THE U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
AGENCY FOR TOXIC SUBSTANCES AND DISEASE REGISTRY

convenes the

EXPERT PANEL MEETING ON BIOMARKERS OF ASBESTOS EXPOSURE AND DISEASE

VOLUME I

The verbatim transcript of the meeting, moderated by Fernando Holguin, taken by Diane Gaffoglio, Certified Merit Reporter, held at 1825 Century Boulevard, Room 1 A/B, Atlanta, Georgia, at 9:00 a.m. on Tuesday, May 9, 2006.

NANCY LEE & ASSOCIATES
Certified Verbatim Reporters
P. O. Box 451196
Atlanta, Georgia 31145-9196
(404) 315-8305

This record was taken and produced via SpeechCAT

C O N T E N T S

Volume I
May 9, 2006

P A N E L I S T S

(In Alphabetical Order)

JERROLD ABRAHAM, M.D.
Professor of Pathology
SUNY Upstate Medical University
Syracuse, New York

MICHELE CARBONE, Ph.D.
Director, Thoracic Oncology Research
Loyola University Medical Center
Cardinal Bernardin Cancer Center
Maywood, Illinois

VINCENT CASTRANOVA, Ph.D.
Chief, Pathology and Physiology Research Branch
CDC-NIOSH
Morgantown, West Virginia

RONALD DODSON, Ph.D.
President
Dodson Environmental Consulting
Tyler, Texas

MICKEY GUNTER, Ph.D.
Professor of Mineralogy
University of Idaho
Moscow, Idaho

GUNNAR HILLERDAL, M.D.
Professor
Karolinska University Hospital
Stockholm, Sweden

VICTOR ROGGLI, M.D.
Professor of Pathology
Duke University Medical Center
Durham, North Carolina

LESLIE STAYNER, Ph.D. (Telephonic Appearance)
Professor and Director of Epidemiology and Biostatistics
University of Illinois at Chicago
Chicago, Illinois

DAVID WEISSMAN, M.D.
Director, Division of Respiratory Disease Studies
CDC-NIOSH
Morgantown, West Virginia

Legend of the transcript:

[sic]	Exactly as said
[phonetic]	Exact spelling unknown
--	Break in speech continuity
...	Trailing speech or omission when reading written material
[inaudible]	Mechanical or speaker failure
[microphone]	Speaker is off microphone

P R O C E E D I N G S

9:03 a.m.

DR. FORRESTER: Good morning, everyone. Can you hear me well?

DR. HOLGUIN: Yes.

DR. FORRESTER: Okay. I'd like to welcome all our guests and our panelists to our first meeting on Expert Panel of Biomarkers of Asbestos Exposure. We are very pleased we have this very prestigious group to help us address this question. We have with us our site team, and we have many visitors from across the United States that are very interested in this topic. At this current time, ATSDR is embarking on several sites where asbestos exposure is becoming a growing concern.

The issue we have is, is that we work closely with the communities to tell them the health effects they may expect from exposure. But asbestos is not a simple question to answer to the community. What are your likely health effects because the latency of disease seems to take a long time? So we're asking you all to help us determine if there is a way to assess exposure at an earlier period in time to give a community some idea if they may have potential health effects.

We have with us today the site team, who is going to give us a brief overview of how this journey began for

this agency. We're working now with naturally occurring asbestos, which is much different than the occupational exposures that most people encounter.

I'd like to briefly go over some of the ground rules for our meeting. Our expert panel will be doing discussions on the charge that we have given them. There's about five to six charge questions that they will extensively discuss throughout this meeting and, at the conclusion, will give us recommendations and key ideas of how to proceed.

We also will have an opportunity for the observers to make comments. There are two periods. There's one this morning. There's one tomorrow. If you would like to make comments to the record, you need to sign up with Erin. She's the lady in the black sweater. She's out front. So you need to register for the comment period. So if you have any comments today, before ten, please go out and register with her.

There will not be questions from the audience to the panelists, but they can take in account what the observers say in their discussions. So this will mainly be observing the discussions of the panel. The team will be allowed to interface with Dr. Holguin, who is our moderator, and help guide the discussion so it stays on track to the particular questions we were addressing in

the charge.

So right now, for housekeeping procedures, if you go back through the lobby and to the left through the wood door, there are restrooms and vending machines for water, snacks, whatever. We will break on schedule. There are a lot of local restaurants within walking distance to the building. We will start and stop on time, according to the agenda.

So I would like to introduce the team now to give you an overview of how we began this journey. I'd like to start with Dr. Jill Dyken, Dr. John Wheeler, Dr. Vik Kapil, and Commander Susan Muza, our site team. And our first adventure with naturally occurring asbestos was El Dorado County, California, and they've all extensively worked on those sites for over a year now.

So, Jill, would you like to start, please.

DR. DYKEN: Thanks, Tina. Hi, everyone. I'm Jill Dyken. And I'm just going to give you just a couple of slides, a little background of how ATSDR began getting involved in asbestos issues and leading up to the formation of this panel. Okay.

ATSDR's mission is to prevent or reduce harmful exposures to the public to hazardous substances in the environment, which, of course, asbestos falls into this category. Since about 1999 -- oh, thank you. That's

better, isn't it?

Since about 1999, we've been evaluating an increasing number of asbestos-related sites. And that basically began with the Libby, Montana, which was a very large vermiculite mine in extreme northwestern Montana. The vermiculite was contaminated with asbestos, and the materials were used throughout the community, resulting in very high exposures there and a number of health-related impacts in that community. An outshoot of that was that many, many sites over the United States processed the Libby vermiculite.

So we have those kind of exposures spreading out all over the United States and the world. And this shows the sites that process the Libby vermiculite, and the stars show prioritization of sites the ATSDR has been evaluating. So again, in this, it was typically occupational exposures to the contaminated vermiculite. The exposures are known to be pretty high, especially for the workers.

Next -- and growing out of that, we started getting questions about naturally occurring asbestos because, as you know, asbestos is a naturally occurring mineral. It's present in many places throughout the country and the world. And this map shows -- the red dots show, documented in the literature, instances of naturally

occurring asbestos. And then the kind of yellow marks there show housing starts. This is becoming more of a problem because, as we develop more and more, these materials can get disturbed, and that's when they can cause a health impact.

So with naturally occurring asbestos, it's starting to get a little bit more complicated because the exposures aren't as well characterized. People are moving in and out. There's changing conditions. And also there's, you know, different types of asbestos that might cause different things. So it's a little bit more complicated than the Libby situation.

So that's currently what we're wrestling with. But now I'm just going to turn it over to John Wheeler, who's going to talk a little bit about some of the questions we've been getting.

DR. WHEELER: What makes this go forward?

DR. DYKEN: Page down.

DR. WHEELER: I wanted to just briefly mention a few sites that we're working on and some of the common themes that we hear from communities at these sites. This is El Dorado County in California. And you can see on the map here the Oak Ridge High School. We got involved with this about three years ago. There's several people here in the audience that are working extensively on this area of

California.

What occurred here was -- over in this area, a soccer field was built, and they hit a naturally occurring vein of amphibole asbestos that runs along this ridge line when they built that soccer field, and some of this material moved into this school.

This is Swift Creek in Washington, upstate Washington. There's a -- you can't see it in this picture very well, but there's a mountain out here that has had an avalanche occur, and material moved down this mountain that was contaminated with a chrysotile vein. And essentially, it filled up this creek. And the creek is a major drainage for this entire area in here, and without the creek there, a lot of flooding was occurring. So they came in and dredged this creek and piled up material along this creek, which is quite high in chrysotile. And now those piles serve as a wonderful place to play on your ATV or do recreating.

This is Ambler, Alaska. We're about 45 miles north of the Arctic Circle. This is Kobuk River that runs over to Barrow. If you can see this road in here, this road runs out to a airport. And then on the other side of the airport is a quarry. And they used that quarry to gravel all these roads. About four or five months of the year, this area is free of snow and it gets pretty muddy, and

they use gravel from that quarry. Well, the quarry is contaminated with chrysotile. And there's some very high levels of chrysotile on all these roads. So we're running into these kinds of problems.

It doesn't matter if we're talking to the Inuits in Alaska or if we're talking to the suburbanites outside of Sacramento or whether we're talking to community members at the end of the runway in Saint Louis that are having their houses demolished, we hear these same common themes over and over and over again, these same questions. They're very simple questions. They're almost eloquent in their simplicity, but they are so very hard to answer.

They ask us if you can test them to see if they've had exposure, what kind of tests that we have available. And if they are exposed, they want to know if that level is going to cause them problems and whether or not the entire community is being exposed from the kinds of activities that are going on there.

We also get a lot of questions about whether we can come there and do a health study. And Dr. Kapil is going to talk, in a few minutes, about some of our experiences with health studies. The only way that we can answer these questions is we have two approaches that we have used. One, the first approach, that I would call an epidemiological approach, similar to what we did in Libby.

We saw disease there. We went in, investigated that site and found exposures and tried to limit the exposures. But that's certainly not the direction we want to take. We don't want to wait until disease is prevalent to go out to a site and make some kind of recommendations on exposure.

The other type of exposure is what I would call the health assessment or risk-assessment paradigm, in which we go into a community and we try to estimate the exposures that are going on there and try to link those exposures to some estimate of risk. This, of course, is fraught with all kinds of uncertainty and problems. If you look at risks, there's all the questions about the epidemiology studies that are used that we base the risk on and whether those studies -- the analytical procedures there are the same as the analytical procedures we use now.

And in asbestos toxicity, since it's not a single chemical entity, we have other problems that we have to worry about: mineralogy, morphology, fiber-size distribution. All these are confounders that lead to uncertainly in our estimation of risk. On the exposure side of the equation, we have uncertainties, of course, associated with the analytical techniques and abilities, but we also have a problem that most of the exposure data comes as population data or at least a subpopulation. We may be looking for a central tendency, or we may be

looking at an upper confidence level. And that doesn't say much for the individual. And when we make recommendations to community members to go see your physician and talk to your physician about your exposures, we don't have the kind of test there for an individual to look at their own exposures.

We also have problems with how best to examine the exposures that are going on in those communities and -- and how we evaluate media. A lot of tests we get back are from soil levels. But how do we correlate that to the risk that is caused from inhalation exposures? In the recent years, we have taken an approach of looking at activity-based sampling, which is simply -- if we're EPA, you hire a contractor, or if you're ATSDR, you go out and buy a dust mask.

And you go out, put on a personal sampler, and participate in activities that you think that would lead to exposure and measure the kinds of exposure that are going on there. We think that's the right direction, but we're still left with these uncertainties.

What I hope we don't do in the next two days is dwell down into these uncertainties and the limits of the types of assessments that we're doing right now. I'm going to leave that up to Aparna to take care of when she looks at the IRIS update of all the -- of all the parameters that

go into those kinds of exposures.

What I hope we do is we take a look at other ways that we can measure exposure and other ways that we can measure disease and, most importantly perhaps, link that kind of exposure data that we can get from whether we're using lung fiber burdens or whatever we've discussed to the disease prevalence in the community.

So with that, Dr. Kapil.

DR. KAPIL: Thank you, John. Okay. It's my pleasure to be here to join you-all today, and I'd also like to thank the panel members as well as the observers and visitors that are here for giving us your time for the next couple of days. We greatly appreciate it. What I'd like to do is talk to you a little bit about where we have been in terms of assessing health impact of these exposures.

Jill talked to you a little bit about our work in Libby and related sites. So I'm going to delve into that a little bit more in terms of specifically what we've done in terms of health studies related to Libby and the Libby sites and also tell you a little bit about what we have in planning stages or are already initiated related to these sites. Most of the health studies work that we have done to date is related to Libby and the vermiculite sites.

You've seen this map. These are the 200-plus sites,

and we're focused right now on these for some epidemiologic activities, like health statistics reviews, about a hundred of these. We're particularly focused on 28 -- what we've called Phase I sites -- the sites that on Jill's map actually had stars.

So the -- in Libby, in 2000 and 2001, we did a fairly comprehensive community medical screening. That screening, for those of you that may have actually seen this in the literature -- and there are several of the co-authors that are actually here -- consisted of history, including health, environmental, and occupational health history; a chest x-ray, which was read by a panel of B-readers; and spirometry.

We've done other work related to Libby. We've done a study on the usefulness of CT scanning. We've looked at some -- a case series of environmental cases. We have an ongoing medical-screening program very similar in design -- not exactly the same, but very similar in design -- to the original medical screening. And that's ongoing in the Libby area. And we've developed a registry, which is called the Tremolite Asbestos Registry, or the TAR, in which we've enrolled eligible persons from the Libby community.

I'm not going to -- this isn't an exhaustive list. I'm not going to talk, for example, about our

epidemiologic activities. We're going to focus, for the purposes of this discussion, on specifically on the -- on the health-study types of activities.

The medical screening, as I mentioned, included chest x-ray with a B-reading panel, spirometry. We screened over 7300 people. Not every single one of those individuals had a chest x-ray, but over 6,000 people actually had chest x-rays. Most of those participants had multiple exposure pathways. And overall, we found that the prevalence of pleural abnormalities in Libby was nearly 18 percent.

The prevalence -- if you looked at specific groups, such as workers or household contacts, the prevalence was much, much higher than 18 percent. So 18 percent is sort of across the board prevalence of pleural abnormalities.

We are also working on a similar -- not exactly the same, but a similar screening at one of the vermiculite sites in Ohio, in Marysville, Ohio. This was sort of a serendipitous thing because in 1980 -- a screening of these workers at this facility in Ohio was actually done back in 1980, and we had all of those records. So we repeated -- about a year and half ago, we repeated chest x-ray and spirometry on those individuals, at least the ones that were living and were willing to participate, and we compared those to the 1980 findings.

This work isn't complete yet. The data collection is complete, but the data analysis is under way. I can share some preliminary results with you. The preliminary results: We found that 26 percent of the individuals, workers, actually have pleural abnormalities. This compares to maybe something like 1 to 2 percent back in 1980, when the original screening was done; same protocol in a panel of B-readers.

In all of these, both in Libby as well as in Marysville, we have seen -- relatively speaking, we've seen very little interstitial disease. Most -- most of the findings have been pleural in nature. And also, on spirometry as well -- although the spirometry data hasn't been totally evaluated yet, but the spirometry, the restrictive findings are also relatively less prevalent as compared to the pleural disease.

We are -- we are conducting a mortality review for deceased workers in Marysville, and this is really the first clear evidence of asbestos-related disease in workers at sites outside of Libby. Of course, no big surprise to most of the people in this room, but it's the first documented evidence. We have a number of things under way that I want to share with you. One is that we, of course, intend to complete the Marysville mortality review. Depending on the availability of funding, we'd

also like to consider screening the household contacts of the workers in Marysville. This is a fairly simple proposition in Marysville, of course, because we have a fairly complete list of workers. And we've already been in touch with and screened those workers.

We have funded a screening of community residents in Minneapolis. This will be the first time that we've actually looked at residents of the community, not workers or household contacts, but residents of the community in the area immediately around the facility. And that should begin later this year. We are also -- again, depending on the availability of funding, we are also contemplating and actually are planning some screening at other vermiculite sites, hopefully at least a couple of additional sites to begin later this year, primarily, again, focusing on workers and household contacts and conducted in a very similar way to what we've done before in Marysville and in Libby: history, health history, environmental/occupational health history, x-rays, and a B-reader panel as well as spirometry. And, of course, we plan to continue our screening and registry activities in Montana.

In addition, we have a number of other epi activities going on; for example, mesothelioma surveillance, piloting in three states, health statistics reviews. But those we'll leave for some future discussion.

That's all I have, and I just -- hopefully that's helpful to you-all; give you some idea of where we're at today and where we hope to be going in the upcoming year. Thank you.

DR. FORRESTER: Thank you. I'd like to introduce our moderator. It's Dr. Fernando Holguin. He is a -- he's independent from ATSDR. He works as a fellow at the National Center of Environmental Health in the respiratory effects branch. He's also a practicing pulmonologist at the Emory School -- Emory Medical School. And he is going to lead our session today. Fernando.

DR. HOLGUIN: Thank you. Good morning and welcome. To begin, I would like to ask the members of the panel to introduce themselves, their affiliation, and provide in two sentences their main area of expertise, if possible, just to keep us on track.

DR. ABRAHAM: Hi. I'm Jerry Abraham. I'm a pathologist and professor of pathology at the State University of New York, Upstate Medical University in Syracuse. And I've been interested in occupational and environmental dust-related diseases since working with NIOSH back in the 1970s and have done studies related to fiber burden analysis in humans and animals.

And most related to this, I've done a study of animals exposed to asbestos in the El Dorado area in

California. And also, we reported a case of a worker at the expansion plant in Glendale, California, whose only exposure was to that material who died of asbestosis and of especially strong pleural disease back in 2002. So that -- that was really the first reported fiber-analysis case of an expansion plant worker that I'm aware of.

And I'm very interested in how to reconcile all the knowledge we have about exposure with attempts to do risk assessment.

DR. CARBONE: Good morning. I'm Michele Carbone. I am a professor of pathology and am the director of thoracic oncology at Loyola University in Chicago -- actually, at the University of Hawaii starting June 1st. My -- I -- too, I'm a pathologist. Most of my work is to conduct research on mesothelioma. I am the principal investigator on a PO1 from the NCI. The title is Pathogenesis of Mesothelioma in the PI, and my co-investigators are Sir Brooke Mossman at the University of Vermont, Joe Testa at Fox Chase Cancer Center, and Harvey Pass at NYU.

In -- in addition -- in P01, we study how different factors interact to cause mesotheliomas. My research is entirely funded by the NIH and the American Cancer Society. I also am the PI of two other ones. In one of them, we study the interaction between SV40 and asbestos

and the pathogenesis of mesothelioma. And in the other PO1, we study the contribution of SV40, per se, to the pathogenesis of mesothelioma.

In the studies that are funded through a grant by the American Cancer Society, we are studying an epidemic of mesothelioma in the villages of Karain, Tuzkoy, and Sarihidir in Cappadocia, Turkey, where 50 percent of people die of malignant mesothelioma, and now this grant -- this project will continue to be peaked out by the PO1 that we just got awarded by the National Cancer Institute.

DR. CASTRANOVA: Good morning. I'm Vincent Castranova. I'm chief of the pathology and physiology research branch at the National Institute for Occupational Safety and Health in Morgantown, West Virginia. I'm a pulmonary toxicologist. I've been involved for the last 28 years in looking at effects of various particulate matters on lung effects.

DR. DODSON: Good morning. My name is Ron Dodson. I spent approximately 27 years in academia before my retirement last fall. The major thrust of my emphasis, being an environmental scientist, focusing on particulate burden and tissue and other body fluids, but with the major portion of that in quantitation of asbestos burden and tissue. I am, by training, an electron microscopist and continue to do research in my present role as the

president of Dodson Environmental Consulting.

DR. GUNTER: I'm Mickey Gunter. I'm a professor of mineralogy from University of Idaho. My major interest in all of this really relates to the characterization/identification of most of these minerals involved in these health-based studies. By training, I was a light microscopist, but like a lot of people involved with these areas, we use light microscopy, electromicroscopy, x-ray diffraction, all the different analytical methods we can to try to identify and characterize these minerals. So my major contribution to this, I hope, will be in providing some mineralogical-based information.

DR. HILLERDAL: Good morning. I'm Gunnar Hillerdal from Sweden. I'm a pulmonologist and a clinician mainly, but I've also done some research on asbestos. My thesis came in 1980 and was about pleural plaques, and since then, I have been studying asbestos-related diseases and changes and published some papers on this. And I'm working at the Karolinska Institute in Stockholm.

DR. ROGGLI: Good morning. Victor Roggli of -- professor of pathology at Duke University Medical Center and Durham VA Medical Center in Durham, North Carolina. I've been interested in asbestos-related diseases for about 30 years and have been involved in analyzing lung

tissue samples, correlating them with disease, and with various types of occupational exposures.

DR. WEISSMAN: I'm David Weissman. I direct the Division of Respiratory Disease Studies at the National Institute for Occupational Safety and Health in Morgantown, West Virginia. And I've had a strong interest and involvement in assessing individuals for the presence of a range of occupational respiratory diseases, including pneumoconioses, through my career. Thank you.

DR. HOLGUIN: Thank you very much to the panel members. I will now read to you the charge to the members of this panel and briefly describe what the agenda consists on.

The purpose of the panel is to discuss and summarize the best current science for each question posed to the panel. Consensus or a specific advice on each of the following questions is not requested. If you're unable -- if any of the panel members are unable to address a question for a particular technique, just reply, "No comments."

We will consider a list potential techniques for assessing asbestos exposure and/or disease in communities and addressing the questions posed below -- and these are the following techniques that will pretty much take both of these days: 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 fluid on living humans; fiber analysis techniques, such as BAL fluid or sputum in sentinel animals, such as 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, for that matter; clinical tests such as spirometry to look for functional changes; clinical tests such as x-ray or CT scans to look for pathological changes, including pleural plaques, pleural thickening, and/or pleural effusions.

For the biomarkers of asbestos exposure -- for each of these techniques that I've just mentioned, we will consider the following questions. Again, if you aren't able to comment on any particular technique, just reply, "No comment."

So for each of these techniques, we'll consider:

(Reading) "What are the advantages and disadvantages of these techniques as a method for assessing community-level exposure 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 exposure above a background level? Are the

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 the test results that would be considered elevated?"

Number 2, which is to rank these techniques, will not be done as part of the discussion.

Number 3, “What is the correlation between each of the above techniques and asbestos-related adverse health effects? As an example, can pleural changes such as pleural plaques, pleural thickening, or pleural effusions be used to assess the risk of disease?"

And then these will be ranked in terms of confidence as high, medium, or low and address both cancer, including lung and mesothelioma, and noncancer asbestosis and pleural disease effects. And lastly, we'll discuss other potential techniques that will include particularly:

(Reading) "Are there any other techniques for assessing asbestos exposure which have not been included in the above-mentioned items?" And I guess that summarizes the -- for the most part, the charge. It's quite extensive to the panel members. We're a little bit ahead of the schedule. Should we proceed to -- are there any questions? Well, you all have a copy of it.

DR. WHEELER: We need to do the public comment period as scheduled because people may be coming in to make

public comments, so...

DR. HOLGUIN: Sure.

DR. WHEELER: So why don't we take a break and --

THE COURT REPORTER: You need to be at a microphone.

DR. DYKEN: Okay. I'll take charge here. We're about 25 minutes ahead of schedule. So what we're going to do -- since we want to have the public comment period exactly when it was scheduled, what we'll do is we'll take our break before the public comment period, and then we'll go straight on into the discussion after the public comment period.

So -- so right now, we've got about 25 minutes that you can take a break to use the restroom, whatever. There's a small pot of coffee over in the corner. There's probably not enough for everyone. So you probably have time -- there is a café in the building that is diagonal to this building. So if you exit, take a right down past the parking deck, and then kind of go that way, and it's on the corner of the building. Just ask somebody. There's a little café. You can get some coffee there.

And if anyone has any questions, you can see us. Also, in preparation for lunch, we have a couple of suggested places and maps that you can think about. I think we've got the panelists covered, but I know there's a lot of people visiting. So we've got some suggested

places that you guys can run out to and get something relatively quickly. So just see us up front. We've got some info for you. Okay.

So we will meet back here at 10:00. So if everyone could try to be in just a few minutes before that so we can get started. Thank you.

(Whereupon, a recess of approximately 23 minutes was taken.)

DR. HOLGUIN: The next item on the agenda is the public and observer comment period. I'm told that the person who had signed up to provide comments is not here and will not be here. Therefore, we've decided to open it up for four people to provide comments during this time. Let me just give you some brief ground rules. Each person has a total of five minutes. And Erin –- where's Erin? She'll be here in a minute. She will prompt you at the end of four minutes to let you know that you have one minute left. And so we have time for four people to provide comments.

Just approach the microphone that's over there on the side of the room. And if no one is available to provide comments, then we'll just continue with the agenda. So we're just going to wait a few minutes for someone to approach and provide comments.

(No audible response)

DR. HOLGUIN: No takers? Okay. Would you mind stating your name and affiliation, please.

DR. MILLER: Hi. I'm Aubrey Miller with U.S. EPA in Region 8. I'm a physician and toxicologist with the region. And I just had a comment on No. 3, which discusses the correlation between biomarkers of exposure and asbestos-related disease. And, I guess, in the way it's phrased or framed, that particular discussion, it suggests that the pleural abnormalities and the pleural disease or the pleural findings are not disease or suggested it the way it's –- the way it's, I guess, framed here is that you consider a pleural finding as something that would lead to disease versus it being an element of disease.

And, I guess, I would like to throw that out for the consideration of pleural disease as its own entity and what might be associated with pleural abnormalities, whether it's progression of pleural findings, reduced pulmonary physiology, whether it be lung-pulmonary function, and the risk for malignancy. So it is an entity and what that entity predisposes would be my suggestion of this discussion. Thank you.

DR. HOLGUIN: Anyone else? Don't be shy.

(No audible response)

DR. HOLGUIN: If there are no other people that are

going to provide comments, what we'll do is we'll move on forward with the agenda items. A couple of housecleaning issues: We will skip the 10:30 break since we just had an unexpected break. And also, for the next –- a technique discussion, which is a fiber burden of lung tissue collected from humans at autopsy, we'll have a phone conferencee join us -- Dr. Leslie Stayner -- who is a professor and director of epidemiology and biostatistics from the University of Illinois at Chicago. Unfortunately, he had a family emergency and could not be here but will join us over the phone.

So I would like to, at this time, open the panel for discussion for the first topic, which is fiber burden of lung tissue collected from humans at autopsy and fiber burden of lung tissue collected from living humans, for the panelists (laughter).

DR. ABRAHAM: I'm not sure what the format is. We've sent in our comments that are summarized or reprinted here, and...

DR. HOLGUIN: Well, for each –- for each of these techniques, when we were charged to this cause for the following points that I read to you earlier. Dr. Dodson.

DR. DODSON: All right. I'll be happy to start if you --

DR. HOLGUIN: Sure.

DR. DODSON: I developed rather, I think, lengthy comments concerning this issue for the panelists to review, at least from my perspective, as well as references to document the points made. I think there are several issues in using fiber burden from tissue at autopsy that are –- that are –- will obtain useful information, given the fact it is a base of information at the point in time the sample is taken. It does not reflect what may have been there in the past and been cleared over time. If that autopsy material is lung, it does not necessarily reflect what is in extrapulmonary sites.

I did go into some detail, which I won't at this discussion, but –- except to touch on a couple of the issues that is imperative, in my opinion, to define what technique is used to prepare the samples. It is, also, at least from my perspective, important to know what is included in the count: length; width; detection limit; background of the lab, background meaning quality control aspects.

And therefore, one can use those sources of information for comparison with other data that's presented. At least if it is done in a different manner with different fiber burden included in the analysis, one can at least compare with that population of fibers,

hopefully, that were counted at another scheme.

I have given, in my opinion, a synopsis of the use of the light to scanning and the transmission electron microscopy and the applications for those and the different types of areas and information that can be achieved and the limits of each and have given the reference, which I believe is correct, from the Health Effects Institute position on the use of ATEM and the reasons that it is a useful instrument for identification of asbestos fibers as dissociated from other types of mineral fibers and tissue samples.

As a comparative base, I have referred to the NVLAP AHERA section under Public Law 99-519 that defined, after looking at the available options for particle analysis -- it happens to be from air samples, but once a sample is on a filter, the instrument and the user do not –- do not have the variable. The preparation has been handled at that stage.

And the discussions and the end points of that were to establish -- just as the PCM method for counting fibers of air with a light microscope was based on a reproducible and acceptable standard as a guidance document, the AHERA document gave rise to a reproducible standard that could be assessed between laboratories for using the ATEM and counting fibers. And again, that has applicability

wherever those fibers happened to have come from once they are on a filter.

So I think all of those issues are variables that are technically important to understand when trying to assess the data that can be obtained from assessing any tissue burden, fluid burden, body fluid, et cetera.

With the other statement I made early on, being, in my opinion, very important, that what you're looking at the lung is a snapshot of what is there at the time the sample is taken and doesn't account for clearance, which impacts selectively on a certain proportion of the fibers dimensionally and does not, at least from our data to hand, reflect necessarily what reaches the extrapulmonary sites.

Thank you.

DR. HOLGUIN: Thank you, Dr. Dodson. Would anybody comment, like to reply?

DR. WEISSMAN: Sure. I guess I'll jump in. Study design is really important, and a choice of individual studied is extremely important. And if the goal is to assess community exposure, picking people who are representative of the community is really important.

It's really important to have good exposure information about the individuals who are studied, which can be a big challenge in autopsy studies. It's important

to know their smoking histories because smoking can affect clearance. So having that kind of data is really important.

So even before getting to the issues that Dr. Dodson talked about with regard to analyzing the tissue, choosing the right people, choosing the right controls because, once again, if you want to know if a community has a excess level of exposure, it's important to choose the appropriate controls so that one knows, you know, what to compare to. You know, those kinds of study issues are extremely important.

I guess one advantage that exists for autopsies, compared to other sorts of studies, is the ability to get lots of tissue from multiple sites, you know, and lower sampling error. So that would be another advantage over, you know, surgical, you know, approaches, which is what we're going to be talking next. But, overall, really emphasizing the study design issues, I think, is important to have good data.

DR. CARBONE: David, can I jump in and go one step back to the study design? I do not –- even assuming that we can design the perfect study and that all the technical problems and issues that Dr. Dodson has brought up can be addressed satisfactorily for everybody, how can you design a study on an autopsy when, in fact, there are no

autopsies? The number of autopsies is decreasing everywhere.

I do not know in your hospitals, but in my hospitals, they became a rarity. The same thing was true when I was at University of Chicago. Autopsies are not done. So it's not that you can design a study because you can choose. You can't choose. Autopsy may be an excellent opportunity to take multiple samples in the very rare occasion in which you will have that case. But the fact is that to do any type of study it's impossible to count on autopsies because they just don't exist.

Concerning the taking samples from living individuals, of course, the lung content analysis remain probably the best way. With all the limitations that there are and that Dr. Dodson has indicated, it probably remains the best way to assess the asbestos presence in somebody.

The fact is that how do you get those samples. Obviously, you are not going to do that on somebody unless the person is extremely sick because you're not going to take a biopsy of people prospectively. So you are, again, limited by people who undergo pleurectomy or some type of major surgery, which means that they have cancer.

Therefore, none of these two issues can address the questions that I saw –- that have been put on the screen

before; that is, the people come to us and ask, “What risk I am? What can be done?” Because what we’re talking about is, "Okay. When you die, we are going to measure the asbestos in your lung." That’s not exactly what they are asking.

So these studies are probably excellent as archeological type of studies. They're studies that allow you to find out what happened in the past. But they’re not studies that are practical to address the questions that I have seen that have been put on the screen before because, obviously, you can’t do that.

DR. CASTRANOVA: Again, if autopsies are not going to be very prevalent and they only –- as I agree -- only give you information what this person was exposed to in the past, doing a history of the person’s activities -- where he worked; where he lived; how long he’s lived in this community; where in the community does he live, as opposed to where the sites of high exposure, you believe, are. All these things have to be very well documented because, again, you’re hoping to project this person’s exposure to the community, which is going to be quite difficult.

DR. WEISSMAN: And addressing the issue of low autopsy rates, that’s obviously a really important barrier. It’s a really important impediment in our country. I mean, autopsy rates have just gone down so

much, as you know, and that's a barrier that any study that involved using autopsies would have to address would be really, really reaching out to providers and really, really reaching out to the community and creating incentives, you know, for people to request and perform autopsies above, you know, the baseline, which is so low. I mean, it's really a good point.

DR. ROGGLI: Well, it's true that the autopsy rates are decreasing in medical centers and in community hospitals and that that is probably not the best source that you're going to get for studying this. But I'm not convinced that there's a decreased rate of autopsies among medical examiner cases.

DR. HOLGUIN: Trauma.

DR. ROGGLI: Trauma cases and individuals who are from certain communities, the medical examiner cases would be the way to go to find out what the fiber burdens are for people living in an area if you want to look at autopsy lung tissue. And for that, as mentioned, I think, in discussion, one of the problems with that is finding exactly what this person's occupational exposure was, exactly how long they lived in an area, and were there other complications.

For the living-tissue cases, there's a couple of different sources that I think you would not want to miss

out on. One would be lung cancer, lobectomies, or pneumonectomies. The vast majority of those are going to be for cigarette smoking. But you've got the lung tissue, which is going to tell you, while you're at it, that what that person was exposed to in terms of asbestos fibers in the environment. And so, if you had a registry of individuals in a community so that you knew an individual has had surgery and if you could get permission to look at their tissues, I think that would give useful information.

One thing you certainly wouldn't want to miss is anybody in the community who had mesothelioma and who had a pneumonectomy for that. To miss the opportunity to look at lung tissue samples in that circumstance would be, I think, quite a shame. You also have to tailor, I think, the studies as to what the question is being asked in any particular location. For example, with the chrysotile issue, as Dr. Dodson mentioned, chrysotile doesn't accumulate in the lungs to the degree that the amphibole fibers do and you're looking at a snapshot of the exposure history.

And since the lung is not a very good measure of what the chrysotile exposure is, maybe, in that circumstance, you're better off looking at what are the environmental levels of exposure, measuring in the environment rather than looking at lung tissue analyses.

On the other hand, there's good data showing that for the amphibole, amphibole fibers, the fibers accumulate progressively with exposure over time, and even though you're looking at a snapshot, you are looking at a cumulative exposure over a lifetime. It's a pretty good measure of what the exposures were.

As far as the instrumentation that you use is concerned, it depends on what the question you're asking. Some really excellent studies were done by Dr. Karjalainen in Finland that indicated that, if you looked at the same samples with SEM versus TEM, you found about three times as many fibers by TEM as you did by SEM. But the difference was almost entirely due to chrysotile. And there was little, if any, difference between the two when you're looking for fibers, amphibole-type fibers.

So for example, in investigating tissues in the Libby area where you're talking about tremolite, actinolite type of fibers or in the El Dorado Hills area, then SEM would be a fine type of instrumentation to use to answer that sort of question. So those are the main comments I have those along those lines.

DR. HOLGUIN: Thank you.

DR. CARBONE: Victor, if I may comment. The -- I worked at the ME Hospital, medical examiner office, in Chicago for a while. We had about 12 deaths a day. Of

those 12 deaths, I would say that, on average, two-thirds were kids who shoot each other, gang kids, and they're 20 year old. And the others were people which you had no clue from where they're coming from and who died for the horrendous reasons.

What I'm saying is that when we design a study, of course, we have to see the cost effectiveness of the study. And if we were to do a study to measure the prevalence of asbestos bodies in autopsy people at the ME office in Chicago, it would take for the next hundred years before you have a number of patients that can give you a P value.

So although I believe that measuring asbestos content in autopsies is very important as snapshots on a particular case, as you indicated, particular case of mesothelioma, particular case that presents to you the opportunity to study it, it's a prospective study. It's a study to assess the exposure, say, of the city of Chicago. By the time you have the study published, the situation in Chicago has changed completely because it's decades from now.

Considering the biopsies that you take from people who develop lung cancer, obviously, they can give us important information. But we need to keep in mind that that is a biased population, and it's a biased population

because they have lung cancer, so you're not getting a true background evidence. You are biasing it from start, your study, saying, "I'm going to study the ones who have lung cancer, who are smokers, who probably have asbestos and get" –- and, in fact, asbestos and smoke work together in causing cancer. So you have a very biased population.

As far as you accept the fact that you are studying a very biased population, then you can do the lung content analysis. As far as you do not conclude that that reflects what happens in the community because, obviously, it can't.

DR. ROGGLI: Well, I don't think that the autopsy rate from gunshots in El Dorado Hills County are going to be the same as what you have in Chicago. And one of the things I think would be a true shame if you had a medical examiner case of an individual who was 80 years old, died of a heart attack, lived his whole life in El Dorado County, and it was an ME case and you didn't analyze the lung tissue. That would be a great opportunity that was lost.

Obviously, in terms of addressing your question about bias, it has to be a carefully designed study, just as Dr. Weissman pointed out. What you have to do, if you're going to do this, is you look at ME cases, individuals who are in the EL Dorado County areas versus ME cases from

elsewhere that are not in areas that are known to be contaminated with asbestos. Again, you have to know what the occupational exposure history and you have to know what the residential history of the individuals were. And you do a case-control series that way.

If you don't do case-control series, you're not going to have any useful information. The same thing is true of looking at lung cancer specimens. Of course, you're looking at a bias if you look at lung cancer resection specimens. But what you look at is lung cancer resection specimens from people who've lived their life in El Dorado Hills versus people who have lung cancer resection specimens who also were smokers who didn't live in El Dorado Hills in an area that was not contaminated.

So you have to do very careful case-control studies if you're going to interpret what it means in terms of your lung fiber analysis and, therefore, risks of disease to live in the El Dorado Hills area or Libby, Montana, for that matter.

DR. CARBONE: But people move.

DR. HOLGUIN: So, I guess, what you're -- what you're describing, would it be useful -- I mean, the question is open to the panel -- to have like a -- I mean, you know, you can't predict the number of autopsies or cases that will be available for living tissue in the hospitals

either. Would it be useful to have a surveillance program in different communities with different levels of exposure? And you're just getting the cases sent and getting information as it comes, and then eventually you would have enough communities to have enough powers, you know, to calculate an effect.

DR. CARBONE: You wouldn't. You wouldn't because people move. And you will never have the history of the people who come in ME office. It's impossible. I mean, I worked there. How are you going to know, of those kids who are dead there, from where are they coming from? It would take a huge team of people to track down those kids who are dead –- and, by the way, who are usually 16, 17 years old and so probably will not have enough exposure.

You can only do a snapshot, as Victor say, of the 80-year-old guy who lived all his life in El Dorado Hill. But if you are in a city like Chicago, most of the people who are there have not lived all their life in El Dorado Hill or in Chicago; have moved around, like me. If I die in Chicago, where are you going to trace my exposure? I've been everywhere.

DR. HOLGUIN: Dr. Dodson.

DR. DODSON: Well, I've just got to, kind of, carry something Dr. Roggli said a little further. And that's, you know, we know what we think an exposure is, what it

consists of. And, I guess, at some point, someone else will deal with preventative issues because autopsy's after the fact. But –- but, you know, we do have a mobile society. And we have to be guarded in looking at tissue assessments, for any of us that have done that, with the surprise that we're told an exposure occurred to something and we found something else.

And you could, in point of fact, have an old person living there but had an intense exposure at some point that resulted in accumulation of a different type of asbestos. That, I guess, comes back to the issue of being inclusive of what is there as far as fiber burden rather than just focus on the type in that area which has some unique characteristics that makes it more easily resolvable in instrumentation.

DR. GUNTER: I have a little –- maybe a little different direction on this. I mentioned this this morning, and there was some –- got some conversation started, so I'll mention it again. As a geologist and a mineralogist, I look at sampling as an issue that we have to do and then sampling of the lung is another issue. And the comment I had this morning -- and it didn't go over that well -- was talking about sampling the entire lung.

And at autopsy, if you had the entire lung, you could digest the entire lung and look at the entire mineral

content instead of these sampling effects. And these sampling effects, when you take a small portion and extrapolate that, does not give a clear analysis of what the content is. There's some discussion that Art Langer had tried some of this work some years ago. But with techniques like powder x-ray diffraction now, some of the new analytical methods with computer programs to refine this data, we can analyze quantitatively the mineralogy down to a percent or less with milligram-sized samples.

So if you had the entire mineral content of the lung, whether they're background or people living at Libby or people living at El Dorado Hills, people who've not maybe been moving around that much, it would be a good way to understand the entire content and not just a portion of it. At the same time, if you knew the entire content or say the amphibole content and then you could then take, with careful sampling, and you could take and figure out the different size ranges for subsets of that.

But I think this is one thing that's missed is looking at that entire –- entire content. And that might not have been able to have been done 20 years ago, but it might be able to be done now, assuming you could remove all the organic material, and that would be probably the biggest problem.

DR. ABRAHAM: Well, just to respond to what you said,

the idea of the entire content means a gravimetric approach, and the issue of looking at fibers really requires individual fiber analysis rather than a gravimetric approach because the lung has a burden of other particles other than asbestos that's usually way higher on a gravimetric basis.

For example, the animals from El Dorado have relatively high concentrations of numbers of tremolite fibers that are long and thin. But they have probably a hundred times higher concentration of nonfibrous tremolite and other dusts in their lungs.

So to try to measure that on a gravimetric basis and the idea of looking at an entire lung is something that the people that do lung fiber burden analyses probably would find difficult to reconcile because, when we look at lungs in different samples, different areas, side by side, or from different lobes, sure, there's variation. But it's not a huge variation. It's not more than an order of magnitude usually from one part of the lung to another. And that's the kind of variability that we live with.

Someone with no excess exposure versus someone with an occupational exposure or even an environmental exposure will have orders of magnitude difference usually. There's rare cases that are near that borderline of background in reality. So I think that's interesting from a mineralogic

point of view, measuring the total dust and measuring down to a tenth percent. But I think it will miss an awful lot of information about detectability for asbestos because it can be present at much less than a tenth of a percent by weight and still be high number of fibers when you look at it in the dust in the lung. So be really careful about that.

And the other thing that I wanted to mention, in response to Michele, is that –- and Victor too -- is that you've done work on pediatric autopsy cases, and there's no reason to not look at that. We're not trying to look for asbestos disease correlations with fiber burden. That's been done quite a bit around the world. We're trying to answer the questions of whether there's exposure going on.

So jumping ahead, both Victor and I pointed out that if we want to measure exposure, we should measure exposure. The measuring of the lung fiber burden may be, as we heard, an indication of retained dose. But the younger the population we look at, the closer it is to recent exposure. And if we're thinking about the disease that occurs with the least exposure, which is mesothelioma, then it's the longest latency. So we want to prevent exposures by measuring what's going on now.

So the studies like the EPA did in El Dorado, showing

that there's asbestos there -- it's getting stirred up into the air in significant amount -- and the studies in animals that show animals are being exposed and retaining it in their lungs, even if the numbers don't match humans, are evidence of exposure. The issue of jumping from that evidence of exposure to risk is one that I hope we spend a lot more time talking about later because that's a real challenge.

DR. GUNTER: Just a quick comment. I don't disagree by any stretch of the imagination. You look at the fiber lung. But what I'm saying, this -- this is a piece of the puzzle no one's looked at before -- the entire lung load, mineral load -- and that might have some effects. So it's a different thing to look at.

The other comment that I think -- and I suggested this also -- is the exposure is, by far, the biggest concern, and now, when you look at the lung, you're looking at what's retained. So if you have ideas -- exposures, and I have some ideas later on, on how we might be able to measure those a little different than we have.

DR. HILLERDAL: Well, this is a mobile society, as you said. And so I wonder, first, how many 80-year-old men have lived in the El Dorado Hills. I was told it was developed 20 years ago. So how could you live there your whole life? And secondly, how many of these 80-year-old

men who die from heart infarction will come to an autopsy? I think it's not realistic.

But I do think that what could be done and what should be done is those kids, young people, who die from accidents but have been living in this community -- that, I think, is a very good idea if you could take out their lungs and measure what they have in their lungs. I think that's the only realistic way of doing it because, otherwise, if you wait until they get the mesotheliomas, they're already in their fifties or in their sixties and they live somewhere else and nobody knows anything about their exposure and where they stayed when they were kids.

DR. HOLGUIN: Sure.

DR. HILLERDAL: Also, I would add here that there is amphiboles. They also get cleared though very slowly. So, I mean, Victor said that the amphiboles is a collective thing you have in the lungs, but that's not quite true. There is data showing that they slowly also get out of the lungs. So it's not really –- you have to –- you have to know how they started from Western Australia, for instance, show that they calculated half-life for crocidolite for about, I think, it was eight years or something like that. I think that's too –- it's too –- I think it's slower than that, but there is a clearance also of amphiboles.

So you -- as was said here, what you get is a snapshot of what you actually are exposed to. And that's why, I think, those kids or youngsters who actually live in the community and die from accidents and get an autopsy -- these are the ones we should concentrate on. Hopefully, there will not be too many.

DR. CARBONE: So the summary of this discussion will be that we want to do the autopsy studies on young kid that was not shot and what is the very close exposure, if there is any exposure to asbestos in that given community, not trying to attach any risk to it, but just to see whether a given community in Chicago is, in fact, exposed to asbestos or is not.

And that could be complemented with air sample studies to see whether there is asbestos in the air. And then you put the two things together and you can determine whether there is asbestos exposure in Hyde Park versus Oak Park, considering whether the kid has been shot from Oak Park or from Hyde Park (laughter).

Yeah. I mean, that's it; right? I think that is a very reasonable approach actually. The 80-year-old doesn't work, but the kid works.

DR. ABRAHAM: Unfortunately, there are, you know, motorcycle-accident victims and...

DR. CARBONE: But how do you go with the background

levels? Because we have all heard about and read about these background levels of asbestos, that we have all millions of asbestos fibers in our lungs. And then there is all the issue that there is below and above background levels. But this is usually in lungs of people who are 50, 60 years old who have been exposed to asbestos.

Now we have to determine what are the background level of a 20-year-old because, obviously, that -- since there is accumulation, the background level of a 20-year-old, there's not going to be the background level of a 40-year-old. So first we need to determine where are the nonexposed kids in Chicago, and then determine whether somebody's above that; right?

DR. HILLERDAL: Yes.

DR. ROGGLI: I think the way you do that though, as indicated, is with the case-control study. If your question is, is there exposure in El Dorado Hills from the tremolite contaminant there that's above the background elsewhere in California that doesn't have that sort of contamination, then you look at individuals of a certain age group. If you want to pick kids who die in motor vehicle accidents, that's fine. And you compare them with somebody who lives elsewhere, not with that sort of exposure, and see how much they have.

There may be just as much tremolite in one group as

the other, in which case you would conclude that there's no significant contribution to the lung burden from living in El Dorado Hills.

DR. GUNTER: I think this is one of the issues of sampling. And I said I'd talk about it later, but I might as well now. The air sampling -- if you knew the background levels because, I mean, these materials are minerals, and by definition, they occur naturally. And by reality, they're spread all around the world. And if humans weren't even here, they would still be here floating around the air.

So the question is what's in the air. And the question is sampling some of that, and many of you -- I've been involved with some air-sampling studies we did in Idaho a decade ago, looking at the quartz content of PM-10, and we had a dichotomous air sampler collecting PM-10 and PM-2.5. Now, that was a very specialized sampler, but the EPA has set up PM-10 collecting networks nationwide, and these are collected on filters.

Those filters exist. People could look at those filters to find out background levels with great difficulty. But those air samples exist. You know, it would seem to me like having a good idea nationwide what's in the air would be a very wise thing to do.

DR. CASTRANOVA: Well, if I could just turn the

question just slightly and give another example that's not asbestos. In central California, they did an autopsy study on accident victims, mainly young adults. And the question was would soil levels of silica, airborne silica, be sufficient to cause fibrosis in the lung. And from an exposure level, they did measure soil, airborne levels of soil-based silica in farming communities. And yes, they have a number, and it's fine.

It's above ambient levels in other areas. But the question is was it sufficient to induce the first events of a disease process, and in the autopsy study was the agricultural workers and accident victims. They were able to show the –- and deposition sites of the silica particles. There were initiations of collagen formation and so forth.

So they –- they –- and I think that's one of the things you're interested in is an early indication what are the levels that would give you an early indication that disease process is beginning. And so perhaps an autopsy study could be used in that regard.

DR. ABRAHAM: Well, just in response to that, I'm not sure that is the interest here. Do we want to know the disease is beginning, or do we want to know that exposure has begun? To me, it seems like we already know that there's exposure.

DR. CASATRANOVA: That's what I think.

DR. ABRAHAM: And so the issue is prevention. We know asbestos causes disease whether it's from the soil or from the shipyard. And we don't have the techniques at present to extrapolate from measuring the dust in animals lungs or from air samples in a simulated aggressive testing, like the EPA did, to measure the risk exactly. But we know it's more than it would be without that exposure.

And that's the answer I would give to the people asking questions. Yes, there's exposure. And to the second part of what the risk is, I don't have a clue at this point.

DR. CASTRANOVA: See, that's where --

DR. ABRAHAM: But I think measuring disease is a separate issue from measuring exposure. We already know about dose-response relationships with asbestos and fibrosis. What we're really concerned about with low level exposure is mesothelioma --

DR. CASTRANOVA: Mm-hmm.

DR. ABRAHAM: -- where there's no known safe threshold. I mean, not everybody agrees with that, but most people agree with that, I think.

DR. DODSON: Let me go back just for a moment to a point Dr. Roggli and Dr. Gunter both made about the

comparative base of exposure. I mean, we're talking about potential here, in many instances, rather than disease -- to take an assessment of that. There's tremendous amount of data availability from folks that have been involved with abatement and other activities for air monitoring throughout the state where there aren't, presumably, outcrops of crystallitic rock.

So, I mean, that would be a good starting point to –- I mean, if someone in that area, for example, came to autopsy and Dr. Roggli assessed the lung and found in a 20-year-old there was a lot of tremolite, that would be pretty logical it had to be from some exposure other than background if there weren't any air samples in that area that dictated that it was in the ambient air. And that data must be available through the state agencies and possibly through the EPA, some of their activities.

DR. HOLGUIN: Do we know what a lot is? I mean, I think one of the questions here is what is the threshold that may represent an elevated exposure, you know, from a background.

DR. DODSON: Well, I'm talking about something as simple as detectability of a type of asbestos in the air.

DR. ABRAHAM: Certainly, we –- various labs have information on background levels, and within that lab, analyzing samples from people or animals can be compared

to whatever they measure. I –- there probably are some borderline cases, but in the case of a significant exposure, the levels of tremolite are so much higher in somebody or some animal with significant exposure than they are in any control group.

We've looked at animals from other places in El Dorado much more extensively than we looked at animals –- and you've looked at animals, Victor -- from other places. And I don't know how much is just asbestiform tremolite found, but in dogs that we looked at from Kansas, where we know what soil they're exposed to, where there was no tremolite of any kind that we could detect looking at thousands of particles, we didn't find any fibrous tremolite.

So those dogs didn't have the same tremolite exposure as the dogs we looked at from El Dorado. But that's not a big surprise. The dogs' lungs reflect the dust that they've been exposed to, subtracting clearance over a period of time. And it's shown with age that the amount of dust goes up in the dogs that live in a certain area.

DR. CARBONE: So we are talking about techniques to verify that exposure takes place as you indicate, and --

DR. ABRAHAM: To convince people.

DR. CARBONE: -- to convince people that, indeed, exposure take place. Of course, none of these techniques,

unfortunately, can address the questions that they put on the panel that say what you should do about it, but you can –- using these different techniques from air samples to studies in animals to the occasional autopsy or lung biopsy verify that, indeed, that there is exposure in a certain area or identify that there is exposure. And then they should, of course, be counseled what you do about it.

DR. GUNTER: In the world of silica -- and I typically just say quartz because we're talking about quartz in general. I mean, I could say fairly confidently that any PM-10 air sample in the United States would probably contain between 10 and 20 percent quartz. I feel good about that statement. But I couldn't tell you what percentage amphibole, just ignoring the fact of asbestiform versus nonasbestiform. I would say if you looked in areas –- because the map that was up there showed where the mountains are. That's where the amphiboles are, and geologically, that makes sense.

In those areas it would be higher, but I don't know what it would be, whether it would be .1 percent, 5 percent. And I think those things matter when you come to the risk assessment of being able to answer the questions to the people in Libby or in El Dorado or anywhere living in any mountainous region because that's where you'd be typically finding those samples.

And it would be different in the mountainous regions in the east -- because of the rain, there's more vegetation, higher rainfall -- than in the mountainous regions in the west. So I think a lot of this does come back to understanding what background levels is, and this is one of the things that interests me, and I do not know what the background level would be in the air of an amphibole.

DR. DODSON: Just as a clarification for this panel, we're talking about asbestiform tremolite, okay, because what you just said was asbestiform and nonasbestiform amphiboles, I think.

DR. GUNTER: Yeah. I'm just saying just --

DR. DODSON: We're not dealing with a nonasbest –- I'm just saying, for clarification, we're talking about the asbestiform because we're talking about asbestos-related diseases or potential thereof, and the fibrous form is what we're concerned about for inducing those. Okay.

DR. GUNTER: One of the –- again, to –- one of the things I like to talk about if you talk about the total amphibole content, then it could either be -- if it's 1 percent, then there wouldn't be 2 percent tremolite asbestos. So if you know the total, the total amount --

DR. DODSON: Right.

DR. GUNTER: And this is the thing I like to come back with the gravimetric analysis of other techniques. If you figure out the total amount with some technique, then the microscopic techniques could be used to figure out the percent of one versus the other.

DR. DODSON: Percent fiber, nonfiber.

DR. GUNTER: And I think in many ways that would be another way to approach it.

DR. ROGGLI: However you go about analyzing this question about exposure, it's not going to be easy to get an answer. And even --

DR. HOLGUIN: We're not leaving this room until we get one (laughter).

DR. ROGGLI: There's all sorts of problems just with exposure measurement because if you try to measure exposure in the environment, where do you measure? There's almost an infinite number of possibilities of size that you can measure and who you're going to measure. I mean, obviously, if you're worried about contamination of tremolite on a soccer field, then you might want to do personal measures of kids playing on the soccer field.

DR. HOLGUIN: Sure.

DR. ROGGLI: Or do other some sort of measurements in the vicinity of where you're worried about particular deposits occurring. But you have to –- if you're going to

make measurements, you've got to decide where you're going to do the measurements. You've got to determine whether the weather's going to affect your results. Will prevailing winds, rainfall, thermal inversions, any of this affect how much you measure in one particular day? How many days you're going to measure and how you're going to determine what a community's exposure is because --

Just because you find an area near a deposit to have increased levels, if somebody's not there breathing that, it's not going to make any difference, which is one of the reasons that sampling of lung tissue samples is important because, whatever they have in the lungs, they actually breathe.

DR. HOLGUIN: Right.

DR. ROGGLI: And even though, as pointed out, there is some clearance of amphibole fibers, there are good studies that show that amphiboles, in spite of clearance, accumulate progressively with exposure. So the total amphibole level is a good measure of what the exposure was over the lifetime.

That's not true for chrysotile, which tends to plateau out after a given exposure and does not increase with further doses. So those are just some of the considerations you have to keep in mind when you're trying to answer this difficult question of who's being exposed

to what.

DR. HOLGUIN: So it's considerable sampling variability.

DR. ROGGLI: Yeah.

DR. ABRAHAM: Well, the EPA did personal sampling of their personnel that had respirators. And other studies have put personal sampling collectors on kids at PM-2.5 and things like that in various places around the world. So if you wanted to follow a group of kids with samplers that could then be analyzed for fiber burden –- for airborne fiber levels, that's theoretically possible. It would just require recruiting a bunch of kids in different communities, control and suspect areas, and sampling them for a few weeks or something like that, different times of year. Then you'd have information about their exposure, which is -- you know, personal samplers would be the best measure of their exposures.

Did EPA do something with the kids too, or was it only the simulated exposures? Are we allowed to ask the audience?

DR. DYKEN: Well, I --

DR. ABRAHAM: No? No.

DR. HOLGUIN: Oh, hold one second. Jill.

DR. DYKEN: I'd just like a little clarification. I just kind of want to get the discussion maybe back on

track towards the autopsy results and maybe –- I mean, this is very interesting where you all are going, but is there a way to take the kind of autopsy studies that you're doing and somehow correlate that to exposures that somebody might be getting that could be measured? So –- so our focus wants to be on, kind of, the autopsy study or the fiber burden in this area and maybe apply that to make a correlation with that.

DR. DODSON: My answer to that would be yes, but you have to die (laughter).

DR. CARBONE: I thought that, in fact, we had addressed that because we had seemed to reach the agreement that the autopsy of a young person could give some information about immediate exposures to that person, that making autopsy of an 80-year-old or anybody who had -- it would be difficult because except for rare cases who lived all their life in the same place is very difficult to extrapolate from what you find in that individual. That, as Dr. Roggli has indicated, is a very good way to measure what that human being has been exposed to.

But when you try to extrapolate what that human being has been exposed to, to what everybody else in that community's been exposed to, that is very, very difficult because people move and because it's very difficult to know where they move.

I am just coming back from three weeks in the erionite villages of Karain and Tuzkoy. If I die, you measure my lung, you want to conclude that in Oak Park there is erionite. So it's very dangerous to extrapolate this thing. However, given this and given the fact that, in fact, autopsies can be very misleading for this precise reason, even in a 20-year-old kid who dies and that you do a lung content analysis -- it's only going to tell you what that kid was exposed to, and unless you know exactly what he did for that 20 years, you are to be very careful to say that everybody else in that community is going to have the same type of exposure.

But given that that's the only possibility that I can see you have to try to make some assumption of community exposure. But you cannot use an autopsy to determine what other people have been exposed to in their community.

DR. HOLGUIN: One thing I haven't heard much in terms -- if you consider a group of either kids or adults who get exposed to the same levels, what are the factors that may affect the position in the lung? For example, if you have –- as a pulmonologist, I'm interested. If you have chronic airway disease, kids tend to have a higher mean of ventilation than adults. Do all of these factors in a given individual may affect the amount of retention and clearance of particles? Is there a lot of variability

across individuals? I.e., if you sample one lung, will that be representative of other people of same age with similar characteristics? Or if they smoke 20 pack-years versus 15, if they happen to be one of, you know, a ratio 46 percent of predicted, how does that affect the overall analysis of particles? Could the panel comment.

DR. ROGGLI: Well, you're not going to come to a conclusion by looking at the lungs of one individual who died in El Dorado Hills and lived there, say, their entire life versus somebody who did not live there. You're going to have to look at groups of patients, and you're going to have to do careful guesstimates of what the difference is going to be to see what the statistical power is, how many cases are you going to need to look at.

DR. HOLGUIN: Uh-huh.

DR. ROGGLI: Probably you're going to need to look at, at least 20 cases in your case versus control groups to come to any conclusion about on the average does this population have an exposure which is measurably different from our control to background population.

DR. HOLGUIN: Would disease, pulmonary disease, be a confounder or a modifier, for that matter?

DR. ROGGLI: You need to look at that. You need to know that. But, hopefully, if you look at a large enough number of samples, it should be similar in both groups;

should cancel out.

DR. HILLERDAL: That's another advantage if you do it with young people because they don't usually have 50 pack-years of smoking. But, also, there are individual differences.

We are talking about these soccer field, of course, and there is differences. Some of the boys will be out there all the time, stirring up the dust and things, and of course, they will get more exposed than the other ones who are a bit lazier or not interested in playing soccer.

So we're talking about background exposure, but, actually, what you have is sudden big peaks of exposure when, for instance, you go out digging in your garden or when there is some construction going on. And in between, there is probably not even measurable levels, and there can be huge differences in these. We know that from studies in Turkey and other places.

So that's why, I think, even if you put these –- if you give a week's respirators to kids and measuring their exposure, that might not –- might not correlate with their real exposure because you have these sudden peaks which you might not even be aware of. So that's why I think the best thing is to make for the studies for those hopefully very few young people who die and who have been living all their life in these surroundings.

But then, of course, you should also like to know how active they were, whether they were standing outside of the soccer field or actually playing on the soccer field.

DR. CARBONE: Never have enough autopsy to repeat.

DR. HILLERDAL: I agree with everything you say, but you can.

DR. ABRAHAM: Well, you don't know. I mean, the data's available on mortality and age distribution of mortality in a number of ME cases in the various counties, and I don't know if anybody's even tabulated. That would be a first step to do before trying to design a project. I mean -- and that information is somewhat difficult to get because of privacy concerns, but it's there. It's public record, even it's not made available to the public easily.

DR. WEISSMAN: But getting back to the question about, you know, what are sort of the confounding variables that might exist that, you know, might affect, you know, levels of fibers in the lungs. I mean, we talked about smoking. Obviously, pulmonary disease does affect particle distribution in the lung. The types of activities was mentioned.

Oral-nasal partitioning of breathing -- so if somebody's breathing through their mouth and, you know, they have a high minute ventilation playing soccer, that's

different than nasal breathing and being sedentary. So –- you know, but I think from the standpoint of smoking history and history of lung disease, those are confounders that have to be considered in study design.

DR. CASTRONOVA: Again, if you were doing an autopsy study, let's say, on accident victims, we're talking a lot about measure of exposure. And it seems to me you have a lot of data on the airborne levels of the asbestos in the community. And so you have a good bit of data on exposure.

But what you don't know is whether that exposure is a level that is causing the risk. And the reason you don't know that is all our dose-response data is up at high exposures. This is down at low exposure. You have no idea.

That's why I'm referring back to accident victims and looking -- matching fiber counts to sites of depositions and early pulmonary changes that may occur histologically so that you could get some handle –- are these levels actually causing a pulmonary reaction, and can we predict that that pulmonary reaction would be bad?

So that's why I think the data would be very helpful. If I were to measure exposure, I would just measure airborne levels. I wouldn't do autopsy studies. It's too expensive.

DR. HOLGUIN: This is one significant limitation is that you –- if you sample fibers in the lung tissue, you really can't tell much about the chronicity of the exposure; is that correct? I mean, you cannot say whether you've been traveling or you were exposed a year before or...

DR. CASTRANOVA: You don't know that exposure is coming unless you have a good history. I've said this before.

DR. HOLGUIN: Okay.

DR. CASTRANOVA: You need a very, very good history to know -- to say that exposure's coming from the community. Now, if it was a young teenager who was born and raised in that community and got in an auto accident, then you have a fairly good idea that the exposure came from that community.

DR. HOLGUIN: Okay.

DR. ROGGLI: I think one thing you have to realize is you have to do very careful coordination with the medical examiner's office because autopsies that they would do on a motor vehicle accident case typically would not involve taking histologic sections. It would not involve saving organs.

It would involve mostly a gross examination and identifying that there hasn't been a head injury and

excluding other diseases you could see with the naked eye. So you have to make careful, careful coordination with medical examiner's office probably to get them just to save both formalin in the fixed lungs in the case for further studies is the way to do it.

DR. HOLGUIN: Dr. Dodson.

DR. DODSON: You know, one step further, you're also going to have to make sure they understand the importance of not cross-contamination with any water that may also be carriers of that material and give the implication it was in your tissue. So your point, one step further, is to make sure they use prefiltered materials, if possible, and wet solutions to protect against their cross-contamination if the water sources have the material in it or where the water source comes from there.

DR. ABRAHAM: You'd also collect samples of the formalin they use in their laboratory --

DR. DODSON: Yes. That's the other point.

DR. ABRAHAM: You have to check all those things.

DR. DODSON: You do. That's correct.

DR. CARBONE: And then another very expensive thing is that you will have to have your staff that is going to go after the families and relatives of the deceased to find the history of these people.

DR. ABRAHAM: Yeah; of course.

DR. CARBONE: Yeah. And if you were to be in Chicago, it wouldn't be easy because it's not the truth. I mean, most of the people are gang people who die. So they may just send another nurse down there to find out who's the family of this kid is and where this kid has been. It's not going be exactly the easiest thing to send your nurses in the gang areas of Chicago to find the history of these kids.

DR. ABRAHAM: Well, I mean, we did a study --

DR. HILLERDAL: California, not Chicago.

DR. ABRAHAM: Yeah. There are other places. And we did a --

DR. CARBONE: Means they have to die and go to an ME hospital.

DR. ABRAHAM: Yes.

DR. CARBONE: Usually, they die for a reason like that.

DR. ABRAHAM: No. But, I mean, even in a city like Syracuse, there's some problems like that with crime, and we did a study where it involved family contact. And there were a few homes that were just excluded from the study because it wasn't safe for the team to go there. Equipment would have been lost, you know -- it was too -- so, I mean, that's built into any study design that you expect some people to be excluded from the study for

whatever reasons, and you just have to build that into your sampling.

DR. HILLERDAL: What is the legal implications? Do you have a right to –- at the autopsy for --

DR. ABRAHAM: Oh, no; not in some states.

DR. HILLERDAL: You have to ask the parents, don't you?

DR. ABRAHAM: You almost have to --

DR. HILLERDAL: When you pave the lines.

DR. ABRAHAM: Yes. You almost have to bring the person back to life to get their permission. In some places, it's really difficult.

DR. HILLERDAL: Yeah. Okay.

DR. GUNTER: We're sort of on the anecdote -- and I'm sorry if this is going farther off the subject. But when you look at communities in America -- I mean, I would agree with what you say in Chicago or in California. But I'm from southern Illinois, and my father has lived his entire life in that little town except for the two years he was on a battleship during World War II. But in the smaller communities in America exposed to asbestos, of course --

(Unidentifiable cross-talk)

DR. GUNTER: But in the smaller communities in America, I don't think this is as big a deal as maybe

people are making it sound, especially in a class of people who aren't as mobile. Many blue-collar people do not move around that much. Again, this is somewhat anecdotal. And the histories, if you live in a small town -- I mean, I could send a letter to the town and just put my father's first name on it, and it would make it. I mean, in Chicago, it's a little different.

But in the smaller communities that might have some of these exposures -- and let's face it. The places you put up earlier on the screen were not major cities. They were rural communities. And those rural communities are in areas that have –- they're more agricultural based, possibly more mining based, and it might be much easier to track personal histories in those areas.

The other thing that –- well, then you can –- the –- is there any place where there are studies where you have good air data and then fiber data of lungs? That correlation. Have those studies been done where you could see those? Because if you look at fibers –- because, again -- what Jill was wanting -- if you look at exposure in the air and then the people are concerned what's in the lung, are there studies that correlate those existing?

DR. CASTRANOVA: Occupational studies.

DR. GUNTER: But, again, we're looking more at --

DR. HOLGUIN: Community.

DR. GUNTER: -- environmental.

DR. DODSON: Mm-hmm.

DR. HILLERDAL: What I have understood that if we're talking about El Dorado Hills, that's not a typical old farming community of the United States. This is newly developed with highly priced houses, and you will have a quite lot of movement of people out and in there. And most of them will commute to other places where they work, won't they? So it's not –- it is not the typical old farming society of America.

DR. DYKEN: We're not just talking about El Dorado County though.

DR. WHEELER: No.

DR. DYKEN: We're talking about communities in general.

DR. HILLERDAL: Okay.

DR. HOLGUIN: So I'd like to ask some questions to the panel members, going back to the autopsy and tissue. So given the uncertainties relating with fibers, detection of these fibers in the lung tissue, and the exposures are quite significant as it has been raised, will it be worthwhile to set a surveillance program in multiple places? Would we learn more about exposure and fiber finding in the lung?

I mean, because I hear you. Like we need to have a

program in place where people come in, and, you know, tissue gets sent out for analysis and that is done in the standardized fashion across different sites with different levels of exposure. Would this be useful or not?

DR. ROGGLI: What do you mean by surveillance program?

DR. HOLGUIN: Cases come in different communities, and they will -- you know, there will be a program in place to take some of the tissue out and send it for analysis; obviously, not every community.

DR. ABRAHAM: A well-designed prospective study like that would be very useful.

DR. CASTRANOVA: And the communities have to be selected to show that you have an air sampling for asbestos fibers.

DR. HOLGUIN: Sure. You would have, you know, background sampling and you would select communities with different profiles of exposure.

DR. DODSON: But in this case you're dealing with a unique asbestiform. So simplistic as it may seem, if you have elevated levels of that type and that tissue is compared to whatever the rest of us of have found in general populations wherever and it's specific, exclusionary of other types of asbestiforms, it seems like that would raise an immediate flag of concern for

potential involvement by itself. I mean, does that make sense, Victor?

DR. ROGGLI: You're referring to Libby?

DR. DODSON: Yeah. No; no. I'm talking about the California scenario. It's tremolite, tremolite --

DR. ROGGLI: Well, at least, in cases which we looked at in North Carolina -- case controls we had there. The problem with that is that tremolite's the most common asbestos mineral which we found in -- for fibers 5 microns or greater in length in a general population.

And of course, the SEM approach is not sensitive to the thinnest chrysotile fibers nor do we even count the real short fibers. But for longer fibers which -- Berman and Crump's analysis with the EPA says the ones you have to worry about -- tremolite was the most common one we found that we –- in the general population.

So that you would have to have a careful control group to make sure that if you found tremolite from individuals from El Dorado Hills or Libby, Montana, or wherever that it was greater than the amount that you might expect from somebody in a similar location except that they did not have the environmental exposure that you're investigating.

DR. CARBONE: Another good question would be why. What would be the reason to do the study if the reason is

to identify places at risk for asbestos or if the reason is to verify that where you have already identified asbestos exposure, indeed, there is asbestos in the lung. The two questions are very different.

If the first –- if it’s the first question, that would be an extremely expensive study because, of course, you are going to have to set out many different places all over the United States if you are using the autopsy system as a sentinel of asbestos exposure. If the autopsy system is only used to verify exposure once you use a sampling to verify that, indeed, there is asbestos in the air and now you want to see whether, in fact, human beings are breathing it because that’s the ultimate way to know that they are exposed, as Dr. Roggli said, then that is much less expensive and much less time consuming and probably doesn’t require either too much of a P value.

You just need a few autopsy to verify that, indeed, the people who live there have asbestos in their lungs to verify that the air sampling that you have taken are valid. But the two questions are very different.

DR. FORRESTER: Can we pause for a minute? Dr. Stayner, can you hear us?

DR. STAYNER: Yes.

DR. FORRESTER: Okay. Fernando, he's ready to join the panel.

DR. HOLGUIN: Okay. Has he been –- has he been listening to the conversation?

DR. FORRESTER: No, he has not.

DR. HOLGUIN: Dr. Stayner?

DR. STAYNER: Yes.

DR. HOLGUIN: Welcome.

DR. STAYNER: Thank you.

DR. HOLGUIN: We were just discussing for the last hour the utility of fiber burden in lung tissue collected from humans at autopsy and fiber burden of lung tissue collected from living humans, such as those that are maybe obtained from lung biopsy of people undergoing other types of surgery. And I think my senses of the panel is its raising significant concerns relating exposure to findings of fibers in the lungs, and I think this is –- and many other discussions, but this is mainly where we're at right now.

DR. STAYNER: I'm sorry. I had a little trouble hearing you. But so we're talking about the lung fiber burden?

DR. HOLGUIN: Yes.

DR. STAYNER: Did you want me to comment on it?

DR. HOLGUIN: Go ahead.

DR. STAYNER: Okay. Well, I think several of you experience the same issues. I mean, the first obvious

issue is if you're talking about trying to document population exposure, there's so few autopsies going on these days that having anything that approaches a representative sample is almost inconceivable.

And the second issue that I highlight is -- because I work on chrysotile asbestos -- and other people pointed this out too -- is that, as a marker of long-term exposure to chrysotile, it does not capture that well at all because of the low biopersistence of chrysotile. Those are really, I think, are just the fundamental issues, you know.

For amphiboles, though, it's pretty decent, and I think that it would be reasonable although I think other people have also pointed out that if our intent is to predict risk, it's really a little bit hard to interpret, as are many of the biomarkers in terms of actual sort of quantification of risks.

And, you know, I think that –- that sort of leads me to another critical point that -- I think at the end of the day none of these measures are really substitutes for good exposure data. Really, that's still the gold standard that we would hope to have ideally. Sometimes we don't have it, so this may be a substitute.

If it's really the intent just to tell communities whether they're at risk or not, I can't see any better

thing than to try to document as much as possible what the exposures would be, and I think what the EPA did in El Dorado County is a good example of how, with some sort of simulations and things, that one can reconstruct what exposures might be for communities.

DR. HOLGUIN: Would any of the panel members like to comment?

DR. ROGGLI: Well, one comment about the exposure issue is that -- Dr. Stayner, we discussed before you got on the phone about possibilities such as kids playing on soccer fields where there is believed to be some contamination with tremolite and doing measurements, individual measurements, say, for a two-week period of time, looking for individual exposure.

So you do that and you find, well, yeah, there's some tremolite present. A question that comes to mind is that significant over the lifetime of exposure of that individual because there's many ways you can be exposed to tremolite. There's many ways you can be exposed to quartz. There's many ways you can be exposed to chrysotile.

And if you did find exposure that was taking place over that two-week period of time, it still wouldn't tell you whether that was a significant contribution to that person's lung burden. And autopsy studies of young

individuals from ME cases, which we think are probably much more stable than the plummeting hospital rates, autopsy rates, we see in community hospitals and medical centers, that that might give useful information about what the lifelong exposure was, provided that you have careful case-control studies from individuals who were and were not subjected to the exposure in question.

DR. STAYNER: Is that Ron Dodson, I think? I think he raised a good point there. I mean, obviously, the EPA simulations of a baseball game are not representative of the entire life history of children or adults in El Dorado. So you raise a good point. It doesn't fully capture. I think it –- in some sense, it's a worst-case example or meant to be, really, worst-case examples of how exposures might be. And you're right. Maybe that's where filling in the pieces with lung burden studies –- that's interesting. I hadn't thought about autopsy rates are much higher in children. I wasn't aware of that.

DR. ROGGLI: No. I mean medical examiner cases, that is, from accidental deaths, suicides, homicides, any of those type. That's pretty consistent over time, whereas the autopsy rates in hospitals are –- have been traditionally plummeting over the last few decades.

DR. ABRAMSON: But in -- actually, in pediatric hospitals, they have a slower decline in autopsy rates.

But there aren’t major pediatric hospitals everywhere.

DR. STAYNER: That would seem to present an opportunity for –- at least for children for documenting exposures with lung burden studies. But it might be close to representative if people –- if children in accidents have a high autopsy rate. That let's us get around the chrysotile problem. I guess with children maybe the half-way tissue isn't expansive, depending on the age.

DR. ROGGLI: Well, one of the things we discussed, I think, before you were on the phone is that chrysotile is a problem with lung fiber burden analyses and perhaps you might get better information in that circumstance by measuring environmental exposures, taking air samples, for example, as opposed to doing lung analyses.

DR. STAYNER: Yeah. I think that’s obvious that, that -- the goal of a lot of people in our confidence study did the same thing. You know, maybe if you’re looking at risk of very young children -- I don’t know what the risk would be to very young children, but chrysotile could be measured in the lung reliably. But I guess generally what we’re talking about are effects. We expect to see lung cancer and mesothelioma 20, 30 years later.

DR. HOLGUIN: Jill.

DR. DYKEN: Yeah. We wondering if any of the

panelists have any additional comments on the fiber burdens from living humans.

DR. HOLGUIN: Repeat the question.

DR. DYKEN: We were wondering if the panelists have any additional comments on measuring fiber burdens in tissue samples from living humans. I think Dr. Stayner might have some comments on that.

DR. STAYNER: You know, I think all of us have pointed out that ethically I don't think you could do that. But –- except that tissue is collected from people with lung resections or for lung cancer. And, obviously, that would be a highly biased estimate of what community exposures would be that people with lung cancer.

Assuming some –- some fraction of them are, in fact, caused by asbestos exposure, you would expect to see a very high concentration of asbestos fibers, much higher than what you would expect from the general population. But I don't think it would be very useful for community purposes. And again, I can't see anybody sanctioning taking lung biopsies from healthy community individuals. That wouldn't, I don't think, pass any IRB board that I know of.

DR. CASTRANOVA: Another question was lung resection is the representativeness of the sample itself. You're going to sample around, I assume, the tumor. And when you

have a disease process going on, that changes the deposition rate in that area. And so that might be –- not be representative of the total deposit of fiber count in the lung.

DR. WEISSMAN: The other issue is the frequency with which lobectomies and, you know, and pneumonectomies are done, you know, in a community. And there will be big differences in cancer rates between, you know, different communities. So, you know, if low autopsy rates are, you know -- are a problem in some communities, you know, having appropriate tissue samples, you know, would be an issue too.

DR. ROGGLI: The problem's going to be tracing these individuals because somebody who comes down with lung cancer in El Dorado Hills might go to a big medical center in a different –- in a different city to have a pneumonectomy or a lobectomy done. And in that case, you need to –- you want to be able to trace the samples, which means you've got to identify the people ahead of time or you'll never get a chance to look at the samples.

And as far as the question of the tumor interfering with deposition, what you typically would do is sample lung tissue as far away from where the tumor was as possible. And we've done that on many occasions. I don't think it makes that much difference in what you find there

compared to elsewhere in the lungs when you consider site-to-site variation.

We've seen cases that had more in the upper than in the lower lobe, some that had more in the lower than in the upper lobes. And some, you find the same amount in the upper and lower lobes. There's no way of predicting, which is why it's better to have sampling from autopsies because you can sample upper and lower lobes of both lungs and either combine them and sample them or do each one separately and do a statistical analysis of what you found.

DR. ABRAHAM: But it would be pretty rare -- not unheard of, but rare -- to have a sample where the upper lobe was at a background level and the lower lobe was elevated.

DR. ROGGLI: Exactly.

DR. ABRAHAM: Both –- usually, both will tell you whether it's within your background range or above that. The issue of retrospective sampling of lung archive tissues is also a possibility because the larger hospitals maintain archives of tissue in paraffin, which can also be used for fiber analyses. The other thing is -- that I forgot because I was going to say before that. The thought will come back to me in a minute. I'm sorry.

DR. WEISSMAN: Aren't there technical issues with

paraffin samples though?

DR. ABRAHAM: They're not insurmountable, and they're widely used. People that are involved in fiber analysis use whatever they get. You know, if it's a small sample of lung, analyses can be tailored to that. The larger the sample, the more reliable it can be, up to some point.

But, as Dr. Roggli said, there is variation from one site to another, but not enough to cloud the issue of whether someone has had substantial exposure or not. I mean, the fiber size distributions might vary also from one site to another if that became an issue. But if you're just wanting to determine whether someone was exposed and whether it's ten times your background or a hundred times, usually, a lung-resection surgery will suffice.

DR. HILLERDAL: You will end up with having very few cases in the first place. Secondly, these will all be in their fifties or their sixties. Most of them have probably lived only a short time in El Dorado or wherever, and they have lots of other exposures. So it will be very difficult to draw any conclusions from these findings on the level of exposure in these villages or areas today, wouldn't it? I mean, I think it would be a waste of time. It seems to me that it's not practical to get any real useful information from that kind of studies.

DR. CARBONE: I agree with you. It seems to me that the only purpose that we were discussing these studies was to verify that exposure is taking place in a certain place once you already suspect that exposure is taking place. So probably the idea of testing young people who could not have accumulated exposure from various places is probably the only way that we'll diminish the bias.

And, in fact, we will not need that many cases because if we are not doing a prospective study to identify where asbestos is, but we are just trying to verify that asbestos is there in a community, you will need a relatively few cases to verify what you already know.

DR. HILLERDAL: I quite agree. The next problem is, of course, a deeper loss. What does this mean? How big is the risk from this and, of course, we can’t answer that, can we?

DR. CARBONE: That’s the next question; right (laughter)?

DR. ABRAHAM: Could I just mention what I forgot to say? The issue of, you know, people going to a major center for surgery is one that we’ve dealt with somewhat is that certain regional hospitals serve as a catchment area. That’s fairly well defined geographically.

So, for example, the people from way upstate New York

that have lived in the talc-mining areas often come to the medical center in Syracuse as the regional tertiary-care center. So a lot of the studies of tissues from people that have worked up in the talc mines have ended up at one of the major hospitals in Syracuse because there hasn't been a major lung surgery center up in that area.

DR. ROGGLI: Yeah. It wouldn't be hard to catch such a patient because the patient came to –- all you'd need to know is in that catchment medical center that they watch for people whose address is El Dorado Hills. And then if you had the permission of the hospital and the people from the area to get that information, then that should be doable.

The advantage of living persons is that you can actually find out the very information that Dr. Hillerdal was mentioning: What is your occupational exposure? What is your smoking history? What is your residential exposure history? What other environmental exposures might you have had? And so, at least, you can identify with what confounding factors there are.

The advantage of doing the autopsy study on young individuals in motor vehicle accidents or other such accidents is that you should be able to get very good information from parents; whereas, when the 80-year-old man dying of a heart attack, you'd be hard-pressed to get

accurate information probably on what that person's entire life exposure history was. So I think that that is -- that does get around that problem. Plus the young individuals are not going to have the complications of occupational exposure.

DR. WEISSMAN: Accepting that surgical samples are complicated because people, you know, move around and because they have multiple, you know, exposures, you know, one advantage that was cited in the, you know, ERS, you know, report on fiber analysis was that at least people having surgery are alive, so at least you can ask them about their exposures; whereas, for autopsies, you have to ask somebody else what their exposures were.

So certainly, for the older people who die and have autopsies, that's very problematic relative to the younger people. But that is one potential plus of the surgical side is you can actually interview the person that the sample came from.

And just a segue to a completely different thing maybe, we talked a lot about looking at asbestos, you know, levels in samples. And I guess I'd like to throw out the idea that we should think more broadly than, you know, things that are traditionally thought of as asbestos in terms of, you know, looking at what's in these samples; that, you know, if one goes to the trouble to, you know,

do a study and collect these samples and analyze them, we really ought to look at all mineral fibers that are present in the sample without regard to whether they're conventionally considered to be asbestos or not.

DR. GUNTER: Yeah. I would second that; and not necessarily just the fibers, but the entire mineral content. And that –- there may be answers there that no one has thought of. And I think not characterizing those has been a problem, but it’s difficult to do.

DR. ABRAHAM: Well, the nonfibrous mineral burden of a lung can be characterized also by -- like a microscopic techniques up to a point of crystallography being somewhat limited. But that often provides a clue when someone has had a mixed exposure to identify the source, at least, in an occupational setting. I’m not sure that’s been used so much in the environmental setting. But in an occupational setting, it can even tell you whether someone worked at one workplace that had certain products used and work practices versus another.

DR. GUNTER: I would say it could be probably used even better in a geologic setting. You'd probably get associations in minerals. And especially with some newer techniques that are coming on -- trace element analysis by using something called laser ablation mass spectrometry. There are many things we can do now in small particles

which would allow us to trace where things came from.

DR. CARBONE: But now you are doing a completely –- I agree. It’s important to find information. But, I mean, you are throwing in completely different things because in the future you may want to revisit what you find in those lung to figure it out what’s going on. It’s a completely different question than answering where somebody has been exposed to asbestos.

The issue is going to be –- I do not know how it works yet, but the issue is that if you’re asking for a grant, that will become an issue because somebody's going to ask you why you want to do that. It’s unrelated to the question that you’re asking. Is it related to the general understanding of lung disease? But it’s totally unrelated to the question that you’re answering: Has been –- has somebody been exposed to asbestos? Is this community exposed to asbestos? That’s the question. If that’s the question, knowing whether there are ceramic fibers there is not part of your question. It’s still something very important in general terms for us to understand the lung disease. Do I make sense?

DR. GUNTER: Oh, yeah; yeah. But I think, again, the –- there may be things that have been missed by not understanding the total content. And, you know, certainly looking just at the fibers is basically just –- it’s –-

the fibers have traditionally been looked at may be missing lots of the point, as far as their risk goes.

DR. HOLGUIN: Hold on a second, Dr. Dodson.

DR. DYKEN: I think there's a clarification from Aparna.

DR. KOPPIKAR: You know, you make a good point, Dr. Carbone. The question is --

DR. WHEELER: Could you say your name and your affiliation?

DR. KOPPIKAR: Oh, I'm Aparna Koppikar. I'm from Environmental Protection Agency, and I'm the project officer for developing IRIS profile for asbestos effects, noncancer effects.

You make a good point. But one other thing is, if you don't look at all the other fiber contents, we wouldn't know whether they are confounders, whether they are effect modifiers, and that's where it will become important. And you can justify that if you are writing a grant, saying that you want to look at all the fibers because they could be contributing or adding to your lung cancer.

DR. ROGGLI: That's actually been looked at. I think that there are a number of laboratories that have looked at nonasbestos mineral fibers in lung tissue samples. I've reported on that; so has Andy Churg. I think Ron

Dodson has reported on that.

And there have been some studies that have actually looked at it compared to risk of disease, particularly mesothelioma, and found that there are certain types of nonasbestos mineral fibers you expect to find in lung tissue samples. There are certain ones that come up over and over again as being the most commonly present. They do not correlate with any disease we've been able to identify.

And it has looked –- been looked at in that regard, and so far, there's no leads to indicate that the usual nonasbestos mineral fibers are doing anything hazardous to our health.

DR. ABRAHAM: I would just like to add that, as part of most protocols doing fiber analysis, you have to analyze each fiber to tell what it is. So that data is there, even if not always reported in a summary related to asbestos. But if you don't analyze the fiber, you don't know if it's an asbestos fiber or not.

DR. DODSON: We've talked a lot about California, but I understood the charge was to talk about generalities. And in context of some of those target sites for distribution from Libby, you may well find a fiber identifier of exposure that is more reliable in tissue burden than you will looking for the regulated asbestos

types.

And I think -- I don't know if you want to comment on that, but –- but I think you might well use the resource of –- of something other than the classical asbestos as an asbestiform fiber common in that formation that may indicate exposure that has a uniqueness to that product.

DR. GUNTER: Like the vermiculite.

DR. DODSON: In the vermiculite product.

DR. GUNTER: Yeah. Like finding vermiculate itself.

DR. DODSON: Or --

DR. GUNTER: Or some of these other --

DR. DODSON: Yes; which happen to be very long asbestiforms.

DR. STAYNER: One point -- I was going to make the same point. If we're talking about documenting noncommercial asbestos like quick-dried or wet, and that would be, obviously, important; and also seems like cleavage fragments that some people don't consider asbestos fibers, I would think, is as important. And even maybe really short fibers that don't meet the definition of OSHA of what an asbestos fiber are worth documenting as well.

DR. DYKEN: Okay. Can everyone hear me?

DR. HOLGUIN: Yeah.

DR. DYKEN: I think it seems like we're kind of

wrapping up this section. So what we thought we would do is just take a five-minute break and then meet back at 11:30 and begin the next discussion item, which is fiber content of collected sputum samples, if that's okay with everyone. Okay. Thank you.

(Whereupon, a recess of approximately 12 minutes was taken.)

DR. HOLGUIN: Should we get started? Erin has yellow and red cards. And if we don't get started, we're going to get a red card, which, in soccer, is a bad thing.

The next section will –- in this next section, the members of the panel will be charged to discuss the techniques on fiber content of collected sputum samples. We have three panel members.

DR. ABRAHAM: We're still missing four, aren't we?

DR. HOLGUIN: We're missing –- so the charges are now to discuss fiber content of collected sputum samples and fiber content of collected BAL fluid. And again, I think this can take on –- could take some different roads, but, ideally, we should follow the questions that are being charged upon, to discuss mainly what are the advantages and disadvantages of this technique as a method for us to see community level of exposure and is the technique more suited to measuring exposure on an individual level.

And I think we could start with this question, and

then move on to the other questions, which is how can we relate these measurements to a background exposure level, and if there is any data to consider measurements related to elevated exposure level.

DR. CARBONE: Fernando --

DR. HOLGUIN: Yes.

DR. CARBONE: –- can you say why we would do that exactly? I mean, what would be the reason to do that because everything else depends on why you do something?

DR. HOLGUIN: Sure. I may have to relay that new question to the ATSDR folks because they’re the ones who did the questions.

DR. WHEELER: Why would we want to do the sputum samples? Is that the question?

DR. CARBONE: What is the question that you want to answer because you may want to do the sputum sample or not, depending on what is the question that you want to answer. So what is the question? And then --

DR. WHEELER: The first part of the question would be do we find significant exposures above what a background population would be at any particular site across the country. Do we do that by going in and taking sputum samples of those people that are there?

The second part of that question would be can we relate the levels of asbestos in the sputum samples to

some kind of outcome, whether that is a progression of disease or whether that's a measure of risk.

DR. CARBONE: But so you are doing that to identify areas in which there is asbestos exposure, or are you doing that to verify that there is asbestos exposure?

DR. WHEELER: It could be either. If we had data like we have in California, of air, we would want to see if the kinds of activity-based sampling that we're doing there that is showing us that there is some kind of exposure going on. Is that actually going on? Do we actually see levels in people that are –- that are participating in those activities in the community?

DR. CARBONE: Because the reason that I ask it is that if you take the sputum sample, for example, they would be very insensitive to verify whether, in a given area that you have no idea of, whether there is asbestos exposure. But they –- if you find that there is asbestos in some sputum samples, since they're very insensitive, they would certainly indicate that there must asbestos exposure in a certain area.

So the same test can give you very –- can be totally inadequate. For example, if you want to screen the United States for exposure to asbestos or can, in fact, be inadequate because even if it's true that most of the sputum sample are going to give false negative results,

the fact is that they're easier to collect than take a BAL. And therefore, you can take a hundred sputum samples, and as far as you find five or six that contain asbestos, then you can verify that, indeed, in that area there has been asbestos exposure.

But then the question would also be how do you design the study because, in other words, do you want really to go out there and do sputum-sample analysis to find out that there is an higher level of asbestos and then see if there is a health outcome that is negative, but you want to go the other way around; that is, you see where there is high level, high incidence of mesothelioma, because that's what we're talking about.

And then, where there is high incidence of mesothelioma, you find out whether there is a higher than background level in the United States of America of asbestos. So you use mesothelioma as the sentinel to identify areas where, in fact, there can be higher levels than background of mesothelioma.

DR. WHEELER: Well, your second suggestion sounds more like a research project to determine whether or not sputum samples could be a marker of possible disease. That is something that we would be less interested in doing than in being able to go into the communities and saying we can confirm that there's an exposure going on

here through this type of sampling.

DR. CARBONE: I suppose you can if my copanelists agree because the test occasionally is going to find asbestos. And as far as you find a few people who have asbestos in their sputum, even if there is a high levels of false negative, all you need is that. Say, you've had three or four positive out of a hundred and that will confirm that there is exposure to asbestos in that area.

DR. HILLERDAL: Unless, of course, they have been occupationally exposed. You have to make a very thorough investigation of that as well.

DR. ABRAHAM: And the mesothelioma issue will tell you whether they had exposure 20, 30, 40 years ago. It won't tell you what's going on in the community right now unless it's an unusually stable community like the small farm town where nobody moves.

DR. KAPIL: Yeah; just a follow-up comment to John's comments. I think we're particularly interested in hearing the panel's perspective on the usefulness of sputum specimens in assessing exposure. Is it a useful method? Is there any utility? Is there a correlation between sputum fiber content and exposure and levels of exposure, cumulative exposure, however you want to look at exposure, and also whether different methods of collecting sputum, you know, invasive, noninvasive ways of collecting

sputum. All of these types of things is sort of what we had in mind when we put this on the table for discussion.

DR. HOLGUIN: Dr. Dodson.

DR. DODSON: You know, I heard a lot of terms that were used in some of this earlier discussion that's got me a bit confused of the target site. You're talking about disease. I mean, to me, that means something like cytopathology screening. But if you're talking about asbestos exposure with the sputum samples, based on the data that my colleague Don Greenberg assembled over a number of years, the sputum marker for asbestos exposure is a ferruginous body.

That marker is defined in a group of amosite workers he exposed to long amphiboles, the type that form ferruginous bodies, and was only a positive find in about a third of those people, about a third of the samples. So you're talking about a lot of samples. Inclusion from all that was if you find one that indicates an exposure of what is above general background based on his data from some studies in Houston with a large number of samples from several hospitals.

And if you're talking about asbestos exposure, you've opened the door to the second aspect of it, which is can sputum samples be used for analysis of fiber content. If you do that, you're talking EM. And I gave a couple of

references, one of which is ours, that I think are the only ones I know of that really have looked at the fiber burden in sputum and the amosite group that was reasonably reliable.

But again, they were heavily –- heavily exposed individuals to amosite asbestos. The uncoated fiber burden of the sputum was much more important in that –- in that very small group than ferruginous bodies is showing –- showing past exposure. You know, my conclusion from my section of that was it's rather insensitive -- the open question of the fibers. And I think that's a really interesting issue that would require some special applications to even try to get that answer.

DR. ROGGLI: Additional comment about that. I agree with what Dr. Dodson is saying that the reason of –- I mean, the obvious reason that the sputum has come up as a possible source of information in these communities is because it's readily accessible. You could –- you could get samples from virtually everybody in El Dorado Hills or Libby, Montana, who's willing to spit in a cup, even though some, I think, in the comments pointed out that you have to make sure that you're really getting what we call sputum samples instead of just saliva.

Well, there's cytological techniques of doing that. You just make a cytology smear and determine whether it's

a satisfactory or unsatisfactory for that particular specimen and analyze it once if it's a satisfactory specimen.

The disadvantages of it, as Dr. Dodson has said, is it's relatively –- it's a very insensitive technique. Only one-third of the Tyler workers that were heavily exposed to amosite did have asbestos bodies in their sputum samples that Dr. Greenberg analyzed, but those workers on average worked for a short period of time. It was –- it was either three weeks or three months, which was the average duration of employment at that plant. It was so dirty that people just wouldn't work there. But, on the other hand, the levels of exposure were hundreds of times greater than the current permissible exposure limit in the workplace.

So there were –- there was heavy exposures going on to everybody in those plants. The sputum asbestos body is exquisitely specific for asbestos exposure, but it's not very sensitive. And the way we know about specificity is that Dr. Greenberg analyzed 11,000 sputum samples from the Harris County Hospital district and found six individuals who had asbestos bodies in their sputums. All six of those individuals worked at one particular plant where they were exposed to asbestos, and five of them had asbestosis. Nobody else had any asbestos bodies in their

sputum. So it's exquisitely specific but not very sensitive for detecting asbestos exposure.

And as Dr. Dodson mentioned, that you get a –- you increase your sensitivity somewhat by doing electron microscopy on the samples as compared to just looking for asbestos bodies. But what you're trying to compare is does this community, with a certain exposure, have more asbestos in its sputum than a control community without that exposure. And I'm not at all convinced that sputum is sensitive enough that it's going to answer that question over the background noise. I don't –- I'm very skeptical that you would get a significant difference in the groups.

DR. CASTRANOVA: What increases the noise is the variability of the collection of the sputum. A sputum's not invasive. Sputum collection is not invasive, but it's not –- not easy to get a sputum sample that came from the same region of the lung, person to person, time to time, day to day. And that variability is on top of the variability in counting the fibers, and so again, that adds to the variability, adds to the lack of sensitivity. So I agree with you. I don't think it's a very good technique.

DR. HOLGUIN: Jill.

DR. DYKEN: I just had a clarifying point that we're

not interested just in measuring asbestos bodies but also the possibility of measuring uncoated fibers in sputum.

DR. ROGGLI: Yeah. That's why I mentioned that. If you use electron microscopy to analyze the uncoated fibers, then it increases your sensitivity a bit. And there's very few studies have done that. Dr. Dodson has published one of them, looking for fibers, and he found amosite fibers in the sputum of workers where he couldn't find asbestos bodies in their sputum. So it does increase your sensitivity.

But because of what we found in terms of asbestos bodies, of the very insensitive nature of it -- even though you pick up a little bit of sensitively with looking at fibers by EM, I don't think it's going to be enough to detect the small differences that you're trying to find between environmental exposures in one community versus one without that info.

DR. HOLGUIN: A quick question. Would the sensitivity of detecting some of the sputum fibers depend on the timing of the exposure? I mean, when you do a biopsy, you find them on interstitial space anatomically. I mean, how often are they on the airways unless you've been exposed recently? So if you were exposed a long time ago, all of them are past beyond the terminal bronchioles into the interstitial space. I mean, I'm just talking

like a pulmonologist. I'm not --

DR. ROGGLI: Yeah. Well, there's -- that's –- I think that's another point into the variability because some individuals who have been heavily exposed to asbestos, you find lots of asbestos bodies and presumably fibers sitting in the alveolar space along with macrophages. In others, you find it mostly in the interstitium.

And you suspect that the ones in which it's mostly in the interstitium and there's very little accumulation in the alveolar space are going to be the ones that are going to be negative on a sputum sample. But as long as that's collecting in the alveolar space, there's a potential for it to move up the mucociliary escalator and then be -- appear in a sputum sample.

DR. HOLGUIN: So it's a huge time component in there.

DR. ROGGLI: Yeah.

DR. ABRAHAM: Also, I don't know of any sputum studies of fibers that have tried to look at induced sputum as opposed to spontaneous sputum, and I –- I've just become aware of, you know, some of the work that's been going on by Dr. Fireman and a group in Israel about using induced sputum to look with much more sensitive. They've compared it to spontaneous sputum for things other than asbestos, for other kinds particulate material mostly

in the occupational setting.

But I think that would require some investigation to see if that would improve the sensitivity to the point where it would be useful for screening because, certainly, even though it's –- I've never had it done. It's mildly annoying, I'm sure, to have induced sputum. It's less annoying than bronchoalveolar lavage.

DR. CARBONE: But we were not talking about screening. We were talking about verifying asbestos exposure, in which case, even if, as we all agreed here, the technique is not sensitive. Since it's very specific, it's valid because you take a hundred samples, you get two or three that are positive. You verify that there is asbestos exposure. It's very simple.

DR. ROGGLI: But the problem is that you may get a hundred samples from a community, say, in El Dorado Hills and a hundred samples from another community, find no difference between the two, and yet if you analyze the lung samples, there would be a significant difference between the two. So that's what I'm worried about is that the sputum is not going to be sensitive enough to detect that difference that might be present.

DR. CASTRANOVA: And also, the sputum, by the definition of the technique, is sampling the conductant airways and not the alveolar region of the lung. So it's

not sampling the site where the disease is occurring. So again, that adds to the variability.

DR. HOLGUIN: Dr. Dodson.

DR. DODSON: Let me just say that, again, what I said about Don Greenberg's study, in those that were positive producers of ferruginous bodies in the sputum, there were approximately a third of the study group, and they found positive samples in a third of those collected in multiple sampling sequences. So it's highly insensitive.

The other aspect is ferruginous bodies form only on longer fibers that are greater than 8 or 10 microns in length, whichever you like as a number. But they form on those, and some people don't readily form them. So the ferruginous body part becomes even more of a problem with sensitivity. Uncoated fiber part was surprisingly sensitive in what we looked at, which was very limited. But it also had the advantage of having a particular type of asbestos exposure to the people whose sputum we looked at.

That has a similarity to the question at hand for this particular group. And I don't know the answer because the water gets fairly deep when you try to do EM of sputum and do the digestion techniques, but –- but as far as I know, that was the basis of –- of our observation that there are applicabilities to this group with the

uniqueness of the type of fiber. But by the same token, there's not a lot of background information. Ferruginous bodies, there's a lot of background and it all seeks the same thing. It's very insensitive.

DR. HOLGUIN: How about specificity? Specificity?

DR. DODSON: Of what?

DR. HOLGUIN: The fibers of the sputum for a technique.

DR. DODSON: Well, if you're going to do the EM part of that, as we've discussed before, you know what the fiber is if you're doing EM. The sample preparation is a challenge.

DR. ABRAHAM: I was just going to mention that there's one example we've looked at without exotic sample preparation, just of making smears of the sputum, from a geologist who did some field sampling in the El Dorado area where we did find tremolite in the sputum without any kind of exotic preparation.

So we know he was working, chipping away at rocks and things like that to collect samples, and he coughed up some sputum -- nonsmoker, I believe -- in which the tremolite actinolite type of fiber could be identified. So it's certainly theoretically possible, but again, it doesn't –- the anecdote doesn't tell you if it's useful for a survey of a community.

DR. CARBONE: So the way I understand it that we seem to agree on the fact that this technique is quite insensitive, not too very specific, and that, therefore, in a situation in which you do not have occupational exposure but you have just a bulk background levels, even if you find that everybody's negative, that doesn't mean that there is not asbestos exposure in that particular area.

And therefore, we cannot rely on the sputum to screen because there is too much risk of false negative even if you analyze a hundred or a thousand sputum samples. The problem is that, as we all know, that's really the only thing that we can work on because bronchoalveolar lavage are absurd to think to get it because nobody's going to want it, and all the other specimens are not easy to get. So the question goes back to the EM possibilities that Dr. Dodson was discussing and whether there is a way to improve on that because the sputum is something we can work with. Anything else is hypothetical and very close to impossible to get.

DR. WEISSMAN: And with sputum, you know, as you say, there's so much developmental work that would need to be done at this point, particularly in terms of doing EM and looking at fibers as opposed to look at asbestos bodies. There's so little background information that exists, you

know, in terms of normal levels, in terms or correlation, you know, with lung burdens.

You know, the, you know, data for asbestos bodies, in terms of looking at large numbers of smears, you know, is really good, in terms of the insensitivity, not specificity. Another issue is the one that Vince raised, which is the issue of –- of paying attention to the technique of obtaining induced sputum.

In asthma, in looking at inflammatory components in sputum as a way to gauge asthma, it’s really critical how you obtain the sputum. It’s really critical which component of the sputum you pick in order to do the analysis for cells and cytokines. And there’s limited data. There’s one, you know, paper from, you know, from Ron’s group actually where it’s mentioned that increased numbers of fibers were found in samples that were induced relative to -- irrelative to spontaneous and that increased numbers of fibers were found in samples when the globs were picked out of the sputum and analyzed as opposed to, you know, taking the whole sputum.

But, I mean, very little has been done, you know, sort of developmentally in terms of saying, how do you collect it. How do you process it? In the large studies that were done in Texas -- I believe that was a retrospective analysis where they went back and looked at

slides that were primarily done for the purposes of looking at sputum cytologies, you know, for cancer, you know, as opposed to actually specifically collecting a specimen and processing it and filtering it, you know, to get the full, you know, fiber asbestos body content. So if you actually were doing the procedure specifically to look at fiber exposures, you know, the performance characteristics, you know, might be different, but we just don't know.

I mean, the bottom line is that there's a lot of developmental work that would need to be done, you know, to apply it, and the likelihood is -- what would be more useful would be EM analysis, you know, rather than, you know, light microscopic analysis because of the issues that have been raised.

DR. DODSON: Just to make sure, since we're on the record and to clarify the point, when you said that about the Tyler project you were totally correct, but you used the term "fiber," and those were ferruginous bodies. Just so they don't get –-

DR. WEISSMAN: Thank you.

DR. DODSON: -- somewhat confused. Fiber is a different animal.

DR. ABRAHAM: One possibility, though, if we look at the size distribution of the fibers, for example, in El

Dorado, is it possible that light microscopic screening would be sufficiently sensitive to detect the uncoated fibers with darkfield or something like that? I don't really know.

DR. WEISSMAN: Based on the R. J. Lee report, which said that most of the fibers were short, you would expect that you wouldn't be making ferruginous bodies.

DR. ABRAHAM: No. I'm talking about uncoated fibers that are long, not short. There are plenty of long fibers there.

DR. WEISSMAN: Okay.

DR. ABRAHAM: Just –- just –- would light microscopy in the matrix of digested sputum be an expedient way to screen for fibers if we know the fibers have a large enough diameter?

DR. DODSON: How would you know what the fiber was?

DR. ABRAHAM: Well, you'd have to do some controls of that.

DR. DODSON: You'd have to analyze some of them to determine --

DR. ABRAHAM: Right.

DR. DODSON: Yeah. I mean, I'd -- there's a lot –- there's a lot of fibers in the environment that aren't asbestos, in any environment.

DR. STAYNER: Could I make a comment? This is an

area that I'm really not an expert in, so I think everything's been said. But one thing I noted is that there seems to be some suggestion in the literature that chrysotile doesn't form ferruginous bodies, so that might be one limitation. And I would think that these methods and probably ELISA BAL would be separate from the same thing as looking at lung burden that chrysotile doesn't persist.

But, you know, it sounds to me that this idea of looking –- it's properly collected and using EM methods is a promising technique that maybe just needs some further research to see how much that increases the sensitivity of the method.

DR. HILLERDAL: I think maybe we should not completely dismiss the lavage. You said it's completely unpractical. And, of course, it is on a large level. But maybe we could pick out some volunteers, maybe even pay them some sum, and –- and because –- the only thing we're looking for is exposure, and I think that is much more sensitive. So if we could have –- maybe we only need 10 or maybe 20 people with some known residence in this area, and we make –- and we make a lavage on them. Maybe that would be enough just to prove that there is an exposure if that's what we are doing because that is much more sensitive; isn't it?

DR. ROGGLI: Well, I don't think we've dismissed lavage yet because I think we were just talking about sputum right now; right?

DR. HOLGUIN: Yeah. But, you know.

DR. DYKEN: We can move on.

DR. ROGGLI: Okay. Because I agree with you about the lavage. I don't think it's impossible to do. There's plenty of studies have been published looking at bronchoalveolar lavage where you pay normal volunteers whatever the market will bear to have a fiberoptic bronchoscope put down their lungs and washed out, and there are people who will do that for money, and it's a pretty safe procedure.

DR. CASTRANOVA: Yes.

DR. ROGGLI: And so that's not an insurmountable difficulty in doing those sort of studies. But again, you'd have to compare it and make a careful comparison between the community which you're trying to study versus an unexposed community.

DR. HOLGUIN: Sure.

DR. CASTRANOVA: And the advantage of the lavage -- it's much more reproducible with techniques of collection --

DR. ROGGLI: More sensitive.

DR. CASTRANOVA: -- than sputum. It's much more

sensitive. It shows a good relationship to exposure, a good relationship to disease.

DR. ROGGLI: And a good relationship to the lung burden as well. That's been demonstrated.

DR. CASTRANOVA: Exactly; exactly.

DR. GUNTER: Just a question about L and K. What were the size of those particles because you're asking about light microscopy. How big were those particles?

DR. CASTRANOVA: Well, many of them are .4 or .5 microns diameter; 5, 10 microns in length.

DR. GUNTER: And that's pushing the adjuvant being able to do -- use some technique called dispersion staining with light microscopy.

DR. ABRAHAM: Yeah. Pushing that --

DR. GUNTER: Pushing the adjuvant, but you could identify them somewhat that way.

DR. ABRAHAM: But probably electromicroscopy is more available than dispersion staining anyway.

DR. GUNTER: Well, if -- more available.

DR. ROGGLI: They still have to pick them up.

DR. GUNTER: But it's not more available. I mean, the light microscopy's readily available.

DR. ABRAHAM: I mean, the expertise --

DR. GUNTER: Yeah. There's no real expertise in light microscopy unfortunately, but –- but those are

techniques that could be used if the particles were a little bigger.

DR. DODSON: [Off microphone]

DR. GUNTER: Yeah. If they're --

THE COURT REPORTER: Microphone.

DR. DODSON: I just said, “Make a mass, concentrate them into a mass, and then use the PLM dispersion staining.”

DR. HILLERDAL: I was just going to say that lavage -- you said it’s reproducible, it’s safe, and so on. And it is, of course. But there are caveats even at that. The difference is because it depend –- what you do actually is that you pull down water, physiological water and body temperature, and then you suck it back. But the -- it depends very much on the patient and his –- and his bronchi. Some have a very flaccid bronchi, and when you start suction, they will go together so you will get very little back.

So you would have to correct for that, and you have to have a certain procedure for doing it. In patients with chronic bronchitis, you will have all kinds of other stuff on it. But with these caveats, I think it’s a very good –- it’s a very good one, and we could actually pick out –- and I think, again, we come back to these young adults who have not had any occupational exposure but have

lived all their lives in these areas. These would be the most interesting ones to investigate. And if you find asbestos in the lungs, you know they have inhaled asbestos.

DR. CARBONE: I don't know how much luck one has in getting the volunteer for bronchoalveolar lavage. But one thing is for sure, and that is that you will be dependent on who volunteers. And so you will never have the cohort of people that you want to sample. And I have right now the same exact problem in my -- in the cohorts that I'm studying in Turkey. And I will never have the people that I want to study if I were to go with bronchoalveolar lavage. That's why there is a huge advantage if you can use sputum.

I understand that unfortunately it's insensitive, but the only hope would be if Dr. Dodson can develop a sensible method using electron microscopy because that's the only thing that I can get from everybody. Otherwise, you are limited by the bias and the fact that the people that you want to sample will not come and you get other people.

DR. HILLERDAL: Well, we have no problems getting volunteers because we pay them when we want. You know, so it's –- but, of course, there is a selection; not everyone we want to do it. But really, it's not –- it's not –-

I've done it. I had it done on myself, and it's no -- it's no big effort really.

DR. HOLGUIN: You wouldn't get me for sure (laughter).

DR. CARBONE: It depends on how much you pay (laughter).

DR. ROGGLI: It sounds like to me like the bias would be selection against rich people.

DR. WEISSMAN: Well, actually there are ethical, you know, issues. You can't pay enough to induce people, you know. But I'll go one up on you, I've been lavaged three times for research studies, and it really isn't, you know, that big of a deal.

But, obviously, you know, the problems in terms of actually implementing and doing a lot of people -- yeah. Those problems are real, and your concerns with that are well taken. And maybe the role would be more confirming the results of sputum, which you could do on a broader range of people, or as, you know, was said earlier, picking a small subpopulation, so...

DR. HOLGUIN: One comment from the ATSDR table.

DR. KAPIL: Just sort of a related question to this discussion. Earlier when we had the discussion on biopsy specimens and there was a concern raised by the group about biopsies usually being done for lung cancer and

there would be sort of a systematic bias introduced if –- would a similar concern be present if –- if lavage samples were utilized in -- from patients in whom lavage was being done for some reason already or bronchoscopy was already being done. Would the panel be able to comment or think about that? In other words, if a patient is already having a bronchoscopy done for some purpose.

DR. ABRAHAM: But why do people have bronchoscopies? You know, either they're being worked up for cancer or suspected for it. Sometimes people with interstitial disease will have a lavage done.

DR. KAPIL: That's the question I'm asking.

DR. ABRAHAM: So certainly, not in a control population.

DR. STAYNER: I'm thinking about a study with someone who's doing bronchoscopies here in Chicago, and it's something like 30 percent of them are lung cancers. Maybe that's just unique to this hospital, but of those, you would expect -- again, a large percentage would have asbestos exposure.

DR. ABRAHAM: There was that national study, the ACCESS study for sarcoidosis which did transbronchial biopsies and, I believe, lavage. And maybe they've archived all their lavage filters that could be looked at. They have extensive information on all the people that

participated. I think there are hundreds of people, maybe more.

DR. WEISSMAN: In terms of the ethics of obtaining samples, I mean, there have been a number of working groups that have looked at this. And it's ethical to perform bronchoscopy and bronchoalveolar lavage on volunteers, you know, even who aren't having the procedure for clinical purposes.

And it's well, well established that people who are undergoing bronchoscopy for clinical indications like cancer that it's ethical to go ahead and add a lavage to the bronchoscopy on the contralateral, you know, side, setting aside the issues of selection bias, you know, which obviously are real concerns. But there are no ethical problems with doing those things.

DR. KAPIL: Go ahead.

DR. WHEELER: Could you comment on my second question I had from the communities there? Is there any test that we can have done on ourselves to confirm or deny whether we've been exposed to asbestos? Would bronchoalveolar lavage be something that you think you have enough confidence in to recommend?

DR. HILLERDAL: Of what everything we have talked of today, I think bronchoalveolar lavage would be the best. Of course, we will have false negatives there as well.

But I think that would be the best test to really establish whether they have been exposed or not, if one could stand it.

DR. CASTRANOVA: Is there a reasonable correlation between fibers in bronchoalveolar lavage and fiber counts in lung?

DR. ROGGLI: It's not quite perfect so that's –- I think that you'd get more information if you had lung tissue, but you're not going to get lung tissue --

DR. CASTRANOVA: Exactly.

DR. ROGGLI: -- on an unselected population. So my own feeling is that the best approach would be a combination of medical examiner cases -- young individuals has been suggested -- looking at their autopsy lung burdens and an analysis of bronchoalveolar lavage by electron microscopy for fibers that have been recovered in careful case-control groups for both types of studies.

DR. CARBONE: Excuse me. I would understand that finding out if there is exposure in a community so that regulatory agencies can try to take measures to reduce the exposure to a community. But I would not understand why you would want to give the answer to somebody, why that would be our concern, whether he has been exposed or not because that should not be, in my opinion, something that we should worry about in particular because once you've

told this individual, “Yes. You have been exposed,” now what?

DR. WEISSMAN: Absolutely. I agree with you completely on that. I mean –- I mean, I don’t think that one would want to lavage an individual for clinical purposes just to do some sort of mineral or fiber analysis on their lavage fluid because I really echo you. You wouldn’t be able to do anything with that data for that individual. I think it’s okay to do it within the context of a designed, you know, ethical research study, you know, where you’re aggregating data, but not to give individual medical advice.

DR. ROGGLI: The only thing you’d be able to say in that circumstance is if you analyzed two groups and you had a large enough in numbers and you did find a difference between the two populations. You could say that in the individual in the exposed population, whether they had a lavage result which was no different from the control groups or was elevated compared to the control groups -- you could give them that much information. But again, what that means in terms of risks, that’s much more difficult to say anything about.

DR. ABRAHAM: I think the individual patients have the right to ask for whatever test they want, and it’s up to the ethics of the physician to decide if the –- if it’s

an ethical request. But I don't think we should say we won't give them that information. I think that's going a bit too far.

DR. CASTRANOVA: Another advantage of bronchoalveolar lavage is while you're collecting the material and counting the fibers, you also have the cells there. And so you can add a component where you actually look at the activity of the cells to cytokines produced by a cell, and you get some feel for dose response in the early stages of, perhaps, a disease process, which -- I don't know what the answers would be right now, but perhaps you could build up a database that would give you some answers.

DR. CARBONE: What would you measure exactly?

DR. CASTRANOVA: Well, you would measure inflammatory cells. You would measure inflammatory cytokines from the cells. For instance, in animal models, they are exposed to asbestos. Look at inflammatory cytokines. Then try and look at fibrogenic factors and try to see early events that are driving the disease process.

DR. CARBONE: How? I mean, what kind of test?

DR. CASTRANOVA: Actually, a relatively simple test would be cell counts and cytokine levels.

DR. CARBONE: So you're basically measuring the inflammatory reaction?

DR. CASTRANOVA: Yes; yes.

DR. ABRAHAM: But you wouldn't know what to correlate that with because you'd be measuring asbestos, but you wouldn't --

DR. CASTRANOVA: No.

DR. ABRAHAM: -- know what it's inflammatory responding to. It could be responding to anything.

DR. CASTRANOVA: Yeah. And you would have to –- you would have to know that. And when you did the lavage, not only would you know the fiber counts, but you would know what the other materials in the lavage, the other particles in lavage as well. So you would know if there was another driver of the inflammation.

DR. ABRAHAM: That would be –- that would be a much bigger, broader research project, which would not be uninteresting, but it would be quite separate from --

DR. CASTRANOVA: No. You have that material. Instead of throwing it away is all I'm saying is if you have –- the hard part is getting the volunteers. Once you have the volunteers, you might as well exploit that material as much as you can.

DR. ABRAHAM: You might approach -- you know, to get young volunteers, approach college students and motorcycle clubs and things like that (laughter).

DR. CASTRANOVA: Actually, that's been my experience. All our volunteers are first-year med students.

DR. ABRAHAM: Dirt-biker clubs, they'll do anything for a couple of hundred dollars.

DR. ROGGLI: Well, another point about the bronchoalveolar lavage fluid is what do you standardize the results to. Typically, results have been reported in terms of milliliters of bronchoalveolar lavage fluid that were recovered, not what was injected.

And as Dr. Hillerdal mentioned, there is variability in how much recovery is depending upon the disease conditions and other variabilities for that particular individual. One of the things which we did in our study was try to normalize to another marker, which was cells recovered, number of cells recovered, to see if that might make a difference. And actually, we got exactly the same results in terms of cutoff for sensitivity and specificity in looking at fibers per milliliter of BAL versus the fibers per million cells recovered. It really didn't make any difference.

So I'm not sure about any other better way to normalize the data than what's been reported in that regard.

DR. ABRAHAM: Yeah. I mean, you'd have to put in some sort of tracer to know what your recovery is, like a dye or albumin or something.

DR. HILLERDAL: That has also been tried, and I'm not

sure that they saw any convincing results from it. This is problem. And it's very individual how much you get back. Also, you have to have a very -- various things of doing. Our model in Stockholm is that we take 50 mil five times, you know, and from the first –- first you get very little back, and the last ones you get more back.

So –- and we say that if we don't get more than half back, then it's really difficult to draw any conclusions. And sometimes I get 150; sometimes I get even over 200 back. And it's all very individual. In some patients, it's very difficult to get –- get enough because they have such flaccid...

DR. HOLGUIN: It's also very dependent on where you sample. You know, typically lower lobes return and --

DR. HILLERDAL: Yes. That's another thing. You have to have gravity on your side. So the best thing is to do the middle lobe or the lingula lobe because they are –- if you do it on the lower lobes or in the upper lobes, you are in trouble. Then you will not get much back. Of course, you could -- I don't know if that has been tried.

DR. ABRAHAM: Despite this problem with varying recovery, it's really amazing that there is such correlation with the tissue burden.

DR. HILLERDAL: Yes.

DR. ABRAHAM: Because you have a denominator that

determines your concentration on that.

DR. HILLERDAL: Yes; yes. What you have to do is you have to have a strict protocol, and you have to do –- you have to have the same protocol with the controls. That's the only way you can make some kind of comparisons. But then, I think, it's very useful.

DR. ROGGLI: Well, I think the reason is because you're sampling millions of alveoli with the washing and the –- I think the latest studies show that adult human lungs have together 700 million alveoli. And if you were sampling several million, you're getting a pretty good statistical sample. And that's why it does correlate pretty well with what lung burden is.

DR. HILLERDAL: Of course, you get only this that is out in the alveoli. You talked about those where the fibers get into the lung proper. Then, of course, you wouldn't get anything out by your lavage, will you? And I think that's another advantage of having people who are young and presumably recently exposed because --

DR. ROGGLI: And healthy.

DR. HILLERDAL: And healthy; yes.

DR. WEISSMAN: But lavage studies, even in people with long-term chronic exposure, you know, still show a good correlation with lung burden, so, you know, it likely is the case that there's not unidirectional movement of

fibers. I mean, they could go the other way, you know, back into the alveolar space too.

DR. HOLGUIN: That's a good question. If you have the asbestos fibers in your airways, do they become aerosolized? I mean, do they –- once you breathe, do they detach from the airways and they're moving around? I mean, is there any way to collect them using -- does anyone have experience in exhaled breath condensate samples? Has anybody reported that? I know we've had some good success measuring, you know, markers of Libby population and other things.

DR. ROGGLI: The mucus blanket in the respiratory track is pretty sticky. Once something lands on that, it's –- it's very unlikely it's going to get re-aerosolized. Certainly, there are fibers that don't deposit at all, particularly very short ones that you breathe in and you breathe right back out. But once, I think, it lands on the airway surface, I don't think it's going to get re-entrained into the air; a very low probability of that.

DR. WEISSMAN: There are huge problems with standardizing exhaled breath condensate, and there's much controversy about that, as you know. Most of what you get is just exhaled water vapor, you know. So in terms of, you know, what you use as your denominator, it –- it still

remains to be worked out even for markers of inflammation.

DR. HOLGUIN: Sure.

DR. DODSON: The -- I guess it's a given that the other thing about that process with those –- with the fiber analysis is the specificity of type exposure. And one study we did was highly –- we can correlate what was retrieved in the lavage with what was projected at least as having been the type of exposure.

So in a case of a general population study group that has exposure to something and is unique, the lavage would let you not only determine the presence of whatever that was but also specifically identify the type that factored back into whatever the exposure area supposedly consisted of.

DR. STAYNER: Can I ask some questions about –- this sounds like a really promising technique of all the things we've talked about. But I wonder, when people talk about a high correlation between lung burdens and measurements of BAL, are those in studies of high-exposure populations? And has this really been sort of validated at environmental levels?

DR. ROGGLI: It's been looked at mostly for asbestos bodies, and the correlation is good over several orders of magnitude of levels in the lung tissue. So it correlates well from low to high lung burdens. I don't know that

there's nearly as much data for uncoated fibers by SEM, but I think there is some -- or by TEM either one.

DR. DODSON: Yeah; both. There is some. Yes. There's quite a bit from the European study groups and their correlations have both been to ferruginous bodies, as Dr. Roggli said, but also uncoated fiber burden extrapolated back to tissue burden in some cases.

DR. STAYNER: But these are in occupational cohorts, or are these in population-based studies, I guess?

DR. ROGGLI: It's a combination, I believe.

DR. WEISSMAN: It's a range. Yes.

DR. DODSON: Yes.

DR. GUNTER: I had a question that I put in my comments. And I was curious -- and again, this just shows my ignorance in some of these areas. I'll give you an example first, not of my ignorance, but something that we did. If we're looking at chrysotile, one of the concerns is the tremolite in chrysotile.

Well, one way that I had the idea to look for that is to do a bulk chemical analysis and use calcium as a proxy for tremolite content. We're not in asbestiform versus non. This is bulk content. So it's an indicator, and if you measure the calcium content –- and we did this. We spiked a lot of samples, and you could then determine the calcium and predict the maximum tremolite in that sample.

Okay. That works.

And that paper will soon be coming out in the *American Mineralogist*. But as an example of that, in these different fluids that exist, have people looked at the chemistry of these fluids and tried to relate that chemistry to anything? Possibly even digesting –- and again, I don’t know the mineral. You could do the calculations. But the mineral load, if you could dissolve those minerals and then measure some of the elemental compositions at low levels as a proxy for the mineral content as a way to cross-check some of your accounting statistics, or is that just too –- too wild, like a geologist would think?

DR. ROGGLI: There was a wide variety, I think, of calcium levels from various disease states you can find in the normal human lung. Plus there’s probably a lot of calcium that’s normally there physiologically. So I think there might be in -- a lot of noise there in terms of looking at the human fluids and trying to figure out how much of the calcium came, for example, from tremolite versus normal physiological solutions.

DR. GUNTER: How about -- not calcium. That was the example in this one point. How about just silica or silicon? How much silicon's there?

DR. ROGGLI: Well, there’s a whole lot more silica in

nonfibrous particles in the lungs than there are from asbestos. So looking at silica alone in a lung sample is not going to give you a good measure of what the asbestos level is, I don't believe.

DR. GUNTER: But again, that might be correlated to mineral content.

DR. ROGGLI: Overall, yeah. Yeah.

DR. GUNTER: I mean, should –-

DR. ROGGLI: Total mineral content?

DR. GUNTER: Yeah; because, I mean, the goal is to try to find something, and some of these things may be new. And these may be new –- you don't want to create entirely new research projects, but if there's some indicator like, again, if you digest the sample, look at the silica content, and then if you knew the ratio of asbestos fibers -- once you know the mineral amount, you could then get an idea there of the exposure.

DR. HOLGUIN: This is the expected break that everybody is thinking about. And we are to be -- to meet back here at two o'clock, is that correct, Jill?

DR. WHEELER: Yep.

DR. HOLGUIN: Have a good lunch.

(Whereupon, a recess of approximately 76 minutes was taken.)

DR. SINKS: I'm Tom Sinks, director of ATSDR, and I

apologize I wasn't here this morning or Dr. Frumkin wasn't able to be here this morning to welcome you all. We had a series of briefings on the things that took us away, and we were over at Clifton Road in the director's office, dealing with them. So we weren't able to get over here. I did get in here about ten o'clock, but I saw that you were all wrapped up in discussion that I didn't want to interrupt and break up your thoughtfulness.

This is –- asbestos has become a very major contaminant for ATSDR over the past five or six years. It is –- it has taken on a significant amount of the work lives of many individuals in this room at ATSDR, particularly -- I see these three people sitting over here, and I know how much they've worked on it. I see some colleagues from EPA. I saw Aubrey Miller before. Where's Aubrey?

DR. KOPPIKAR: He's coming back.

DR. SINKS: The biggest mistake Aubrey made was not –- was going to NIOSH and not moving with me to the National Center for Environmental Health in 1991 when he was an EIS officer.

But, anyway, I did want to thank you all for coming. There are –- as I get more involved with asbestos, I see that there are a lot of questions. Aubrey, I just said something about you. I'm sorry. I'm sorry you were out

of the room.

DR. MILLER: I was going to look for you.

DR. SINKS: There –- it seems to me that there are –- there are always unanswered questions or questions you'd love to be able to answer and you can't really answer them yet. And this issue of biomarkers for asbestos is one of them.

We have other significant ones related to naturally occurring asbestos that we'll be taking on and dealing with, but, hopefully, your getting together and giving us some good advice will be able to provide us some direction on this issue, and we'll be able to use that information in our upcoming health consultations. So thanks a lot for being here. If there are any questions I can answer for you, I'd be happy to. And I'll let you guys get on with your work. Thanks.

DR. HOLGUIN: Welcome back. Before we open the afternoon session, I'm going to –- I think Tina has some –- Jill has some announcements.

DR. DYKEN: Well, I don't have anything really formulated that I wanted to say. But I did want to expand a little bit about some of the –- some of our focus on this because I think there are a number of questions on, you know, why we want to do these studies, what is our overall goal.

You know, as an agency, we're asked to make general public health recommendations in these areas. If people know they're exposed to elevated levels of asbestos, you know, they have some –- some more general decisions that need to be made.

Basically, we can tell them they have an increased risk of disease, but what level of an increased risk of disease? And is that enough to justify, you know, doing expensive mitigation methods to reduce the risk on a community level and spending their resources on –- on air monitoring or other kind of mitigation methods to –- that could be used in developing schools and parks and fighting other big risks and diseases in their community?

So I think what we're not looking for is an exact answer, like which technique is going to tell you exactly, you know, how much asbestos exposure, but is there a way to generally see -- like, on a community level is this risk really big? Is this something that really requires a lot of resource? They really need to focus on –- on addressing these exposures, or is this like –- or is it just slightly elevated that –- but that you might never even be able to see an increased degree –- rate of disease in that population?

So –- so we don't need, like, an exact answer, but are there some techniques or combination of techniques

that might be able to give people a better picture of the risk they're facing from this –- these exposures? And I don't know if that was very clear, but –- but I hope that kind of lets you know that we're not looking for exact answers, but just more general. Like, is there –- is the science progressing enough that we might be able to give people some general answers to these questions? So we can make better recommendations for what people should do.

DR. CARBONE: May I continue on your question because I was the one who kept asking you the question?

DR. DYKEN: Yes; yes.

DR. CARBONE: And thank you for addressing that. In fact, it's very helpful. The –- the answer are always more complicated we want. And we always like simple answer, and unfortunately, they're not that simple. But even if you have a technique that we all agree here that is the real technique to determine asbestos exposure, then we have seen that there are various methods that we can use to make it more precise.

The risk is not the same. And that has to be clear, in that the risk is not the same among exposed individuals and different individuals react to different carcinogens -- this is true for all carcinogenesis -- react to different carcinogens differently. So while you can give a general, average response to the answer, are some people

at higher risk because they're exposed to asbestos, and the answer's general response is, sure, yes.

It's like going to the beach. There is an increased risk to getting skin cancer, but, obviously, if you come from Italy or you come from Sweden, the risk is completely different. The sun is the same. And it's the same situation or a very similar situation with asbestos in which the number of exposure that you have had, in addition to asbestos, in your genetic background are going to influence your sensitivity to the disease.

Now, when we talk about the disease, I suppose that we are talking mainly about malignant mesothelioma. And –- because that's the cancer that is mostly associated with asbestos exposure. The risk is always going to be relatively minor except for a few places where there is an epidemic of mesothelioma like the one that I'm studying in Cappadocia. But besides that, the risk is always going to be minor because the incidence of mesothelioma, even among asbestos-exposed individual, is, fortunately, quite low.

So when you talk about the large population, the incidence is not going to be such that you are going to see an epidemic of mesothelioma unless you have a particular situation in which you have an epidemic of mesothelioma. What should be discussed, at some point somewhere, is what type of resources are available out

there to see what we can do among people that are exposed, to see if we can come up with novel ideas and new therapies to prevent the development of the disease because then simple analysis or finding, yes, there is asbestos here, then you deal with these people who come to you and say, "Now what? And now what?"

So in fact, certainly, it's important to find out if the population is exposed, but I think we need also to discuss if there is something or what could we do in order to come up with novel preventive or therapeutic approaches or screening approaches that I see that is part of the discussion. So that we can be proactive, not just reactive to the fact, "Yes. You have been exposed, and now what?"

DR. DYKEN: Thank you.

DR. ABRAHAM: It probably is too much to ask, but would anybody from ATSDR or anybody else care to say what, pray tell, is an acceptable risk for an individual or a community?

DR. DYKEN: We're all struggling with that question, I think.

DR. ABRAHAM: To me, it's one thing; but to you, it might be something else.

DR. KOPPIKAR: [Off microphone]

THE COURT REPORTER: I need you to go to a

microphone.

DR. DYKEN: Well, I think what Aparna is saying is that basically ten to the minus six is an acceptable level according to EPA. And they have ranges, of course, at SUPERFUND that range up to ten to the minus four –-

DR. KOPPIKAR: I think --

THE COURT REPORTER: Microphone.

DR. DYKEN: But, you know, that’s a different question, I think, you know, numerical risk versus overall community risk.

MR. DEN: If you want to use an example, use the example for cleaning --

DR. DYKEN: Would you identify yourself?

MR. DEN: Arnold Den, EPA, San Francisco. I think the example would be the cleaning up of the apartments from the World Trade Center. And that was a ten to minus four risk. And I think, if you look at Libby, it’s around a ten to a minus four risk. And other sites that EPA is working on, it seems to be around ten to a minus four.

DR. ABRAHAM: So that would be a hundredfold increase in the risk of mesothelioma compared to the one in a million in the background?

MR. DEN: Yeah; yeah.

DR. KOPPIKAR: Right.

DR. ABRAHAM: So a hundredfold increase in risk is --

we’re going to tell people is acceptable?

MR. DEN: Generally, because of the analytical sensitivity and some background issues, we really can’t go beyond ten a minus four, maybe ten a minus five. But, generally, three zeros and a nine PCME fibers per cc is what they cleaned up the apartments.

DR. ABRAHAM: So that points to the methodological overlay of any risk assessment like the default counting mechanism for fibers based on the available technology that was practical.

MR. DEN: Right; yeah. Just chrysotile background will be ten to a minus five. You put a monitor by a stop sign from that.

DR. ABRAHAM: All right. So that’s really interesting to think about is a hundredfold increase in risk being acceptable.

DR. KOPPIKAR: One clarification here is –- I’m Aparna Koppikar.

DR. DYKEN: Aparna, we're not really -- but move on though. We’re not really --

DR. KOPPIKAR: Yeah. Now, since you asked about the acceptable risk is ten to the minus six as far as risk assessment that ORD does, but what Arnold is talking about is when you start talking about cleaning and this and that. You cannot wait 'til ten to the minus six. And you

may not be able to get to that level. And at the ten to the minus four, you start doing cleaning.

DR. FORRESTER: I'm Tina Forrester from ATSDR. When we identify exposures like in El Dorado County, our goal as a public health measure is to mitigate the exposures. So what our hope would be to stop things like El Dorado development from occurring when there are veins and issues that we can work with developers to prevent them exposing the veins and people ever being exposed. So we need to go back to some of the first steps of pure public health: stop exposure.

DR. CARBONE: Don't you think that we also should try to understand how is it that asbestos is causing mesothelioma and see if we can intervene in the process before the disease comes? Because people who have been exposed have been exposed. We're not going to take -- extricate the asbestos out of their lungs, so we can reduce the further exposure. But still we should see if we can do something for the exposures that already has taken place.

DR. FORRESTER: That is true, but as good public health practice and the easiest thing that we can do –- that any of us can do is to make sure the exposures don't occur in the environment, and that's not taking away from people that are already exposed. It's just there's a lot

of naturally occurring asbestos across the United States, and it's an issue that needs to be addressed.

DR. ABRAHAM: I won't belabor this now, but that –- there's a conflict between that approach, which is –- I agree with you. The primary preventive goal versus telling people what their risk is -- because you say they want us to tell them what their risk is, and yet you say we don't really need to tell them what their risk is -- we just want to prevent the exposure -- which would be my approach. Or you want to prevent the exposure without worrying about what the risk is as long as you know there's some exposure going on; right?

DR. FORRESTER: No. We should tell them the estimate of risks once they've been exposed. But the overall goal in public health would be prevention in the first place. Now that we know –- if we know we have a situation where exposure can result in disease, we should put prevention actions in effect to predict -- to protect the broader population.

DR. ABRAHAM: I don't have any argument with that.

DR. FORRESTER: Okay.

DR. HOLGUIN: Well, both approaches are not mutually exclusive. It's just a matter of where do you allocate resources initially. Okay. Can we get on the with the program?

There's been some changes in the schedule. I'm told that what we will do -- we have a break around 3:15 or so, and then we'll do –- talk about fiber analysis techniques in tissue, BAL fluid, or sputum in sentinel animals, either household pets or other resident-animal species; then counting asbestos bodies in human tissue, BAL fluid, or sputum.

Now, for tomorrow, we had scheduled at 9:30 to talk about blood mesothelin and osteopontin levels and all clinical tests such as spirometry or CT scans. I think ATSDR would like to maybe talk about both of those -- the fibers and the other clinical tests -- this afternoon, and then tomorrow we'll have more time for questions.

So I guess we could start by discussing fiber analysis techniques in sentinel animals. I know there's been some –- I'm sort of aware on the briefing there was some animal samples in El Dorado County. But again, this is not just relative to California, but -- anybody would like to talk about...

DR. ROGGLI: Well, I think, based on the premeeting comments, it seems like the panel members are pretty much in agreement that sentinel animal studies can tell you that exposure has occurred in an area. They won't tell you anything, based on our current knowledge, about levels or whether there is human exposure or what the risk might

be for the human exposure.

And since there have already been some sentinel studies, animal studies, that said, yes, there's exposure here, I'm not –- I'm not convinced we need to do any -- spend any more money in that direction.

DR. HOLGUIN: Anybody?

DR. CASTRANOVA: Also, if we're trying to use the sentinel animals to tell the exposure in a population, which I think was the charge, and from what I heard from the EPA people in the audience, the exposures go up during certain activities: playing on a ball field, riding an all-terrain vehicle around, and stuff like that. Well, a sentinel animal won't be doing that necessarily and won't be in that location necessarily. And so my argument would be it would be an underestimate of possible exposure.

DR. ROGGLI: Or it might even be an overestimate. If you've got a sentinel animal who decides to go over to an outcropping of tremolite and snoop around a bit (laughter). You're not going to find humans doing that.

DR. HOLGUIN: I guess a thing -- the exposure history of the animal, compare it.

DR. ROGGLI: Yeah; exactly.

DR. ABRAHAM: Right. Well, I think the study that we did in the small number of animals did have the sort of residential history of the animals, and there was a

correlation between the residential history of time spent in the area and the amount of tremolite in their lungs. I should say tremolite actinolite to make the mineralogists happier.

But although it doesn't prove human exposure, it certainly parallels other situations where animals, such as in Corsica, have had exposure and the humans living in the same area have also had exposure in mesotheliomas.

So I think having animals with that exposure is pretty strong evidence that people living in the same area have had exposure, although it remains to be seen by tissue analysis of the humans, I suppose.

DR. ROGGLI: Right. So now you have that early information. So it's time to move on and look and see what the people have.

DR. ABRAHAM: Certainly, there's fibers in the air that some beings are inhaling and retaining in their lungs.

DR. HOLGUIN: I guess one particular question is: What do you want? People to sacrifice their own animal? Or do you wait for them to die? Or --

DR. GUNTER: That was --

DR. HOLGUIN: -- perform BAL on them?

DR. GUNTER: This is an area that's of interest to me, like so many of these, for a long time, and I've

thought –- I haven’t thought about the house pets as much as -- we have a slaughterhouse on campus, and they slaughter sheep. So there’s almost an infinite amount of sheep lungs that are available at the slaughterhouse.

The -- at the same time, in hunting -- I mean, you live in the West. Anytime that you kill elk, they have to go to cleaning stations. So if you wanted air samples in the West, you’re not looking at house pets. If you want to get outdoor exposure background levels, the animals killed in hunting would be a great way to do that. So it’s not –- and I read this. It all seemed to come back to the house-pet issue. But in the western U.S., there are many other sources of animals.

DR. ABRAHAM: Yeah. The house pets were used because they were animals that belonged to people who lived in the community and were concerned about the exposures. And the animals were being euthanized, not for the study. But the study was a byproduct of their being euthanized anyway. But the study in Corsica did use goats that were roaming, and they were harvested that way.

DR. CASTRANOVA: The other comment would be, as far as BAL fluid in sputum, if you were going to have difficulty getting human volunteers, you’re never going to get a human donor to volunteer their pet to do that.

DR. HILLERDAL: Well, I don’t know that animals can

spit.

DR. CASTRANOVA: No, they can't.

DR. WEISSMAN: You can't get informed consent.

DR. HOLGUIN: They cannot give informed consent.

DR. WEISSMAN: And I would echo what other –- you know, what Victor said in terms of not having a really good handle quantitatively on what the relationship would be between exposure of a particular species of animal, you know, and human exposure.

So for instance, you know, Jerry, in your work, you know, cats seem not to have much fibers, if I remember correctly, and dogs did. And, you know, then we have the, you know, work from Europe, from Sicily and from Corsica, with goats and sheep, and we just have no idea what the right species is to use and what the relationship is. So I think that we get the categorical yes/no. There is exposure, but in terms of quantitation, you know, for humans it's –- we still need more work.

DR. ABRAHAM: Just one comment as far as the categorical. The cat category did have evidence of exposure in the cat that was mostly an indoor cat and none in the cat that didn't live in the region. So it's hard to know whether it's a species thing or just that it's part of a correlation between the amount of exposure they had. You could argue either way. It fits with the

history of exposure.

DR. HILLERDAL: But I don't think you can ever do with some kind of exposure study in animals, and I think the difference –- you talk about species difference. I think the difference in different dog races. I mean, a big dog, all the time digging in the forest, would not be as exposed as an dachshund that likes digging around in your back yard or whatever.

And I think –- I don't think that any more animal studies, at this moment, would do any good because we have studies showing that these pets have been exposed. And I think the amount of elk and sheep that walk around in the El Dorado Hills are not very great, are they?

DR. ABRAHAM: I don't know. We also have the –- the exposure studies that have been done by the EPA. So there's plenty of evidence in the fibers in the air.

DR. HILLERDAL: So I think further investigation of pet animals will not add much actually. Squirrels, maybe. They get around a little bit.

DR. HOLGUIN: Is there anyone in the panel that feels that animal studies need to be done? I mean, I think I sense that everybody's on the same level that no more further animal studies are needed.

DR. GUNTER: What was interesting is to listen to that the comments about dogs behaving differently. But in

many ways, humans are like dogs because the human exposure is very different.

DR. HOLGUIN: Clarify.

DR. GUNTER: But no; because humans are going to be –- if you happen to –- if you happen to work on a road grader in El Dorado County, your exposures are going to be much different than if you're an attorney. So again, the human exposures are going to be just as different as the animal exposures. And that can be something that would be difficult with some of the earlier discussions this morning on looking at human tissue.

DR. CARBONE: So there can be particular circumstances in which you may want to do an animal study. One cannot be, categorically, I think, saying that they can't be done. But, in general, probably they don't need to be done.

But say that you are in a situation like that you live in Arizona, and you want, for example, to find out if you want –- go and run in the desert if you are exposed to erionite. I suppose you could kill a few animals and see whether they have erionite in their lung because I don't see any other way you could figure it out.

But short of situation like that, that are pretty unique and unusual, I think that probably is difficult to get any information from animals because, as he said,

animals don’t play soccer or maybe they can dig the soccer field over night and breathe all the erionite or whatever is there.

DR. HILLERDAL: Which animal would you suggest to kill in the Arizona desert?

DR. CARBONE: I would suggest not to kill any animal because I hate to kill animals. Having said that, I suppose that the only way that you could get some type of information, if there is, in fact, erionite in the area around there because there is plenty of erionite in the soil for sure is some older horse who dies and who has lived there for a while and see whether he has erionite in his lung.

DR. ABRAHAM: Or road-kill. There’s enough animals killed on the highways.

DR. ROGGLI: I think one of the issues is if we had infinite resources, what you'd probably want to do is do all the studies that have been suggested and just see what comes out. But the reality is there are not infinite resources and taxpayers are not happy to shell out more money than they need to, to learn useful information.

DR. HOLGUIN: Sure.

DR. ROGGLI: So you have to prioritize which are the things that are going to give you the information that you’re really looking into. And at this point, I think

animal studies would be low on that priority list.

DR. HOLGUIN: Anyone else care to comment?

DR. ABRAHAM: I'd just say that in a community where there hasn't been any evidence for exposure, that might be a place where animals could be used as an initial screening if they're available. And I wouldn't, you know -- again, I wouldn't suggest sacrificing pets or something like that. But if the animals are available anyway, their tissue should be archived and examined when they would add information to what we need to know.

DR. HOLGUIN: More on animals?

DR. ABRAHAM: No.

DR. HOLGUIN: Okay.

DR. CARBONE: The animals are safe (laughter).

DR. HOLGUIN: All right.

DR. CARBONE: We saved the animals.

DR. HOLGUIN: Let's talk about counting asbestos bodies in human tissue, BAL fluid, or sputum. Open for discussion. Again, the main topics are advantage and disadvantage of the technique and how they will represent the background exposure in a community.

DR. ROGGLI: Well, I thought Dr. Dodson's analysis was really excellent. He pointed out that –- well, as several of us have pointed out, the advantages of asbestos bodies is that they're easy to identify. You can use

regular light microscopy. You don't have to use any special techniques. The reproducibility from laboratory to laboratory is probably better for looking for asbestos bodies than any other parameter of asbestos exposure in human lung tissue samples.

But the disadvantages are that it's only telling you a tip-of-the-iceberg story, and there's not a perfect correlation between asbestos body counts and other fiber types. Even for amphibole fibers, for which asbestos bodies are a good marker, there's a wide variation in the percentage of the longer amphibole fibers that are coated from one individual to another.

And you get away from amphiboles and look at chrysotile, then chrysotile is just not a very good asbestos body former, accounting for a couple of percent of the asbestos bodies in our laboratory, and I think others have found similar to that. They're a low percentage.

So asbestos bodies are cheap and easy to do compared to EM, but they should not be done alone without looking at the electron microscopy as well. One advantage would be to do both. If you're looking at human tissue samples, it would be to look at both asbestos bodies or ferruginous bodies and the fibers by EM. And the reason for looking at both is because there's more data in the literature on

what the normal ranges are for asbestos bodies in sputum, in BAL fluid, in lung tissue samples than there is for uncoated fiber counts.

So it's –- the data are better grounded for asbestos bodies than they are for other parameters. But I wouldn't recommend looking at them in vacuo without also looking at the fibers.

DR. HOLGUIN: If it's less specific but more sensitive, could it be used –- could it be a better screening tool?

DR. ROGGLI: Well, in sputum, it's going to be a worse screening tool because its sensitivity is so poor.

DR. HOLGUIN: Okay; okay.

DR. ROGGLI: But in BAL fluid, it's –- it might be a pretty good screening –- screening because it's cheap. But again, if you're going to go –- if you're going to go to the trouble to collect BAL fluid --

DR. HOLGUIN: You might as well do the whole thing.

DR. ROGGLI: There's no reason to look just at ferruginous bodies and not also look at the fibers by EM.

DR. HOLGUIN: So sputum doesn't really offer any advantage over the previous?

DR. ROGGLI: I don't think so.

DR. HOLGUIN: Dr. Dodson.

DR. DODSON: No. I agree with what Dr. Roggli said

that ferruginous bodies is an indicator of a portion of the population of longer fibers inhaled in the lung for those people that coat those longer fibers, and that excludes chrysotile for several reasons. But there are rare instances where there are numbers of chrysotile-cored ferruginous bodies. But most of the time it is exactly on the –- on the numbers that Dr. Roggli said of 1 percent or less of all the total you see in a given study that are on chrysotile.

So it tells you nothing about it. It tells you that there was potentially, when you see them, a exposure –- an exposure to longer amphiboles, unless, of course, the person is not a very good coater of those longer amphiboles. It tells you nothing about the population of uncoated fibers.

DR. ROGGLI: One other point that I'd make about asbestos bodies is that Dr. Dodson says they form on fibers 8 to 10 microns in length, whichever you like. And what I actually like is 15 to 20 microns in length because I don’t think I’ve ever seen an intact entire asbestos body coated on both ends that was less than about 15 or 20 microns in length.

You can get halves of asbestos bodies that are 8 to 10 microns in length where you’ve cut it in half by your procedure. But –- so the point of this is, is that in a

number of cases we've analyzed, we found increased levels of tremolite fibers in the lung tissues but the asbestos fibers were within normal range -- asbestos bodies were in the normal range.

And the problem there is that the tremolite fibers that we have seen in most cases -- not all but in the vast majority -- are less than 20 microns in length. And so they're less apt to be coated to form asbestos bodies; whereas, if you've got a population of amosite and crocidolite fibers, you're almost always going to have a significant proportion that are going to be more than 20 microns in length. So you'll get lots of asbestos bodies.

So asbestos bodies may really underestimate your exposure to a significant number of tremolite fibers that are 5 microns or greater in length.

DR. HOLGUIN: Jill.

DR. DYKEN: I'd like to ask a question related to asbestos bodies. Does [sic] the asbestos body itself thought to cause disease, or is it a symptom of exposure that might be leading to disease? Or if somebody could expand on that, please.

DR. ROGGLI: Well, basically, the asbestos body's a marker of exposure and not of disease. And there have been a number of studies that have looked in different ways at the asbestos body themselves and found that they

are less toxic than the uncoated asbestos fibers. So one hypothesis has been that etiologically that is a way that the body has of detoxifying asbestos fibers is by coating them and creating them into an asbestos body.

And one of my friend and colleagues, Dr. Andy Ghio, wasn't convinced at all of this argument because he is, like Vincent, very much interested in iron metabolism and iron –- or free radicals that are generated from the iron-redox cycling. And so he thought that you might actually increase toxicity by coating it with iron. But when we did the studies, he found out that wasn't true.

And what happens with the asbestos body, you coordinate a form of iron around the surface that actually reduces the amount of redoxable iron. And so it's actually less toxic, even in terms of our metabolism, than the uncoated fibers.

DR. CASTRANOVA: Yeah. I agree with that. And so that if you're looking only at asbestos bodies, you're looking at a subfraction of all the fibers, but a subfraction of all the fibers that is less toxic than the rest. So it may actually mislead you a little bit.

DR. CARBONE: Excuse me. But the mean -- the issue is what we mean for toxicity because toxicity and cancer are two things that are at the opposite. If something is toxic enough, it's going to kill the cell and you get no

cancer. So in fact, by reducing toxicity, now you can induce an agent that is not a carcinogen to become a carcinogen.

So it would not take the reduction in toxicity in any way as a measure that the substance is less oncogenic. It doesn't mean that it's not, but just you cannot make the equation.

DR. CASTRANOVA: Well, let me expand it. Instead of toxicity, less biological activity.

DR. CARBONE: Excuse me. How do you measure it?

DR. CASTRANOVA: Response to the cells, you know, growth factors, cytokine response.

DR. CARBONE: None of that has anything to do with predicting whether that is going to cause mesothelioma. We do not have any test that you can point to me that has been published in the literature in which you can say that asbestos caused cancer because of. So we do not have any way to predict exactly what type of reactions would more likely cause cancer versus those that will not.

So since you cannot measure it, you cannot establish whether the toxicity, whatever is reduced, is something that is related to the ultimate outcome that is cancer unless you were to be able to say, for example, that by coating the asbestos fibers, you are reducing the inflammation, which, obviously, the chronic inflammation

process that asbestos causes is related to cancer. So now you have a general phenomenon there.

And you say that this asbestos fiber will not elicit a chronic inflammatory response. And obviously, the chronic inflammatory response by producing a number of cytokines promotes the growth of malignant cells and of tumors. Then that probably would be a good argument. But most arguments that have been are based on these toxicity things that you're talking about in which they are measuring things that has not been shown to have anything to do with cancer in the first place.

DR. CASTRANOVA: I agree. And I think I was referring to the second: the production of growth factors, the production of oxidant stress in the cell that would change –- that would change growth regulation of the cell.

DR. HILLERDAL: It's such a small portion anyway of the fibers that get counted that become asbestos markers. That's probably completely marginal. Whether they are less –- more or less toxic, I don't think that matters at all. But what matters is that some people –- it's –- as we said, it's a marker, but we have also to be aware of that some people are good producers of asbestos bodies. Still that doesn't mean they're less than 1 percent. I think it's much less than 1 percent that gets coated with the best coaters. Others don't coat anything, so –- but I

think toxicity has nothing to do with this. It's just a marker.

DR. DODSON: The –- I'm aware of Andy Ghio's work, and I think it's some good work. We isolated some ferruginous bodies in a different way and Ann Hosein seemed to find that there was a mobilized iron involvement with the ferritin-type reaction.

But just some very fundamental comments, the ferruginous body may represent a small portion in those people that coat. It's also the type material that's much harder to get eliminated from the lung and stays there. It is a foreign structure. It does continue to induce an inflammatory reaction. And if it cannot be removed, then also it has macrophages that are not going to outlive the stimulus. And so there is a local spin-down effect of a release of materials that's not supposed to be in the lung, the surface of the lung, from them.

And they are –- they are, when found in people who've produced them, they are –- and it is true a percent of the fiber population. But there are also are a percent that, because of their simple size and dimensions, are much harder to ever relocate.

The smaller ferruginous bodies that -- back to Dr. Roggli's comment -- generally are those we find with the electron microscope, the shorter ones. And ferruginous

bodies, in part, tend to also not only be determinant, as far as their formation on length, but also their internal composition of diameter and multifibrillar components instead of single fibrillar units.

DR. HOLGUIN: John, were you going to comment something? No? Kelly, were you going to comment something?

UNIDENTIFIED SPEAKER: No.

DR. HOLGUIN: Okay. Have the presence been associated with -- I mean, people who you fairly exclude other lung diseases if you see these bodies in BAL, have there been any reports associating them with, you know, BAL lymphocytosis or, you know, changes in any clustering or things like that? Other kind? No?

Any more comments on asbestos bodies?

(No audible response)

DR. HOLGUIN: No one? Should we move on to the other clinical tests? I think we might be hitting the hyping of the postperennial state here (laughter).

We have a break coming soon. Let's start with blood mesothelin or osteopontin levels or other blood tests in the same fashion that we discussed the other techniques. You want to open it?

DR. CARBONE: Sure. I was quite skeptical about this stuff, and usually, you are very skeptical when you've not

done something. So you see something -- you can't be to look at it and do it, promise not to. So anyway, actually, I was part of the study that Harvey published on osteopontin. But I was just the pathologist who made the diagnosis on the mesothelioma and that I didn’t do much.

So I have –- I am studying this population of high incidence of mesothelioma in Cappadocia, which is an incredible place. Okay. 50 percent of people die of malignant mesothelioma in that place, and that includes traffic accidents. It includes everything. It’s unbelievable. In the –- we are determined that the reason is mostly caused by erionite, that it is this fiber, that, in a way, I understand resembles crocidolite. And then there is a very different in risk among different families, and now we are trying to isolate the gene that predisposes some families to this erionite.

Having given this background, the situation there is a tragedy because people just wait to die. And so they do not tend to do anything because they’re quite depressed. So the issue is what can you do for these people. And one of the things that we thought we could do was to try to see if we can detect mesothelioma in the early stages. So we run a first test on this mesothelin. And I’m just coming back from Cappadocia looking at this –- results of this test, which were really remarkable -- I mean, really

remarkable -- which made me change my mind about the test.

We did detect the high levels of mesothelin in those that had mesothelioma. And then, among the normal population, we tested some 70 samples. Four of them had bulk background levels of mesothelin, and one of them has already come down with malignant mesothelioma. I have organized another collection of sera for next week -- this weekend actually. And then we're going to go there and do the test again. If the data hold true, then the Minister of Health in Turkey will provide all the economic support to do radiological analysis, CAT scans, on patients who have high levels of mesothelin.

The hope is that, in fact, we have a test that allows us to detect mesothelioma earlier than other tests and that is sensitive enough that you do not have a very large number of people that you have to refer to radiation. Based on the first test that we ran, that's exactly what it looks like. It's a relatively simple test to do because all you have to do is to collect sera from people, which is easier than many other things. It's even easier than to convince people to get their radiological exams, at least in that part of the world.

And the issue is, however, in this patient that we detect at high levels, did she have already a mesothelioma that would have been detectable by radiological image or

not. How good is this test? How early can we detect the disease? Based on Bruce Robinson's study and on Harvey's studies on osteopontin, in fact, that should be the case. But we need to verify that.

And what we have there is this unfortunate laboratory of mesothelioma of human beings that allow us to verify the reliability of this test in a time fashion that would be impossible in any other part of the world because here I would have to study 100,000 people to come down with the same numbers that I have over there. So I hope that this mesothelin test and possibly the osteopontin test that we're going to try this time are going to prove effective for early detection of mesothelioma.

Then, of course, the question becomes, well, now that you have detect the mesothelioma, what should you do about it. And the –- that's a very valid question. The only hope for some effective treatment right now is to detect mesothelioma in Stage 1-A or so. If you look at the data of Harvey Pass, Sugarbaker, and Rusch, all of them show that there is really nothing to do unless you are so lucky to get the Stage 1-A mesothelioma that tend to live longer. But to see a Stage 1-A mesothelioma is very, very rare.

So the hope would be that if, in fact, the best hypothesis here works out, we have a test that allows for

early detection of mesothelioma. Now, that test could be a test that you can offer to people at risk. But, you see, you can offer that test, I think, in the village of Tuzkoy or Karain where these people die like flies of mesothelioma. You could offer to the three or four mesothelioma families that I'm studying in the United States where half of the people in the family died of malignant mesothelioma. I am not sure that you would want to offer –- and this is just my personal opinion -- as a general test to a population that has just a limited increase of bulk background of detecting mesothelioma.

I'm not saying that you have to withhold it from them, but, of course, there are advantages and disadvantages of offering any type of test. There is morbidity associated with the simple fact that some of these people will be referred to a hospital, and so it will be your decision to decide whether the risk outweighs the advantage.

Certainly, there is a big advantage in a high-risk population, exposed population, such as could be if you are dealing with former shipyard workers or former asbestos miners. Then I would see the advantage. If you have -- it's just slighter increased risk, I don't. But I've taken too much time already, so I better stop and let you speak.

DR. ROGGLI: Well, I think I would echo a lot of those comments. I think you have to put the situation into some perspective, and the –- in the group of asbestos-exposed workers that we've looked at, not genetically related, the highest –- the highest exposed group we've studied have been the insulators.

And according to Selikoff's work, 8 percent of the insulators got mesothelioma. That means 92 percent of them never got the disease. Shipyard workers, 2 to 3 percent get mesothelioma; 97 to 98 percent never get the disease. Chrysotile miners and millers in Quebec, half a percent get mesothelioma; 99-1/2 percent never get the disease.

When you start using markers such as this, which have –- do not have perfect specificity and perfect sensitivity, and you start looking at populations whose risk is much less than the chrysotile miners and millers from Quebec, you're going to do nothing but ask for trouble because you're going to get killed by your false positives.

And it's the same problem as you have with the disaster which will occur in this country if we start doing routine CT screening of cigarette smokers for lung cancer because you're trying to catch a disease which comes and goes pretty quick on a background of stable

nodules that are present there all the time.

DR. HOLGUIN: It happens though.

DR. ROGGLI: Well, let me answer –- point out a couple of other things. The problem with even discovering mesothelioma in its early stage at 1-A lesions, which are uncommon, and you've got some invasion by the time you're there or you don't know it's mesothelioma. So you do have some invasion of 1-A diseases. You don't know at this point in time from what information we have that the increased survival you have is not all due to lead-time bias, simply discovering disease in earlier stages.

DR. HOLGUIN: True.

DR. ROGGLI: And even in using these procedures in high-risk groups, we don't know what the results of mesothelin and osteopontin would be in people who have atypical mesothelial hyperplasia which would never go onto develop mesothelioma versus those that have mesothelioma in situ, whatever that disease is; that is, we have no way of predicting which ones would become progressive.

So are we going to offer extrapleural pulmonectomies for people who have atypical mesothelial hyperplasia that you detect by a slightly elevated osteopontin-mesothelin test? I think it's a can of worms that you can't get into. At this point, there's just too many unanswered questions, and it's not ready for prime time.

DR. HOLGUIN: Thank you.

DR. CARBONE: May I?

DR. ROGGLI: Sure.

DR. CARBONE: Thank you. Victor, I agree with you that it's not ready for prime time on a larger population such as the United States of America by offering a test for everybody to use it. And nobody, except one person, has suggested that you do an extrapleural pulmonectomy on somebody who has high levels mesothelin or osteopontin.

The fact that I was trying to explain is that we have a test that seems to be very promising and that justifies doing more work on this test to determine the sensitivity and the specificity of the test so that we will know -- because today we do not know the answer of the many questions that you have raised.

But because the test appears very promising, I think that it's important, especially in populations such as the one that I described, which I think is unique, where if you find other mesothelioma families that we use this test to determine the specificity and sensitivity because, in fact, we could have a test that is going to be useful for certain group of people.

The next –- the other issue becomes what can we do, if anything, among people who are exposed to –- who are –- who have high levels of mesothelin who, therefore, could

be at higher risks of developing mesothelioma to prevent the mesothelioma starts. We have heard before that the issue here is to prevent mesothelioma by removing asbestos or by reducing exposure, which is a good idea. Another way to do it is to see if we can act in the chain of the events that leads to the development of mesothelioma to block that series of event to take place.

So if, in fact, we have a test that allows us to identify people at higher risk, then therapies over those individuals may be more effective than therapies once you really have an invasive disease where the therapy cannot work. And for example -- and again, nothing of this is prime time, but it's something that you need to work on. It's becoming pretty clear that the inflammatory process that is evoked by asbestos indirectly plays an important role in the pathogenesis of mesothelioma.

We have a paper that is coming out in *PNIS* defining the molecular mechanism by which this happens. And the inflammatory response has as a general role in causing cancer in different places. And for example, we are now testing COX-2 inhibitors for colon cancer, for lung cancer.

These are not therapies that are invasive therapies. These are not therapies that are going to make anybody sick. However, these are therapies that could be tested

and tried on individuals who we believe are at higher risk of developing mesothelioma to see if, in fact, we can interfere with the process in time before the disease develops. And that's what I think we should also consider in this meeting: what therapy things that we have available today to interfere in the course of the disease for people who have been already exposed because there is always going to be a group of people who are exposed. You cannot prevent completely exposure to everybody.

There are other drugs that specifically inactivate some specific pathways that are out there. For example, drugs to block TNF-alfa, drugs that block NFkB. Some of these drugs can be tested to –- in population at risk to see whether, in fact, we can reduce this risk. It doesn't mean that works, but the only way to find out something that works is to try.

DR. HILLERDAL: All this is some –- this is very good when we have it. But today we don't have that, and today it would be -- I think it would be a serious mistake to take these tests on hundreds of people with, as you say, low risk of mesothelioma.

And if you look at Robinson's paper on Western Australia, he went back and investigated serum and he found out that many years before they had clinical mesothelioma they had high levels.

So what do you if –- I mean, you have a high level and you have no –- you make a CT scan. What you would have to do is, I suppose, a CT scan every six months, and if that takes many years until you really develop mesothelioma, it gives you some trouble.

And also, you make the CT scan and you will find some small changes, some small pleural changes. It's a little thicker there or something like that. Then what do you do? And the other thing, as you point out, we don't really know that we do these patients any good by finding early mesothelioma.

Of course, Dr. Sugarbaker and others would say we operate them and we -- and that will prolong their life, but this has never been tested in any randomized study. And a pleural pulmonectomy -- and especially these new things where you connect that. You give them cytostatics. You take out the hoola and everything around it, and then you give radiation afterwards, and that's very –- that's a very heavy treatment, which has both morbidity and mortality.

And you don't really know if you're doing them any good. You might prolong their lives, and I think you do actually. I think you actually do, but most of them will come down in their disease anyway later on. And some of them will die from treatment, and until you know –- until

you know that you can really do something good by discovering a disease early, you should not screen for it, I think.

DR. CARBONE: So you agree that we should screen known populations at high risk to verify whether the test is specific because otherwise how am I going to determine if it's specific?

DR. HILLERDAL: No, no, no. Yes. That, you should do, but only in a very strict scientific investigation. The patient should be fully informed about this. And you should have some very interesting studies and hypotheses which you could test on these patients because, otherwise, I think you will do more harm than good for time.

DR. CARBONE: You do more harm than good because of what? I mean, say that you take a population of insulators. Okay.

DR. HILLERDAL: But if you were exposed to asbestos --

DR. CARBONE: Yes.

DR. HILLERDAL: -- and you go and take this test and say, "Okay. Yes. You have four times higher mesothelin level. You might have mesothelioma." Then what? What do you do? Well, you do a CT scan; right? You do it, and you see nothing. And then you say, "Okay. Come back in six months. We'll make another CT scan." You come back

next six months, and you make another CT scan. You keep it up for many years.

Now that you get very –- you get some radiation. Maybe that’s not very dangerous. I don’t know. But it is quite a lot of radiation anyway. And what about the psychological burden for these patients, especially in this group? He says, "Well, I have mesothelioma. They can’t find it." And he goes –- I’m not sure that you’re doing that patient any good. I think you’re doing him some harm. Of course, these are very difficult ethical questions.

DR. CARBONE: It is a difficult ethical question because, as you understand, the only way that you can do progress and understand how specific and sensitive this is, is of doing it. If we do what you suggest, that is, do nothing because we don’t have yet the answer, six years from now or ten years from now, we are exactly where we are right now.

DR. HILLERDAL: I said you shouldn’t do nothing. I said you should not do that in a grand scale without really putting up research program. You should do something. For instance, it’s possible. I mean, what I've been thinking of is that this guy who has this high mesothelin levels, what would the next thing be? Well, I would try to take –- to make minor investigation of his

thoracic –- you know, you could put in some catheter into his pleura and see –- and see if you because of the mesothelioma. Certainly, it must come from there.

So you can see. And if you see that from his dry thorax there comes -- there comes a high level of left side you don’t have it, then you could go on and you make a thoracoscopy or some -- even open him up and see if you can find it, something like that, some kind of investigation.

You must know what to do with it. And you have to do that in some kind of research program. That’s the important point, you know, not at this level. Unless you know exactly if that patient is positive, then we do this. We take him in there, and we make that...

DR. CARBONE: At this point, the role of this testing is to verify how sensitive and specific it is, to address the questions that Victor indicated before because, at the moment, for example, we do not know whether mesothelial hyperplasia is going to bring it up and how much it’s going to bring it up. So you need to be able to address these questions first. And that’s why I was suggesting not to do a thoracoscopy. I was not suggesting to do an extrapleural pulmonectomy. I was suggesting to give them ibuprofen.

DR. HILLERDAL: That's been suggested.

DR. CARBONE: Okay. And I was suggesting –- I know. Just one person said that, and we know who he is. But that's why I was suggesting to give them ibuprofen because with ibuprofen I'm not going to make the person sick, and at the same time, I'm making the person think that I'm doing something about it because I have to deal with the problem that you told me that, in fact, that he's going to be worried about it and because there is a chance that ibuprofen can also help him. And certainly, there is a logic behind it, where there is not much logic in the lung cancer studies that are done right now.

DR. HILLERDAL: Then you should do that in a randomized study and see if they come out with mesotheliomas.

DR. CARBONE: Exactly. That's what needs to be done.

DR. HILLERDAL: Yes; yes.

DR. CARBONE: And so that you can offer them something, and if you see that there is advantage, you move in steps. You first verify how specific and sensitive the test is. Then you verify whether, in fact, for example, the COX-2 inhibitors, the Onconase, all these dry here, the blocks, the inflammatory response are able to help these people in their progression.

If they are, then you have something to offer to these people in case the mesothelin in there is high and

then you can justify why you would want to offer this to a larger population. Until then, I agree with you. You're doing a very selected group of patients because you need to have the answers to the questions that we have stated.

Having said all that, I still think that this is the most exciting thing that we can do because we need to move forward. We need to be proactive. We need to come up with solution to the problem. And the only way to find solution to the problem is to work on these biomarkers and to try to find out ways to detect airway disease and to see if we can stop the process of the disease. If we sit and don't do anything, then we are going to be in the same situation 20 year from now.

DR. HILLERDAL: I quite agree with you, but I'm just pointing out the very difficult ethical questions that you have in here because you're dealing with human beings.

Dr. HOLGUIN: I'm assuming this -- you know, someone who's not an expert on the topic. But I'm assuming these levels of mesothelin are not related to the exposure. I mean, they're related to --

DR. HILLERDAL: [Indistinguishable cross-talk]

DR. HOLGUIN: -- risk of developing mesothelioma, not exposure.

DR. CARBONE: Mesothelin is not. Onconase -- excuse me. What's its name? Osteopontin. That is the marker

that Pass described in his paper in *New England Journal of Medicine* was found higher than background in people exposed to asbestos. And so what he suggested is that osteopontin can be a marker of exposure. Now we need to verify that, and it could very well be that this marker is so sensitive that it's going to be difficult to do so.

We're going to try that with erionite. We don't know that erionite is going to do the same thing that asbestos does, but the hypothesis is that osteopontin is a marker of exposure and that mesothelin is a marker of disease.

DR. WEISSMAN: In osteopontin, I guess, the primary end point for the *New England Journal* paper was the presence of mesothelioma. In terms of asbestos exposure, the group was dichotomized according to numbers of years of exposure, you know, greater than ten, less than ten. And there was extensive overlap between the two groups. So the conclusion of the paper was that, you know, there was potential, you know, to use it, you know, as a marker of exposure. But the jury is really still out on that.

DR. CARBONE: Correct; exactly.

DR. WEISSMAN: And, I guess –- I guess -- you know, to jump into the previous, you know, flow of conversation, you know, I think everybody really shares, you know, your enthusiasm and excitement about, you know –- you know, about the positive, you know, findings with mesothelin and

osteopontin for, you know, identifying, you know, malignant mesothelioma.

And I think –- I think we all agree that more research needs to be done to further, you know, characterize their usefulness and define the performance characteristics in different populations, including the low-prevalence populations, you know, that you were describing. It –- I mean, it's really exciting. And no doubt, we should move forward.

But in terms of ATSDR using the tests, you know, in communities at this point in time, you know, I would agree that it's not to that point yet. But, I mean, I think you wouldn't find anybody in this room that wouldn't be supportive of doing more research.

DR. HOLGUIN: How about osteopontin for exposure? Is it ready for prime time to be used in the --

DR. WEISSMAN: No; no.

DR. CASTRANOVA: I don't think so either.

DR. ROGGLI: Well, either for either marker. I mean, just –- just to give you an example, even in a highly exposed, high-risk population -- let's suppose you've got a population has a 50 percent risk of mesothelioma, like the villages in Cappadocia. If your test finds that 50 percent of the people in that village test positive for mesothelin or osteopontin, whichever one, and it

correlates perfectly with the ones who later develop disease, then all you've done is predict who's going to get the disease, and you've got to be sure that you have a mechanism that's going to stop that from progressing if that's going to be –- that that's going to be helpful.

If you find that 75 percent of the people in the population test positive for that disease, then there's 25 percent that are not going to ever get mesothelioma that you've now made worry about it because they had a positive test. And if only 25 percent test positive in a pretest situation, then you've given false assurance to half of the people who are going to eventually get mesothelioma that they're okay.

So I agree that more research needs to be done, but what you need to do it in is good experimental animal models where you can control the situation. You can measure the markers and show that noninvasive techniques such as ibuprofen or some other drugs work in a controlled situation to prevent progression of disease before you're really ready to even test that, I think, in human population.

DR. HILLERDAL: So also let me answer that. Not all mesotheliomas are positive for mesothelin. There are a number of mesothelioma who are not. I think about –- was it about 20 percent in Robinson's paper who did not have

increased levels? And of course, that means you have -- as well as false positives, you have false negatives.

DR. WHEELER: How about from a community study point of view? Would they be useful at all in that kind of situation, say, like the Schenker study that investigated your living distance from outcroppings of asbestos containing rock. He measured mesothelioma as the end point. Could you use one of these biomarkers as the end point?

DR. CARBONE: See, what I would hope is that although too I agree right now that none of these tests is ready for prime time. Since we have a unique population with such high incidence of mesothelioma, it's not going to take five or ten years to figure it out, how specific and how sensitive these markers are. I really think that testing these markers in this population will allow us to give an answer relatively soon.

So yesterday, we do not have the answer to so many questions. But, hopefully, within a year or so, we will know more about the specificity and the sensitivity of this test, and at that time, maybe, one can answer the question that you've asked.

DR. WHEELER: Well, I think in Schenker's study he had a large number of mesothelioma cases that they studied and so, in that circumstance, was able to detect a two- or

threefold increased risk of disease related to where you lived in regard to these geological outcrops.

The problem is when you're dealing with the low levels and low risks of disease, considering how rare mesothelioma is. And if you're looking at something that has the risk of ten to minus four, for example, anything that's that low a risk, there's no test available that comes close to specificity or sensitivity that you would need to be able to apply such a test usefully in a community or a population situation that would useful.

DR. WEISSMAN: The denominator in the Schenker studies was really huge, so –- well, and you know, but that's the numerator. The denominator being the entire population, you know, living in proximity to those deposits is huge. And so doing this blood test on that number of people is obviously a very expensive proposition.

DR. KAPIL: I think it's actually a very interesting line of conversation from my perspective. I –- I don't think –- I'm not personally at all opposed to also generating some research hypotheses, for lack of a better term. Obviously, there are limitations based on the discussion that's gone on so far, but I –- but I do agree, Michele, that there may be some opportunities along these lines too.

So I have a specific question for you about osteopontin in some of the communities that we've already done some screening, like x-ray screening or spirometric. Let's stick with x-ray screening for a minute. In communities like Libby and some of the other populations related to Libby, we have a fairly high prevalence of people with pleural abnormalities in some subsets of those populations: 50 percent, for example, among workers in Libby; 26 percent among workers in Marysville.

What about the potential for looking at osteopontin, not necessarily as a clinically useful biomarker, but to look at osteopontin levels in subsets like that and perhaps trying to correlate with the presence or absence of pleural disease and then also looking at nonexposed populations without pleural disease?

DR. CARBONE: I am a co-investigator on a grant sponsored by the EDRN from the NIH, NCI, Early Detection Research Network. The title of the grant is Australia/U.S. Mesothelioma Consortium. And we are going to do exactly that, and that is to study the Wittenoom miners in Australia and study the Libby, Montana, and other populations here in the United States. And they will be tested for mesothelin and for osteopontin to verify the reliability and specificity of those markers.

Those studies, of course, will have a large number of

people. And, in the meantime, I'm doing the studies in the Cappadocian population.

DR. HOLGUIN: Yes.

DR. HILLERDAL: Have you decided what to do with the positive cases in this study?

DR. CARBONE: Look, I am a co-investigator on this (laughter). The PI, the principal investigator, is Harvey Pass. I am a co-investigator. Bruce Robinson is an investigator –- is a co-investigator too. We have agreed that we are not going to do extrapleural pulmonectomy if that's you're worried about. We have discussed at length the problem of identifying high levels of mesothelin and the ethical problem with that.

At the same time, it was concluded and decided that the advantages outweighed the disadvantages and that we needed to continue to do research on this test to verify the specificity and the sensitivity. I think that it would make sense to offer something to people who may have high levels of mesothelin. The something should be not an extrapleural pulmonectomy, should not be any type of toxic treatment.

And that's why I was suggesting -- but this was just a suggestion that has not been implemented into a clinical trial -- to use drugs such as COX-2 inhibitors, such as drugs that block specific part when in inflammation, the

TNF-alpha, Onconase, things like that that are not toxic and that you can offer to these people. Whether that is going to happen or not, I do not know. At the moment, the trial is going exactly as I told you.

DR. HILLERDAL: Well, they might not be toxic, but they do have side effects. As we know, both COX-2 and the TNF-alpha inhibitors do have some serious side effects.

DR. CARBONE: But they also have some advantages.

DR. HILLERDAL: Yes, I know.

DR. CARBONE: I mean, ibuprofen, for people who have arthritis --

DR. HILLERDAL: Of course.

DR. CARBONE: -- they feel better. So it’s not that bad.

DR. HOLGUIN: Okay. We’re going to take a break. How does that sound?

(Whereupon, a recess of approximately 33 minutes was taken.)

DR. WHEELER: The panel's been doing so well in sticking -- sticking to schedule so well, we thought we'd show movies this afternoon. And sorry we don't have any popcorn, but that's one of those government things.

I showed you a picture earlier of a creek that was all damned up from a slide. This is a heck of a -- heck of an exposure scenario. This is the mountain that sits

above that creek. Erin Larson from our regional office brought this in. It's a time-lapsed photograph, but you can see the -- you can see the mountain moving down the side of the hill towards the creek. Now the community wants to know what that's going to do to their health.

DR. CARBONE: How did you do that?

DR. WHEEELER: Yeah. How did you simulate that activity (laughter)?

DR. DODSON: Government can move mountains.

DR. WHEELER: [Off microphone]

THE COURT REPORTER: Microphone, please.

DR. WHEELER: I think those are individual pictures over a year period that have been linked together, and that's -- so you can see the mountain moving down into the --

DR. GUNTER: Where was that? Is this the Washington site? I'm sorry. I missed it.

DR. LARSON: [Off microphone]

DR. WHEELER: Seven miles south of the British Columbia border.

DR. GUNTER: The British Columbia -- I mean, the British Columbia-Washington border's 300 miles long, and where about in there? Do you know?

DR. LARSON: [Off microphone]

DR. WHEELER: Use this mike.

DR. GUNTER: I live in this area. That's why I'm more curious than normal.

DR. LARSON: I'm Dr. Karen Larson from the Seattle regional office of ATSDR. This is a site directly north -- well, almost north of Bellingham --

DR. GUNTER: Okay.

DR. LARSON: -- along the British Columbia-Washington border.

DR. GUNTER: Thank you.

DR. WHEELER: All right. That's it. Sorry. Short movie. Do you want to turn the lights up?

DR. HOLGUIN: Are those the previews (laughter)? There is coffee available. I think it's not as dark as the one I just made, so...

We had a very good discussion of osteopontin and mesothelin, and I think we should probably take it up to the same level with some of the other clinical tests that we have pending discussion. These are clinical tests such as spirometry to look for functional changes; clinical tests such as x-ray or CT scans to look for pathological changes, including plaques, pleural thickening, and pleural effusions.

And again, any comments related to exposures and relationship to risk, visibility of usage, public health studies, et cetera. If anybody wants to comment. Do you

want to start with -- there's like three tests in here. We could start with spirometry and functional changes and how they relate to disease risk or disease progression or exposure, if any. If nothing, let's move to the next one. Any comment on spirometry?

DR. HILLERDAL: Spirometry is a not the test. It's a test for the disease, not for an exposure. And if we're talking about asbestos -- now, if you get an asbestosis, you either have to -- if you have low exposure, you might get that, but that would be very late in your lifetime. On the other hand, if you have a very high exposure, then you can have an earlier asbestosis, but I don't think that's something we can expect from environmental.

You can find that sometimes in Turkey actually with the elderly -- elderly farmers have been living there environmentally exposed. They can have asbestosis, but it's a rare finding. And another thing is that this is very unspecific. The early changes are very unspecific. You can, in a bigger group of asbestos-exposed persons -- if you have a big cohort, then you can see that on the group level you do have -- you do have a somewhat diminished function, but on the individual level, there is no way of doing that. And smoking is much more -- it's much more common to affect these spirometry tests.

DR. CASTRANOVA: Often, not only is it nonspecific,

but it's not very sensitive, certainly, to exposures. At the levels we're talking about, I wouldn't think spirometry would find something until you had chronic disease.

DR. HILLERDAL: Right. It's a measure of disease, not of exposure. That's what I was saying.

DR. ROGGLI: And if you had 1,000 abnormal results in a big population like this, 999, if not 1,000, of them would be something else besides the exposure issue --

DR. HOLGUIN: Sure; sure.

DR. ROGGLI: -- because of the confounding factors.

DR. KAPIL: I agree with pretty much everything that's been said about this being really a measure trying to assess pulmonary function, looking for abnormalities of disease. But I do want to say just one thing about the context for why it's -- and actually mentioned for the panel to consider.

One of the things we hear quite a bit about -- I think Aubrey alluded to this earlier -- is -- there are a couple of things. One is that our measures of exposure, what we've traditionally considered measures of exposure, such as presence of pleural abnormalities on radiographic finding -- as a radiographic finding, are those in any way correlated to any functional impairment? So can spirometry be helpful in assessing functional

abnormalities in those types of settings?

The other thing which is perhaps even more important that we hear a lot from our communities which we're dealing with amphibole exposures, particularly Libby and related sites, is that the fiber exposures that we're dealing with here are different than what we know about asbestos in general and that, for some reason, there is a unique, more severe, more rapidly progressing kind of condition, pulmonary condition, associated with these exposures.

So, you know, there's been -- there have been some sort of case reports, anecdotal reports, of very rapid progression of pulmonary function, of spirometric abnormalities, in very -- over very short periods of time.

So that's sort of the background in terms of the context. It may -- it may not necessarily still be relevant for your discussion. But are there ways to use spirometry data to get at these types of things? Either trends over time in individuals or in a population of people or in relationship to pleural abnormalities, for example.

DR. CASTRANOVA: In the Libby group -- I have a question. In the Libby group, do you see pulmonary function changes earlier than the pleural changes?

DR. KAPIL: I'm hesitating a little bit in answering

that question because -- because really what we've done is sort of a snapshot look. You know, we've done one big screening in Libby, and then we've done once screening in Marysville. We are doing some ongoing screening in Libby, some of which are people that have already been screened. But we don't have that data available yet to either -- and we haven't analyzed the data yet. So I can't really tell you a whole lot about temporal sort of trends. However, my sense is that, in general, what we have seen in a lot of folks in Libby is pleural abnormalities or disease first.

DR. CASTRANOVA: Right.

DR. KAPIL: And many of those people don't have any functional abnormalities on spirometry, on baseline spirometry.

DR. CASTRANOVA: That would have been my prediction. Yeah.

DR. MILLER: Hi. This is Aubrey Miller with Region 8, EPA. The problem with that is you don't have a baseline prior to that, so while those people may be physiologically within normal bounds by our criteria of age and, you know, body habitus, the fact is -- is they may have gone from, you know, a much higher level and change, and you just can't see it, given the wide range of what's a normal criteria for pulmonary physiology.

So, you know, it really depends on watching what Vik alluded to, which is looking at the progression of disease over time. There's one paper that Dr. Alan Whitehouse published about his patient population from Libby that showed decrease in pulmonary physiology in individuals with pleural disease only, without interstitial abnormalities, and has been following this population for a while.

So I think this data is incredibly important, and we'll continue to follow along and see what we show. ATSDR is doing some additional studies to look at progression of disease in this population as well as Jim Lockey at University of Cincinnati.

DR. CARBONE: What is the number of mesothelioma and in what population?

DR. WHEELER: Do you want me to take a stab at it?

DR. CARBONE: How many mesotheliomas have been reported in Libby, and what is the total population?

DR. MILLER: The total population of Libby is around 10,000 people. The mesotheliomas is -- we have death certificates over time and probably have death certificates over about 25 years that have come to our attention, and we have about 25.

DR. ROGGLI: How many of those were people who actually worked in the vicinity --

DR. MILLER: Predominantly, those --

DR. ROGGLI: -- or were contacts?

DR. MILLER: Predominantly, those who worked. Now, ATSDR did a mortality study. They used -- and I'll let Vik comment further about the mortality study. Identified a number of mesotheliomas, but the limits of the mortality studies -- when you're going to do a standardized mortality study, they have to have died in that geographic location, so there's a fair amount of folks that have died elsewhere. Three were used in the ATSDR mortality study. Is that right, Vik? I think it was three.

DR. KAPIL: Yes.

DR. MILLER: Two of those were occupational. One was not occupational. And as you would expect, you know, most of the folks have been identified with disease in the population, at least with respect to mortality statistics, were, you know, former workers. And that's where the -- that's where the clinical observations were being made in the population.

DR. KAPIL: Was that clear, Michele? Did that answer your question?

DR. CARBONE: Yes.

DR. KAPIL: It depends on who you -- it depends on what data you look at. The answer is it depends on who you talk to. So we did a 20-year mortality study. I

think the years were '79 to '99 or something -- '79 to end of '98. We found three cases based on review of the death certificates.

However, from the community and the physicians in the community and members of the community looking at -- looking at cases outside of the strict sort of definition that we established for cases, they have identified other cases. However, that's not work that ATSDR has done. I'm not sure. Has that been published, Aubrey?

DR. MILLER: No. These are just cases that are available -- you know, death certificates that are available that most of them have been cross-referenced to former workers in Libby. So that was one way they were able to establish those as being related mesotheliomas to the Libby population. But again, we've given the limitations of mortality statistics and migration of folks away from Libby. When the mine closed, a number of folks, you know, relocated elsewhere.

DR. CARBONE: And the percent incidence among workers, how much was that?

DR. MILLER: A study was -- an updated study was done by J.C. McDonald in 2002 and 2004 and found a much increased rate of mesothelioma in the original worker cohort population -- around -- I'm thinking around 4 or 4-1/2 percent.

DR. KOPPIKAR: Five percent.

DR. MILLER: About 5 percent was the amount. Yeah; upper 4 percent; about 5 percent, according to Aparna. So you compare that as about equivalent to the rates that we're seeing in the Wittenoom population, the crocidolite-exposed miners.

DR. CASTRANOVA: In the pulmonary function in Libby, is it more restrictive disease or obstructive?

DR. KAPIL: The -- that's a -- that's a tricky question because, as an absolute number, I suspect that, you know, there are probably a lot of people with obstructive abnormalities. But we were specifically, of course, interested in restrictive or mixed abnormalities, and the percentage of people with those restrictive or mixed abnormalities is relatively very -- you know, it was a very small number.

However, as Aubrey said, you know, one of the issues is we don't have baselines on these folks and we're only looking at spirometry. So there's some limitations. One of the things that I think would probably be helpful for the panel to understand is that the screening that we've done is it’s truly screening. I mean, we haven't done any diagnostic evaluation of these folks in any way, shape, or form. There's no exam. There's no CT scanning. There's no complete pulmonary function testing done, no diffusion

capacity, or anything.

So all of that kind of stuff is left to physicians in the community. So some of the things that Aubrey's mentioned -- he's got a lot of additional information that's from community physicians and from his experience in Libby, so it's not necessarily exactly what we've reported in our reports. Is that fair?

DR. MILLER: Yeah. I think so. And, you know, we did it as a collaborative effort --

DR. KAPIL: Right.

DR. MILLER: -- you know, so between the federal agencies, including NIOSH, at the time, to some extent.

So the -- you know, it was a standard -- the medical screening was a standard B-reading x-ray. It's with pulmonary function tests and a questionnaire, which include occupational history, nonoccupational exposures, medical history; a very kind of standard format. And the case definition for identification of those with pleural abnormalities was agreement by two of three B-readers, using ILO criteria; so, you know, very kind of standard approach.

DR. HOLGUIN: Just a quick question. So there's -- again, is there anything known about other pulmonary tests besides spirometry, like diffusion capacity? Has anybody done or anybody knows about using, first, oscillation

techniques? I know you can look at airway impedance and sort of partition how much of that is respiratory, how much of the impedance comes from the airway, how much comes from the tissue, how much comes from the chest wall even. Has any -- and that's actually very applicable in the field. Has anybody -- impulse oscillometry or forced inhalation techniques, have they been used? No? It sounds kind of weird.

(No audible response)

DR. HOLGUIN: All right. I thought it was a good try. Any more on spirometry? No?

DR. WEISSMAN: Just one comment is that the issue of following longitudinal spirometry in looking at declines over time was brought up, and I think anybody who gets into that needs to appreciate that it's a lot more complicated than it might appear on the surface. There's a lot of noise in spirometry normally, and that noise exceeds, often exceeds, the annual declines that you might expect. So it's not a trivial matter to have really high-quality spirometry done, and it needs to be done over a period of years for you to be able to say anything about longitudinal.

DR. HOLGUIN: Sure. And it's certainly confounded, you know -- also, particulates can affect lung growth or rate of lung-airway function decline over time.

X-ray, CT scans: comments? Do you want to steer the discussion -- make a little bit of CT scans and x-rays?

DR. KAPIL: Yeah. We would very much appreciate hearing from the panel. I think everybody has a pretty good feel for limitations of x-rays, plain films. We would appreciate hearing from the panel -- obviously, it's a noninvasive test. It's fairly cheap. It's fairly easily doable -- on the use of a panel of B-readers, as opposed to using a single B-reader; what the issues are related to B-readers, which I think, again, most of us are reasonably familiar with.

CT scans have, in some circles, been sort of considered sort of the gold standard, if you will, and we'd like to hear from the panel on that perspective. We have had issues in some of these communities even with CT scans in terms of interpretation of CT scans. So we'd like to hear from folks who have some familiarity with interpreting CT scans for -- again, for the more subtle kinds of abnormalities. I think most people can agree on the obvious disease and the obvious abnormalities.

I'm sorry. One more thing. And, of course, again, things were probably -- most of us are familiar with the use of CT scanning as a screening tool. I think it's been already alluded to in the context of smoking and lung cancer, but in this context. Thank you.

DR. HILLERDAL: The problem is that pleural changes -- they usually take 20 or 30 years to develop, and they slowly progress. And the early ones -- if you take pleural plaques, which is the most common lesion really, and they develop -- and the early cases, they are very unspecific.

And if you use the ILO system, you know, they have a graded scale, and the lowest grades, they are really not very good. But you get a lot of background noise, if you like, and there are things like if you have a heavy-weight people, which tends to have more air in them than we have back home in Europe, then you can get lots -- you get a lot of false positives, even with B-readers actually.

So I think if you're going to do something like this, you should have a control group and you should really mix these x-rays so that readers have no idea which are exposed and which are not. That is for the early lesions. Now, the more advanced lesions, they are -- I mean, they are -- obviously, that's no problem.

What about CT scan? Well, CT scan can really discover small plaques much earlier than you can see them on the chest x-ray. But, again, this has not been really evaluated, compared. You know, we have a number of studies where we have compared findings of chest degrade with findings at autopsy, and it's a big discrepancy of

area. You find many more at autopsy than you do at the chest x-ray. But this has not been done, to my knowledge, with CT scan, and I don't think it ever will be done because the autopsy rate is down so very much.

DR. HOLGUIN: How about this -- it's more specific for asbestos than pleural findings. How about this pleural line, subpleural lines?

DR. HILLERDAL: Yes. But they are unspecific. You know, they can come with diseases; like, you have the diffused pleural thickening. That is much more common in asbestos workers, but it's also nonspecific finding. Really, you can find that in many other cohorts as well, so you have to be careful there. So it's not easy, and really, if you want to find -- if you want to find -- if you want to find a high incidence of pleural plaques, what you should have is workers who had been exposed to asbestos 20 or 30 years ago because that's the first time when you will be able to see them.

DR. HOLGUIN: Okay.

DR. WEISSMAN: I think chest x-ray definitely has limitations that people know. Already mentioned, that in autopsy studies, you know, about 20 percent of exposed people that have, you know, histologic changes, have normal, you know, x-rays. So, you know, there are limitations to the technique itself.

It's been estimated that in a population -- if you have a population prevalence of about 5 percent of asbestosis in an exposed population, at 5 percent, there's a positive predictive value of the chest film alone in terms of interstitial changes of about 40 percent when you figure in the sensitivity and specificity of the x-ray. So x-ray isn't perfect. But, you know, that being said, it's, you know -- it's inexpensive. It's practical. Chest radiograph, you know, especially in the more advanced changes, you know, gives reproducible results.

Vik was asking about some of the specifics about ILO classification should be done, and the ILO has really good guidelines on how to apply ILO classifications to populations. So it's extremely important to select readers who, you know, have mainstream, you know, reading tendencies so you can use quality-assurance films to screen perspective readers that you use and, you know, make sure, you know, that they read, you know, in a mainstream way.

It's important to use quality-assurance films. Spike films into packets that are read, you know, to be sure that people maintain, you know, their central reading tendencies, and there are publications in terms of giving feedback to people. The ILO recommends using at least two and preferably more individuals to classify films in

epidemiologic studies, and that would apply to this.

The ILO also recommends blinding so that when people read films, they're not aware of the exposure status or where the films come from. An NIH panel, like, 20 years ago recommended spiking of films that were from normal films from low-exposed populations into packets, you know, to make sure that the background reading wasn't, you know, unacceptably high in reads.

So there are really good criteria for how to do it, recognizing that the technique itself isn't perfect, but it's still pretty good.

DR. HOLGUIN: What kind of kappa scores do you get from pulling a few B-readers and looking at an x-ray?

DR. WEISSMAN: Well, you know, if you look at individual B-readers -- and, you know, as you know, I mean, there's a big literature of taking individual reads, you know, and looking at kappas from individuals, you know, and you can often -- and it's not uncommon in a big reading study to get relatively poor kappa scores, and that's why you need to have a group of readers read and use a summary reading that's at the central, you know, tendency of a group of readers, and then you do better. But if you -- you can't use single reads by individual readers.

DR. ROGGLI: I think one thing that you could say

positive for x-ray screening is that, in our studies, we've found -- and others have found -- that there's a high percentage of patients with mesothelioma have pleural plaques. It's more than 70 percent of the cases in our study. Others reported more than 80 percent, depending upon the population. And I believe if you were to screen a population with adequate latency, at least 30 years, and found no evidence of increased plaques in that population -- at least that you couldn't explain by occupational exposure -- that it would be highly unlikely that you'd ever be able to demonstrate an increased risk of mesothelioma in that population.

DR. WEISSMAN: Good point.

DR. HILLERDAL: Maybe with the exception of the kainite and of the erionite people because they don't have very many plaques that -- what are you saying?

DR. CARBONE: Because in mesothelioma that it happens some 20 years earlier than in the United States, it could be that they die before they develop that many. But I agree with you that there is not 70 percent incidence of pleural plaque. There are some pleural plaques. And actually, the first person who was ever diagnosed by Baris is somebody who was diagnosed because of pleural plaque. He was his first patient, and every time you go to the villages, you meet him and he is absolutely fine, which is

an anecdotal thing to say that the plaques do not necessarily mean that you're going to get mesothelioma fortunately.

I don't understand why it takes 30 years for the plaques to develop. That's what I was trying to think when you were talking about it. It doesn't make sense to me, but, obviously, it takes 30 years.

DR. WEISSMAN: And I think that one -- with regard to pleural plaques, one thing I would bring up would be the ATSDR, you know, publication recently where groups of three readers, you know, read x-rays for the presence of pleural changes. And so ATSDR did a study looking at of the subset of films where one of the three individuals doing ILO classifications said there were, you know, pleural changes and the other two did not.

And they found that in about a third of those films, if you did CT, you actually identified the presence of plaque. So in terms of looking for plaque, it seems that an integrated approach that perhaps used both plain film and CT in a subset might be a better way to go than just using plain film alone.

DR. CARBONE: Since you are all tired, let me tell you one thing to relax very by, and then we continue. December of last year, we went to the village, the Cappadosian villages, with Baris and Emri, and we did the

screen with a normal radiologic x-ray machine of 65 people who we found outside. They are sitting there. Out of 65 people, five had pleural-based tumors, which gives you the idea of the incredible situation that happens over there.

DR. HILLERDAL: How many had plaques?

DR. CARBONE: I don't remember. I was trying to think about that. I don't remember.

DR. ABRAHAM: That's amazing.

DR. KAPIL: So just a follow-up question for Vik. The -- you said that most cases of mesothelioma, at least 70 percent or something, have pleural plaques. Would the panel be able to comment on the -- on sort of the corollary of that? If you have a pleural plaque -- and this is the issue that we're facing a lot in our communities. If you have pleural plaques -- let's say for a moment -- in the absence of any other functional change and any other x-ray functional abnormalities, what is sort of the bottom line on your future lung cancer and/or mesothelioma risk?

DR. ROGGLI: It probably depends on the population, and it depends on how you define plaque. Gunter did an excellent study published in *JAS* back in '94 -- wasn't it? -- that showed if you define bilateral plaques -- they had to be bilateral, first of all; had to have at least 5 millimeter thickness or calcification. In a population

that met that criteria, there was 11-fold increase of mesothelioma and a very modest increase of lung cancer, which I'm not convinced wasn't related to subclinical asbestosis or even misclassification of smoking, as far as that's concerned.

DR. HILLERDAL: Exactly. It depends on the population, and if you go to Finland, they have these environmental anthopyllite exposure there, so they have the most beautiful plaques you can see, and they have absolutely normal lung function, and they have very, very little incidence of mesothelioma.

Actually, a few years ago, they said that anthopyllite doesn't cause mesotheliomas, but now they have shown a few cases. But it's a very low incidence, and we have to remember that most people with pleural plaques will die of normal causes -- I mean, unasbestos-related causes. And that's what we have to say to our patients. If the patient says, "Oh, I have pleural plaques now. It's my death certificate." But it is not. Most people will -- will live all their life with those plaques, and they will die from heart infarction and whatever.

DR. WEISSMAN: And I'm probably not the one to say it at the table, but there are, you know, others at the table that have looked at lung burdens associated, you know,

with plaques, and, you know, clearly, you know, they're not as high as lung burdens associated with some of the other manifestations.

DR. HILLERDAL: No. They are somewhere in between. You get one group unexposed. You get one group with pleural plaques, and then you get another group with mesothelioma. And there is a clear difference on them. Of course, they're overlapping. That's the problem. They are overlapping.

You can find people with beautiful pleural plaques who have very low fiber levels, and you can find people with high levels of fibers who have no pleural plaques. So it's very -- it's very difficult, and there is no absolute correlation. But I would say that having pleural plaques is an indication of being exposed to asbestos, and because of that, you have an increased risk of mesothelioma and, I think, of lung cancer and of asbestosis, which are the diseases really we are talking about.

DR. GUNTER: Do the increased pleural plaques relate to any specific kind of asbestos?

DR. HILLERDAL: Well, as I said, there is a definite difference between, you know, Finnish anthopyllite and crocidolite. And I would be much more worried if I had a patient that had been exposed to crocidolite and had

beautiful plaques than if it was a man who had been exposed to anthopyllite and had the same plaques. I think the risk for the crocidolite man would be much higher than the one for the anthopyllites. So they don't go hand in hand. And why this is so, I have no idea, but it would be very interesting to investigate.

DR. GUNTER: And how about chrysotile?

DR. HILLERDAL: Chrysotile, I think -- well, I don't know if we should take up that discussion here: What does chrysotile do, and what does it not do? But, basically, I think if you are exposed -- we have some cohorts who have been exposed to very low levels of chrysotile and pure chrysotile and no amphiboles mixed in, and they have no increased disease really nor do they have any increased pleural plaques. That's my personal opinion.

DR. GUNTER: Now, was it -- part of this was a conversation we were having that I was curious, you know, if minerals do change in the lung. Minerals dissolve, and if they contain certain elements, maybe those elements are translocated to the pleura to form the pleural plaques. So that's why I was searching -- we had that discussion this morning.

DR. HILLERDAL: Yes.

DR. GUNTER: -- searching for a mineralogical reason and the alteration in the metal that might create them.

DR. HILLERDAL: Yeah. Well, that's an interesting hypothesis. I have no other comments on that.

DR. ROGGLI: One of the obvious differences between the anthopyllite and the crocidolite is diameter, fiber diameter.

DR. HILLERDAL: Yes; yes.

DR. ROGGLI: And probably the -- some mechanism we don't understand yet that that's important in the carcinogenic process. But the few Finnish cases that have been related to anthopyllite have been in the miners, haven't they?

DR. HILLERDAL: Yes; yes. And they have had quite a considerable exposure and lots of fibers. I was told that in -- I think it was in Bolivia. They have a crocidolite mine, but that crocidolite is much thicker. It's much more like anthopyllite, and they claim that there are no -- they have no mesotheliomas there, and that would be very interesting to investigate to see whether that is true.

But that would make sense because -- this is another problem -- that the same fiber -- I mean, tremolite from that mine or from that area is not the same tremolite as we can find somewhere else. And the same goes for crocidolite and, I think, for anthopyllite because when I -- when I read the -- I think it was your paper about

finding anthopyllite in mesotheliomas in the United States, and I looked at the diameter of that, and this was much thinner anthopyllite than what they find in Finland.

So I think it's much more complicated than just putting them in different categories, which leads into another question we discussed in the lunch, if it will be possible to find -- to define the fiber we find in the lung and say that this one comes from Libby. This is not -- this is not from -- from Tyler of something like that. That would be very interesting, and I think it's been done. There are studies on that.

DR. CASTRANOVA: If I remember right --

DR. DYKEN: I wonder is I could ask a question. If you could, clarify what you mean by thicker fibers and thinner fibers. Do you have any range of diameters?

DR. ROGGLI: Yeah. The average diameter of a crocidolite fibers in populations that have been studied, that many of them two-tenths of a micron. The average diameter we find in the lungs of amosite are probably around three-tenths to four-tenths of a micron. The average diameter for tremolite's probably more like half a micron or a little larger, and anthopyllite runs about a micron in our lab in thickness on average.

We've seen some thinner. I mean, there's ranges of values that overlap, and there would be individual fibers

you can see and you predict it's going to be one type of fiber. When you analyze it, it's not. So there is overlap, but this is just average values that I think we and others have found.

DR. DODSON: There's a study --

DR. CARBONE: What about chrysotile? What's the size?

DR. ROGGLI: Well, once it's been in the lung for a while, it's broken down into diameters which are well less than a tenth of a micron.

DR. DODSON: As a continuation of and in response to that question, you get slightly thicker fibers. You're going to when you coat with an SEM. The TEM, where you don't do the coating, crocidolite and chrysotile both have diameters that are very similar, and the fibril or the single fiber thickness is in hundreds of a micron.

There is no difference, by the way, regarding the thickness of Bolivian blue crocidolite. It only happens to be in a higher concentration of magnesium than the Australian or the South African. So it was a good try, but that's not the case.

DR. HILLERDAL: That's good.

DR. CASTRANOVA: If I remember, David Bernstein was studying the Brazilian crocidolite. And although the data are very controversial, he claims that it's not

biopersistent in the lung, and he's taken some lung slices and done confocal microscopy, time postexposure, at least in a rat lung, and sees the fibers actually getting shorter, which is very unusual. And maybe that had something to do with the Brazilian result.

DR. ROGGLI: Are you talking about Bolivian or Brazilian?

DR. CASTRANOVA: Brazilian.

DR. DODSON: He's talking about chrysotile, not crocidolite.

DR. CASTRANOVA: Yes.

DR. ROGGLI: Brazilian crocidolite?

DR. DODSON: Chrysotile.

DR. CASTRANOVA: Chrysotile.

DR. DODSON: We mixed it with Brazilian crocidolite a minute ago. So no, it's Bolivian blue, which is crocidolite. He's talking about Bernstein's animal study.

DR. HILLERDAL: This question about pleural plaques versus amphiboles and chrysotile -- there has been a lot of studies going on up in Canada, and there were conflicting results, and it's difficult to really -- for an outsider to decide what is what.

But there are big mines. There is a big mine in Russia, and that mine has a very low level of tremolite. And I heard this from my Finnish friends who have been

doing studies there, and they have a low level of pleural plaques and low level of mesothelioma, and they have low levels of tremolite in the lungs.

You know that if you take a Quebec miner, you will find more tremolite than you will find chrysotile in his lungs. But the same lungs in the Russian mine will have only -- one mine is a low level of tremolite. That's what my Finnish friends tells me, so I think there is some truth in that, I think.

DR. CARBONE: So you say that chrysotile do not cause pleural plaques?

DR. HILLERDAL: I say that chrysotile has not such a high tendency to cause pleural plaques as do the amphiboles.

DR. CARBONE: And on the other hand, if I remember, was it Sebastien who said what you find in Dabara is mostly chrysotile rather than crocidolite; right?

DR. HILLERDAL: Yes. That is quite true. Yes. But there are -- you do find amphiboles also in the pleura, and that's another thing. How do the pleural plaques get there? And that's very interesting, but we have no idea of that. And of course, Ron, you have done studies with the pleura, and you have found quite large amphiboles as well in the pleura, haven’t you?

DR. DODSON: We have found both amphiboles and

chrysotile in the pleura, but preferentially, in the plaques, it was chrysotile, just like Sebastien reported. And there are -- there are -- there is a population of some longer fibers, greater than five, that reach those sites, but it's not the same as you find in the lung of distribution at all. It's a very minority component.

DR. CARBONE: So basically, you're saying that chrysotile could contribute to pleural plaques when there is also crocidolite?

DR. DODSON: No. I think what you heard me say is I found chrysotile in pleural plaques, and I've also, in some cases, found some amphiboles.

DR. CARBONE: Yes. I just have to put it --

DR. DODSON: It just happened to be crocidolite and the amosite.

DR. CARBONE: I was trying to put it together with what he say, that chrysotile -- that there were studies that didn't find that chrysotile caused pleural plaque.

DR. HILLERDAL: But it's the same problem because you never -- it's very, very difficult to find a cohort which has been exposed to only one single fiber. There seems always to be mixture in the lungs. So if you have amphiboles, you will find also chrysotile. And if you find chrysotile, you will find other sorts. So it's very difficult to really decide whether chrysotile is innocent

or not in causing plaques, for instance.

But if you look on the -- it the other way around -- if you look at, for instance, that our cohorts in Sweden, you have asbestos-cement workers and things like that, and those who are exposed to early chrysotile have a very low level of disease and of pleural plaques. I don't count plaques as a disease.

But whenever you mix amphiboles into that cement, you will have trouble with mesotheliomas and with pleural plaques later on. So I definitely think that the amphiboles are at least much more danger than is chrysotile. And I hope nobody will kill me for that. But I'm not sure that that's what we should discuss at this meeting here.

DR. ROGGLI: No. But I'll kill you instead for the pleural plaques not being a disease (laughter). It's an interesting question because back in 1986 we submitted an article to the *British Journal of Industrial Medicine,* and we had described 110 cases of asbestos-related diseases, and one of the reviewers said, "Well, 40-some-odd of your cases are pleural plaques only, and that's not a disease." So I had to respond to that, so I went to *Stedman's Medical Dictionary* to see how if defined disease.

And it gave -- they gave three criteria. One is that you had definable morphological features, which plaques

have; that you have a recognized symptoms or signs related to the disease, which plaques don't have; or it has a recognized cause, which plaques do have. And it said if any two of those three are met, it's a disease (laughter). And so that's when we wrote back to the editor, and they didn't make us change our paper. So according to *Stedman's Medical Dictionary*, pleural plaques are a disease (laughter).

DR. ABRAHAM: Or it shouldn't be called pleural asbestosis. We should all agree to that.

DR. ROGGLI: Right. I agree with that.

DR. WEISSMAN: Well, and more to the point of this conversation, it's useful to document their presence, particularly if they're bilateral --

DR. HILLERDAL: Absolutely; yes.

DR. WEISSMAN: -- and calcified.

DR. CARBONE: But if you say to somebody that because he has a pleural plaque he has a disease, then he or she thinks that he's sick. Maybe it's better to explain to them that in spite of the fact that they have disease that they are not sick.

DR. ROGGLI: Then you have to have the discussion of what do you mean by sick.

DR. CARBONE: Well, sick means that you have to have some symptoms. I mean, otherwise we are nothing.

DR. ROGGLI: Well, just explain that *Stedman's Medical Dictionary* does not require you to have symptoms to have a disease.

DR. CARBONE: Where is this dictionary from?

DR. ABRAHAM: The word "disease" means not at ease; right? It's some sort of unease.

DR. HILLERDAL: Well, in Sweden, when this thing came up about 20 years ago, this became an issue, and labor unions demanded that everybody who had pleural plaque should get compensated, irrespective of whether he was sick or not, because that's a disease and it should be compensated. And for a society that everyone who had that should have -- I think it was something -- almost $2,000 cash, tax-free, for showing plaques.

And of course, there was a big storm of people running up and of lots of fat people who were compensated because of that. So after some years, they took it away, and now you need pleural plaques and some proven disease, if you will, that is, some low lung function. So now, instead, you have heavy smokers with pleural plaques. They get compensated.

DR. WEISSMAN: But pleural fat -- pleural fat is not a pleural plaque.

DR. HILLERDAL: No. But that's how many of my x-ray -- my chest x-ray colleagues, you know -- many

radiologists define that as that, and we get that all the time. And of course, if you specifically ask for pleural plaques, you will get a lot of -- because that was new, B-reading, like that. It was just accepted, you know.

Somebody said that you had pleural plaques -- and I looked at many of these cases and said, "This is not pleural plaques." But the man was compensated anyway. Even worse is sometimes he was registered as having asbestosis in his records, which -- well, that's another problem.

DR. HOLGUIN: I haven't heard -- I mean, maybe you were talking about it when I left the room. Has there been any -- you know, this is a diagnosis we sometimes consider in clinical practice, but benign-based pleural effusions. Is that something you see? don't see? Do they occur more frequently or at a more rapid pace than after exposure?

DR. HILLERDAL: We saw many more cases earlier because this is the only disease or -- even if you count pleural plaques, this is the only disease that has a very short latency time from asbestos exposure. And now we have -- so now we see them very rarely. And also, of course, it's very difficult to make the diagnosis because this is an exclusion diagnosis. You have to exclude other courses.

But my personal impression is that now, when asbestos exposure is very low generally in society, we see much fewer of them. What we do see are the diffuse pleural thickenings. They are a real disease, and I think many of them are remnants of such a pleurisy but because -- it's really surprising. The thing with these pleurisy is when we did regular scans, we sometimes found the people who were completely healthy and they had 1 liter of effusion in the lungs. And we took it out, and then, of course, after -- when we had done that, they admitted to having some symptoms. But before that, they had no symptoms; a little flu maybe.

So this is something that can pass without anybody noticing it, and sometimes they heal completely and you could see no remnants of it. Very often, you see a rounding of the sinuses and sometimes you see quite thick, big thickenings around it. And that gives a very -- can give a very restrictive disease.

DR. KAPIL: I do want to just remind the panel that we would like to hear very briefly about CT scanning, but I have comment about your pleural effusions. Just a point of interest sort of. The 1980 screening that was done in Marysville, Ohio, back in 1980 by the University of Cincinnati folks, was originally done because there were several reports of bloody pleural effusions among the

workers at that plant. Among the 500-odd workers, at least six, seven, eight bloody effusions were reported, and that was the precipitating event for the original screening back in 1980.

DR. HOLGUIN: Did you see much in Turkey? Do you see pleural effusions over there as a common occurrence?

DR. CARBONE: Yes. Don't ask me the percentage because I don't remember. But, certainly, you do see pleural effusion.

DR. ROGGLI: As I recall, the cases -- the studies that looked at it show evidence of a dose-response relationship as well for them. So in a low-dose-exposed population, you can expect to see a low, very low, if any, number of cases of benign asbestos effusion-related dose exposures. And you're going to have a very big problem again with noise from effusions caused by the numerous --

DR. HOLGUIN: Sure; sure.

DR. ABRAHAM: What about in Libby, where there's extensive pleural disease?

DR. KAPIL: We didn't see any in our screening that I'm aware of. But again, from physicians in the community, they've reported several cases of pleural effusion in the community, just not in our screening.

DR. CARBONE: What about chrysotile? Does it cause pleural effusions?

DR. HILLERDAL: I don't think so. It does in animals if you put it in the pleura.

DR. CARBONE: Excuse me?

DR. HILLERDAL: If you put -- if you put it in the pleura in animals, you will get the big effusion, but not in human beings. No. I don't think so.

DR. CARBONE: Among workers of mines of chrysotile, they don't get it?

DR. HILLERDAL: No. I haven't seen it.

DR. HOLGUIN: Any comments on CT for -- or should we leave it for tomorrow? No?

DR. KAPIL: That's fine. Wrap up.

DR. HOLGUIN: Jill's asked me to -- I'm going to pass this along to the panelists and -- just some questions for you to continue to think overnight about these issues.

DR. ROGGLI: Oh, boy; homework.

DR. HOLGUIN: This is your homework, so I'm going to read it. I'm just going to briefly read it for the -- so the public can be of service and take notice.

The first question is, "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" -- in parentheses -- "or in conjunction with health assessment techniques?"

Second question: "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 or increased risk?"

Third question. "Please consider two exposures: a long-term, relatively continuous versus a high-level burst or bursts" -- quote -- "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" -- parentheses -- "autopsy, BAL, sputum? Would the expected risk of disease be similar or different?"

Question 4. And please don't -- I know you might find it hard, but don't reply right now; tomorrow.

(Reading) "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?

Five: "How do fiber dimensions change over time after deposition in the lungs? Is there a correlation with exposure fiber dimensions on which risk models are based?"

Six: "Would serum biomarkers be useful for

populations/communities exposed to asbestos and other similar asbestiform fibers, particularly amphiboles" -- in parentheses -- "like in Libby or Montana?" Montana, question mark.

(Reading) "Would osteopontin be useful as a marker of exposure in exposed communities as a research tool or to correlate with pleural disease absence or presence?"

And last question, "Please comment specifically on carbon monoxide diffusing capacity as a clinically useful means for evaluating restrictive disease."

That's a lot of homework (laughter). Please provide more than yes/no answers.

DR. ROGGLI: Darn.

DR. GUNTER: There's also unsure.

DR. HOLGUIN: Thank you all for your participation today (applause).

(Whereupon, the proceeding was adjourned at approximately 4:46 p.m.)

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COUNTY OF COBB)

I, DIANE GAFFOGLIO, being a Certified Court Reporter in and for the state of Georgia, do hereby certify that the foregoing transcript was reduced to typewriting by me personally or under my direct supervision and is a true, complete, and correct transcript of the aforesaid proceedings reported by me.

I further certify that I am not related to, employed by, counsel to, or attorney for any parties, attorneys, or counsel involved herein; nor am I financially interested in this matter.

This transcript is not deemed to be certified unless this certificate page is dated and signed by me.

WITNESS MY HAND AND OFFICIAL SEAL this 22nd day of May, 2006.

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DIANE GAFFOGLIO, CCR, CVR-CM
Nationally Certified Merit Reporter
Certificate No. B-2372