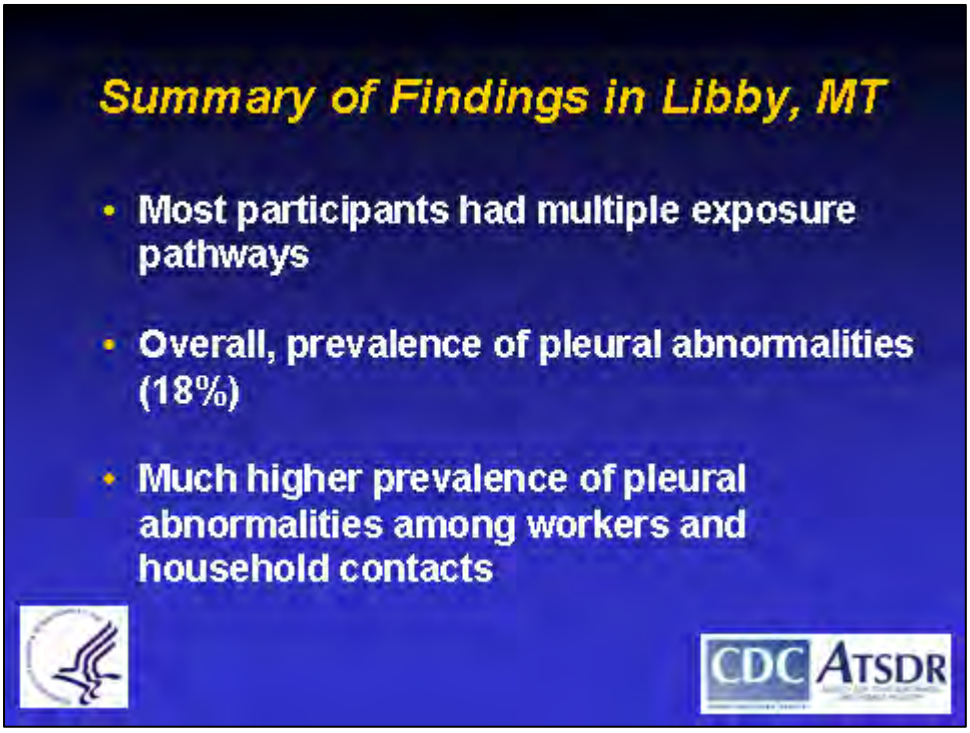
CDC ATSDR


Overview
• Health studies in Libby and related sites
• Future plans
CDC ATSDR

Some Relevant ATSDR Activities

- Community medical screening (history, CXR and spirometry)
- Usefulness of CT scanning
- Case series of environmental cases
- Ongoing periodic medical screening in Montana
- Tremolite Asbestos Registry (TAR)


Medical Screening in Libby
• Health history
• Chest X-ray and B-reading panel
• Spirometry
• A total of 7,307 persons were screened.
CDC ATSDR

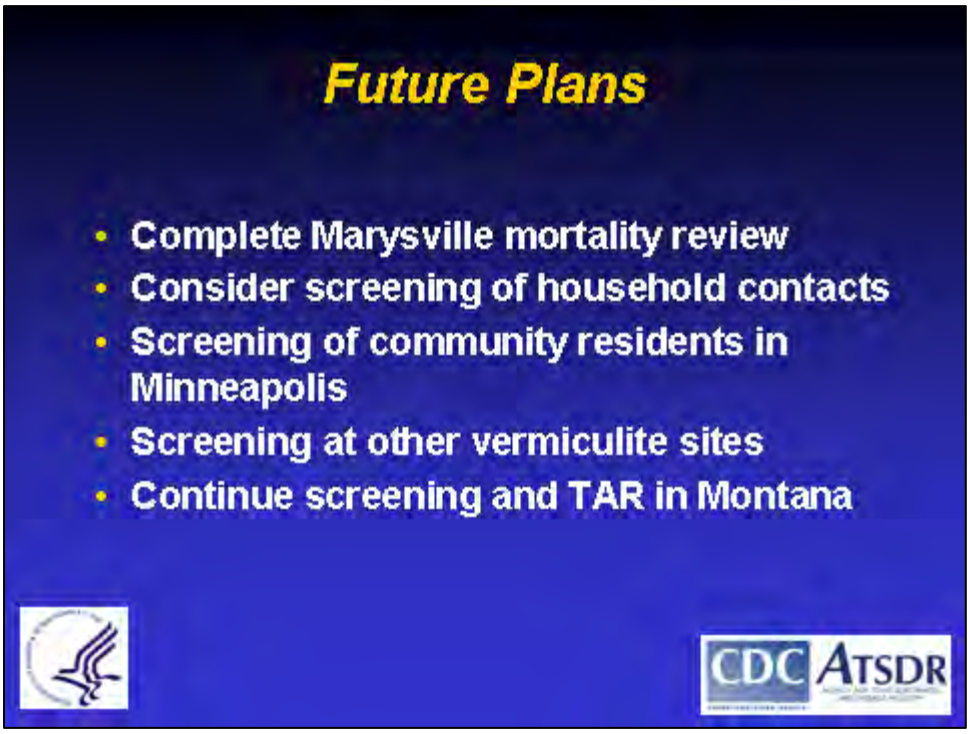

Summary of Findings in Libby, MT
• Most participants had multiple exposure pathways
• Overall, prevalence of pleural abnormalities (18%)
• Much higher prevalence of pleural abnormalities among workers and household contacts
CDC ATSDR

Disease Progression in Former Vermiculite Workers in Marysville, Ohio

- Follow-up medical screening of workers who were originally screened in 1980
- Current chest x-ray and spirometry findings compared to 1980 findings
- Data collection complete and data analysis is under way

Disease Progression in Former Vermiculite Workers in Marysville, Ohio (Cont.)

- Preliminary results indicate 26% with pleural abnormalities
- Mortality review for deceased workers is underway
- First clear evidence of ARD in workers at sites outside of Libby


Future Plans
Complete Marysville mortality review
Consider screening of household contacts
Screening of community residents in Minneapolis
Screening at other vermiculite sites
Continue screening and TAR in Montana
CDC ATSDR